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Translational Pharmacology Should Treat Biomarkers as Decision Tools Rather Than Decorative Correlates

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ABSTRACT

Biomarkers are often presented as evidence of biological relevance even when the development decision they are meant to change is unspecified. This creates a recurrent translational error: a statistically associated or mechanistically plausible measurement is treated as though it already has decision utility. Biomarker usefulness instead depends on context of use, analytical fitness, biological proximity to the pharmacological question, timing, population, treatment, dose, and the consequences of an incorrect result. This Perspective argues that biomarker interpretation should be organized around the decision a measurement is intended to change. Target engagement, pharmacodynamic response, patient stratification, and dose selection are distinct functions, and evidence supporting one role should not be silently transferred to another. Examples from circulating tumor DNA, imaging, target-engagement studies, biosimilar pharmacodynamic programs, and model-informed dose selection show that useful biomarker evidence is conditional. We propose that translational pharmacology distinguish measurement validity, biological relevance, action threshold, consequence, and transferability as separate evidentiary questions. This decision-utility view clarifies when biomarkers are descriptive, when they support pharmacological inference, and when they are sufficiently qualified to alter development or treatment choices.

Keywords: Biomarker context of use, Target engagement, Pharmacodynamic biomarkers, Dose selection, Patient stratification, Translational pharmacology

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INTRODUCTION

Biomarkers compress complex biological states into measurements that can appear immediately actionable. The danger is that actionability is often assumed before the intended decision is specified. Regulatory biomarker science instead treats usefulness as context dependent: the evidence needed for a biomarker depends on what it is meant to do, in which population, under which intervention, and with what consequence if the result is wrong [1]. A reproducible marker may therefore be valuable for one decision and inadequate for another.

The Biomarkers Consortium has similarly organized biomarker development around explicit need, context of use, benefit-risk considerations, and evidentiary mapping rather than association alone [2]. This does not mean that every exploratory marker requires formal qualification. It means that a biomarker cannot be judged independently of the claim attached to it. The shared context-of-use emphasis in regulatory and consortium scholarship provides a foundation for a decision-oriented interpretation [1, 2].

Model-informed drug development offers a parallel lesson: models are judged partly by how they will be used and the risk attached to the decision they support [3]. Biomarkers should be treated similarly. The central question is not only whether a marker correlates with exposure, biology, or outcome, but what choice should change because the marker changed and what evidence is required before that choice is defensible.

Correlation is not decision utility

A biomarker can predict, correlate, discriminate, or track and still fail to improve a decision. Decision-curve methodology makes this distinction explicit by evaluating whether acting on a model produces net benefit across plausible thresholds rather than assuming that discrimination or calibration alone determines usefulness [4]. The broader lesson is that utility requires a specified action and consequence structure.

Circulating tumor DNA illustrates the point. ESMO recommendations distinguish settings in which ctDNA has established or promising clinical validity from settings in which evidence remains insufficient for routine treatment-directed use [5]. The same platform can therefore occupy different evidentiary positions depending on whether the question is mutation detection, disease monitoring, minimal residual disease, treatment selection, or treatment adaptation.

The PRISM precision-medicine study also shows attrition between molecular information and changed treatment. Large-panel ctDNA sequencing generated contributive and actionable findings in many patients, yet far fewer ultimately received matched therapy [6]. Treatment availability, clinical eligibility, access, competing options, and patient-clinician choice intervene between detection and action. Actionability is therefore a chain, not an assay property.

Dynamic biomarkers add another category error. Early ctDNA changes during immunotherapy have been associated with subsequent outcomes [7]. Such findings can justify prospective testing, but they do not automatically define a treatment-switch rule. A decision tool must establish not only association with outcome but also when, how, and with what consequence the measurement should change action.

Biomarker context of use

Context of use binds a biomarker to an intended purpose. EMA experience shows how often qualification problems arise when this binding is incomplete: recurrent shortcomings have involved biomarker properties, assay validation, and context-of-use definition [8]. Qualification is therefore relational; evidence is judged against a proposed use rather than against an abstract label of “validated biomarker.”

This is especially important in patient-selection programs. EMA Scientific Advice procedures involving predictive or prognostic biomarkers repeatedly raised issues of cutoff choice, multiplicity, study design, and data-driven subgroup selection [9]. Once a marker determines eligibility, uncertainty can alter who is exposed to treatment, who is excluded, and how treatment effects are interpreted.

Neurofilament light chain in amyotrophic lateral sclerosis provides a useful example of use-specific qualification thinking [10]. Evidence assembled for one biomarker role should not be assumed to support every other role. This Perspective therefore treats “fit for this decision in this context” as more informative than the unqualified label “validated.”

Target engagement

Target engagement often spans several distinct states: systemic exposure, delivery to the relevant tissue, local target access, binding or functional perturbation, and downstream response. Tumor pharmacology makes this separation visible because adequate plasma exposure can coexist with heterogeneous intratumoral penetration, and target expression does not itself prove drug-target interaction [11]. A target-engagement biomarker must therefore identify which state it measures.

For the CXCR7 antagonist ACT-1004-1239, plasma CXCL12 increased with exposure in a pattern consistent with CXCR7 antagonism, whereas CXCL11 did not show the same response [12]. This strengthens a target-linked interpretation without converting an indirect systemic biomarker into direct receptor-occupancy evidence. Interpretation still depends on mechanistic specificity, dose-response behavior, and compartment.

Population pharmacokinetic and target-engagement modeling of tozorakimab similarly linked regimen and systemic engagement of the IL-33 pathway [13]. Such models can inform regimen evaluation while remaining conditional on model structure and transfer from systemic engagement to disease-relevant tissue. Across access, indirect engagement biomarkers, and PK/target-engagement models, different evidence layers answer different questions [11-13].

Imaging can move measurement closer to the tissue of interest. In a pilot study of [18F]FluorThanatrace PET in ovarian cancer, on-treatment change in tracer uptake was more informative for response-related interpretation than baseline uptake alone [14]. Timing therefore forms part of context of use.

MAPTRx in mild Alzheimer disease provides the complementary boundary. Dose-related reductions in cerebrospinal-fluid tau demonstrated biological activity consistent with the intended molecular intervention, but not clinical efficacy [15]. Target engagement and target-proximal pharmacodynamics can reduce mechanistic uncertainty while leaving patient benefit unresolved.

The target-engagement evidence is therefore better represented as sequential inference bottlenecks than as a binary “engaged/not engaged” claim. **Table 1** identifies where each readout permits a development statement and where transfer remains unproven.

Table 1. Target-engagement evidence as sequential inference bottlenecks rather than a binary biomarker claim

Target-engagement inference scenario	Evidence structure	Boundary and consequence	Target-engagement inference scenario	Evidence structure	Boundary and consequence
Adequate systemic drug exposure	Transfer boundary Plasma exposure may not represent the disease-relevant site	Development claim that is defensible The regimen produces systemic exposure compatible with pharmacological activity	Drug or tracer reaches target-containing tissue	Transfer boundary Tissue presence does not establish binding or functional perturbation	Development claim that is defensible The target is physically accessible under the tested regimen
	Next validation step Demonstrate tissue or compartment access when biologically necessary	Translational question that remains unresolved Does sufficient active drug reach the relevant compartment?		Next validation step Add direct occupancy or mechanism-linked evidence when feasible	Translational question that remains unresolved Is local exposure sufficient to engage the intended target?
A biomarker changes in a mechanism-consistent direction	Transfer boundary The change may be indirect, compensatory, or generated outside the target tissue	Development claim that is defensible The response is compatible with intended engagement	On-treatment imaging or direct local measurement changes	Transfer boundary Local occupancy or accessibility may remain heterogeneous	Development claim that is defensible The intervention alters a target-proximal state at the measured site
	Next validation step Test specificity, dose response, alternatives, and compartment concordance	Translational question that remains unresolved How uniquely does the marker identify the proposed interaction?		Next validation step Relate engagement to pharmacodynamic change across dose and time	Translational question that remains unresolved What degree and duration of engagement are pharmacologically sufficient?
Target-proximal pharmacodynamics are demonstrated	Transfer boundary Biological activity does not establish clinical benefit	Development claim that is defensible The drug produces biological activity consistent with mechanism			
	Next validation step Link response to dose, safety, patient-relevant outcome, and reproducibility	Translational question that remains unresolved Is the response sufficient, durable, and clinically consequential?			

Note: This table is an original synthesis of the preceding target-engagement distinctions. The row sequence is proposed as a reasoning aid, not a universal mandatory development pathway.

Pharmacodynamic response

Pharmacodynamic biomarkers sit downstream of exposure and can provide sensitive evidence that a drug perturbed a biological system. Their utility nevertheless depends on the question. In biosimilar clinical

pharmacology, appropriately selected pharmacodynamic endpoints can sometimes detect product-related differences more sensitively than conventional clinical endpoints [16]. Their value comes from alignment with a narrow comparative purpose, not from intrinsic superiority over clinical outcomes.

Randomized studies of PCSK9 inhibitors, interferon beta-1a products, and IL-5 antagonists show that candidate pharmacodynamic biomarkers differ in dose-response behavior, baseline variability, dynamic range, and practical sensitivity [17-19]. The common lesson is that pharmacodynamic performance should be characterized empirically before a marker carries a development decision [17-19]. Mechanistic plausibility narrows the candidate set; it does not replace measurement characterization.

The distance from a pharmacodynamic readout to the patient-level outcome also matters. A proximal marker may be excellent for showing pathway perturbation while remaining insufficient to show that the magnitude or duration of change will produce benefit. Translational interpretation must therefore state which uncertainty the marker is meant to reduce: exposure, mechanism, biological activity, comparative product performance, or clinical response.

Patient stratification

Patient stratification creates a stronger decision claim because a biomarker influences who receives or is prioritized for treatment. In KEYNOTE-042, tissue tumor mutational burden was evaluated in the context of pembrolizumab versus chemotherapy and showed treatment-context-dependent associations with outcome [20]. Such evidence is more informative for treatment selection than a purely prognostic association, but it remains bounded by tumor type, assay, treatment setting, and the exploratory biomarker analysis.

Prognostic and predictive roles are methodologically distinct. A prognostic marker carries information about outcome, whereas a predictive marker in the treatment-selection sense carries information about differential treatment response [21]. A marker can therefore be strongly prognostic yet useless for choosing between therapies if relative treatment effects do not vary across marker states.

Dynamic response adds a temporal dimension. In ALK-positive non-small-cell lung cancer, early ctDNA molecular response during lorlatinib therapy was associated with subsequent progression-free survival, and the relationship was treatment dependent [22]. This does not create a universal treatment-switch rule. It shows that context of use must include decision timepoint: a baseline marker may select treatment, whereas an on-treatment marker may monitor response or support adaptation.

Dose selection

Dose selection is where biomarker reasoning fails most easily if a pharmacodynamic signal is mistaken for the decision itself. A dose that maximizes target engagement or a proximal biomarker is not necessarily the dose that optimizes benefit-risk. In first-in-human development of roblitinib, dose selection integrated pharmacokinetics, pharmacodynamics, safety, and emerging efficacy rather than assigning decision authority to one signal [23].

The PRMT5 inhibitor PF-06939999 illustrates competing constraints. Pharmacodynamic information related to PRMT5 inhibition was modeled together with platelet effects to support selection of an expansion dose [24]. The biomarker was useful precisely because it was interpreted alongside what it did not capture: safety. Maximizing pharmacodynamic effect alone would have produced an incomplete dose objective.

The same logic extends into later development. Model-informed dose selection for datopotamab deruxtecan integrated population pharmacokinetics and exposure-response relationships for efficacy and safety [25]. Contemporary oncology dose-optimization recommendations likewise emphasize totality of evidence rather than a maximum-tolerated-dose paradigm alone [26]. Biomarkers are most useful when they help define where pharmacology begins, where response approaches a useful range, or where mechanistic benefit separates from increasing toxicity.

Route and formulation changes add another transfer boundary. Development of subcutaneous nivolumab used model-based exposure bridging to select a regimen for further evaluation relative to established intravenous experience [27]. Exposure similarity can support a dosing bridge but does not prove superior efficacy or complete equivalence of every clinically relevant property.

Finally, statistical significance does not automatically create a dosing action. Population pharmacokinetic and exposure-response analyses of risankizumab in ulcerative colitis supported induction and maintenance regimens without converting every statistically detected covariate relationship into a clinically meaningful dose adjustment [28]. A biomarker or covariate becomes dose relevant only when its effect is sufficiently reliable and consequential to change the choice.

Figure 1 therefore treats dose selection as a convergence problem rather than a biomarker-maximization problem. It marks where exposure, access, engagement, pharmacodynamic response, safety, and efficacy can inform the same regimen while retaining the boundaries that prevent one evidence stream from substituting for another.

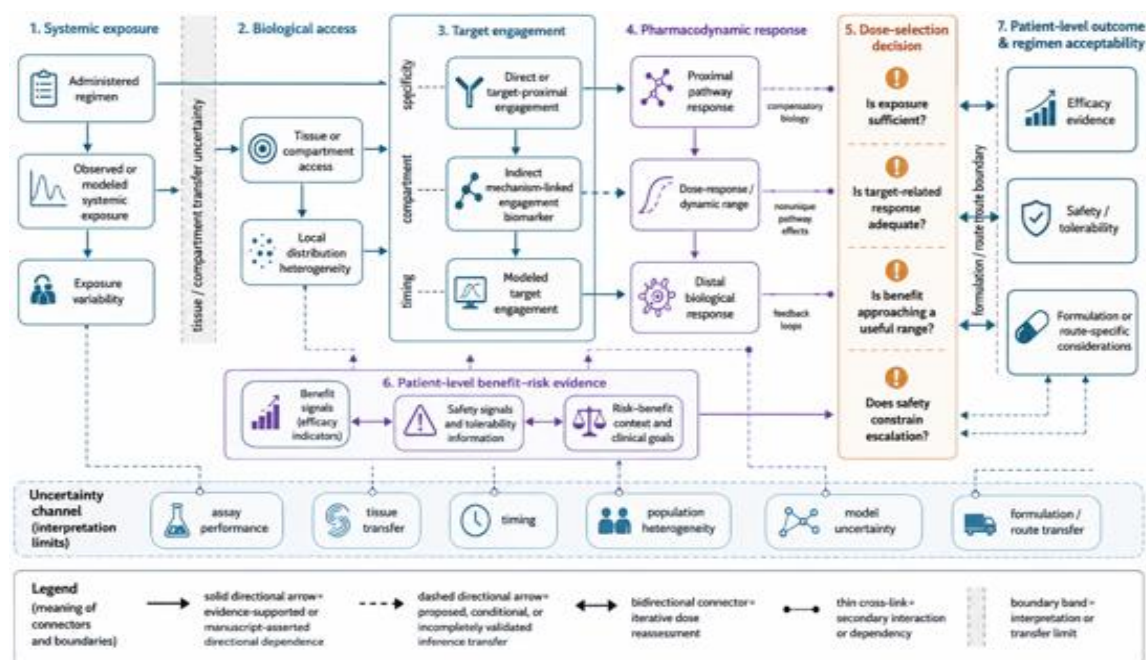


Figure 1. Dose information becomes decision-worthy only where exposure, engagement, pharmacodynamic response, and consequence converge

Predictive and prognostic roles

Calling a biomarker “predictive” should describe the decision it can inform, not simply the strength of its association with outcome. A prognostic biomarker provides information about likely outcome irrespective of a treatment contrast, whereas a predictive biomarker, in the treatment-selection sense, contains information about differential response between therapeutic options [21]. Confusing these roles can make an apparently strong biomarker clinically decorative: it identifies higher-risk patients without establishing which treatment should change that risk.

Treatment context is therefore indispensable. In KEYNOTE-042, tissue tumor mutational burden was evaluated within a randomized comparison of pembrolizumab and chemotherapy, allowing its relationship with outcome to be interpreted against a treatment contrast [20]. Even there, the result remains bounded by the trial population, assay, disease state, treatment alternatives, and exploratory nature of the biomarker analysis. A treatment-associated signal in one setting should not acquire a universal “predictive” label merely because the same molecular feature is measurable elsewhere.

Timing can also change the biomarker's role. Early circulating tumor DNA response in ALK-positive non-small-cell lung cancer was associated with progression-free survival during lorlatinib treatment [22]. That evidence addresses an on-treatment response state rather than the same decision addressed by a pretreatment selection biomarker. Similarly, early ctDNA kinetics during immunotherapy can carry outcome information without establishing a validated treatment-adaptation rule [7]. The molecule being measured may be unchanged, while its context of use changes from selection to monitoring.

This distinction becomes particularly important when clinically valid assays are moved into intervention strategies. ctDNA can identify molecular alterations or residual disease with substantial analytical and clinical relevance while evidence that treatment should be changed because of a specific result remains incomplete in some contexts [5]. The evidentiary question is therefore not “Is ctDNA useful?” but “Which ctDNA measurement, at which time, in which disease and treatment context, changes which decision with demonstrated benefit?”

Narrative terminology alone is poorly suited to separating these overlapping biomarker states. The comparison in **Table 2** therefore distinguishes what is observed from what may legitimately be inferred and identifies the additional evidence needed before a biomarker state can direct treatment.

Table 2. Distinguishing biomarker observations from treatment-selection claims when prognostic and predictive roles overlap

Manuscript-derived biomarker state	What is directly observed	What may reasonably be inferred	What would distinguish the competing in... Transfer boundary	Decision consequence if the stronger interpretation is supported
Scientific anchor	What is directly observed	What may reasonably be inferred	What would distinguish the competing in... Transfer boundary	Decision consequence if the stronger interpretation is supported
Baseline marker associated with outcome irrespective of therapy	Outcome differs across marker-defined groups	The marker may identify different underlying risk	What would distinguish the competing interpretation Demonstrate whether relative treatment effects differ across marker states Transfer boundary Population, disease stage, assay, endpoint	Risk estimation or trial stratification may be justified; treatment selection is not yet established
Baseline marker associated with different outcomes between treatment options	Marker status and treatment are jointly associated with outcome	A treatment-specific predictive role is plausible	What would distinguish the competing interpretation Replicate a biomarker-by-treatment interaction with prespecified analysis Transfer boundary Treatment alternatives, trial design, multiplicity, cutoff	Marker may influence treatment selection if benefit-risk and assay performance are adequate
Early on-treatment biomarker decline associated with later favorable outcome	Biomarker trajectory changes after treatment begins	The trajectory may report pharmacological or disease response	What would distinguish the competing interpretation Show whether acting on the early trajectory improves the subsequent decision Transfer boundary Timing, treatment mechanism, disease kinetics	Monitoring or adaptive treatment may become possible
Molecularly actionable alteration identified by an assay	A potentially targetable alteration is present	A matched therapy may be biologically rational	What would distinguish the competing interpretation Establish treatment availability, patient eligibility, and treatment-specific benefit Transfer boundary Access, resistance, co-alterations, competing therapies	Molecular profiling can alter therapy rather than merely describe disease
Minimal or residual disease signal associated with recurrence risk	Residual molecular signal predicts subsequent risk	The marker may identify patients who could benefit from escalation or earlier intervention	What would distinguish the competing interpretation Demonstrate that biomarker-triggered intervention improves outcomes relative to usual care Transfer boundary Assay sensitivity, shedding, disease type, intervention effectiveness	Treatment escalation, de-escalation, or surveillance could change
Biomarker-negative subgroup with apparently favorable outcome	Marker absence is associated with lower observed risk	Treatment may be unnecessary or less beneficial	What would distinguish the competing interpretation Test whether withholding treatment preserves outcomes while reducing harm Transfer boundary False-negative risk, follow-up duration, alternative mechanisms	De-escalation may become a defensible decision

Note: The distinctions and decision tests in this table are a proposed synthesis. They are intended to prevent prognostic, predictive, monitoring, and treatment-directing claims from being treated as interchangeable.

Decision thresholds and consequences of error

Even a well-characterized biomarker cannot change a decision until an action threshold is specified. The relevant threshold is not necessarily the analytical limit of detection, the population median, or the point that maximizes sensitivity and specificity. Stakeholder-informed decision analysis shows that positivity thresholds depend on the relative consequences of false-positive and false-negative classifications [29].

This matters because biomarker errors are rarely symmetric. A false-positive target-engagement signal may encourage continued development of an inadequately active regimen. A false-negative pharmacodynamic result may terminate an effective program. A false-positive predictive marker may expose a patient to ineffective treatment, whereas a false-negative result may exclude a patient who could benefit. Decision-curve methodology makes the same general point: model value depends on the benefit and harm attached to actions at a particular threshold, not only on discrimination [4].

Cutoff derivation becomes still more consequential when a biomarker defines trial eligibility. Regulatory Scientific Advice experience has repeatedly highlighted cutoff choice, multiplicity, and data-driven subgroup identification as methodological concerns [9]. Exploratory thresholds can generate hypotheses, but using the same data to discover a cutoff and then treating that cutoff as a confirmed treatment-selection rule risks converting sampling variation into an apparently mechanistic boundary.

A translational threshold should therefore be described by three linked properties: the measurement boundary, the action that follows crossing it, and the consequence of being wrong. Where those consequences are large, prospective confirmation should be correspondingly stronger. This Perspective does not propose a universal numerical loss function; the relative cost of errors depends on disease severity, treatment toxicity, reversibility of the decision, alternatives, clinical stage, and whether the biomarker is being used for development or direct patient care.

A biomarker decision-utility framework

We propose a biomarker decision-utility framework that begins with the decision rather than the measurement. The framework is deliberately relational: no biomarker is inherently “decision useful” outside a defined context. Emerging precision-dosing approaches based on drug-response phenotypes reinforce the potential value of connecting measurements to patient-specific actions while also highlighting requirements for reliable, representative, longitudinal data [30].

The first element is decision specification. The intended action must be stated before the biomarker evidence is interpreted. Examples include continuing a candidate dose, escalating exposure, selecting a patient subgroup, comparing products, adapting treatment, or terminating development. This follows the established context-of-use principle that biomarker evidence is evaluated against an intended purpose [1].

The second element is measurement fitness. Analytical performance must be adequate for the distinctions the decision requires. Reproducibility alone is insufficient if the assay cannot discriminate the biological states that alter action. Conversely, a highly sensitive assay can create more detected states without making those states clinically meaningful.

The third element is pharmacological relevance. A marker should be located explicitly relative to exposure, tissue access, target engagement, pharmacodynamic change, disease biology, and patient outcome. The more distal the marker is from the intended mechanism, the greater the number of alternative explanations that generally remain. Mechanistic proximity improves interpretability but does not abolish confounding or guarantee clinical consequence.

The fourth element is an action threshold. An association becomes actionable only when a marker state changes a named choice. Decision analysis provides a formal rationale for incorporating the consequences of alternative actions rather than relying solely on statistical accuracy [4]. The PRISM experience illustrates why this element cannot be reduced to molecular “actionability”: a potentially targetable finding must still pass through recommendation, feasibility, and treatment delivery before it changes care [6].

The fifth element is evidence convergence. Biomarker evidence should be interpreted alongside the other information necessary for the decision. Integrated first-in-human dose selection demonstrates that pharmacokinetics, pharmacodynamics, safety, and emerging efficacy can each constrain the selected regimen [23]. The framework therefore assigns biomarkers decision weight rather than decision sovereignty.

The sixth element is consequence and transferability. Before acting, investigators should ask what happens if the biomarker is wrong and whether evidence transfers across population, disease stage, assay, tissue, timing, treatment, formulation, or route. Threshold methodology shows why error costs are context specific [29]. A

biomarker may therefore remain useful even when not transferable: its valid scope simply needs to be stated rather than silently expanded.

Together, these elements create a proposed sequence of questions: What decision is being made? Is the measurement fit for that purpose? Which biological or pharmacological state does it actually represent? What action changes at the relevant marker state? What other evidence must converge before acting? What are the consequences of error, and where does the evidence stop transferring? The value of this sequence is not that every program must follow an identical regulatory path, but that each biomarker claim becomes falsifiable and decision specific.

Qualification strategy

Qualification should follow the intended decision rather than precede it as an abstract certification exercise. Digital health technology-derived endpoints illustrate this clearly: regulatory pathways depend on the particular endpoint, technology, validation evidence, and context of use [31]. The availability of a measurement technology does not itself make its output acceptable for every trial or development purpose.

Experience with EMA biomarker qualification similarly shows that assay validation, biomarker characterization, and context-of-use definition frequently determine whether an evidentiary package is mature enough for qualification [8]. Analytical validation is therefore necessary but not terminal. The question after “Can this be measured reliably?” remains “What does the result justify us doing?”

Evidence transfer should be treated explicitly. The neurofilament light-chain experience in amyotrophic lateral sclerosis illustrates qualification tied to a specified use rather than to the analyte in every conceivable neurological setting [10]. When the population, disease stage, specimen, platform, intervention, decision, or consequence changes materially, the evidentiary argument should be revisited. We propose this as a scientific transfer rule, not as a claim that every change legally requires a new formal qualification procedure.

Qualification intensity should also be proportional to decision risk. Model-informed development already emphasizes credibility relative to the intended application [3]. Biomarker qualification can use the same logic. An exploratory marker used to prioritize a mechanistic experiment does not require the same evidentiary burden as a marker that excludes patients from effective therapy or determines a pivotal dose. Where the consequences of incorrect classification are substantial, decision-analysis principles favor stronger validation of both the biomarker and the action it triggers [4].

The practical endpoint of qualification is therefore not a decorative label of validation. It is a defensible statement with boundaries: in this population, using this measurement method, at this time, under this treatment or development context, this biomarker result is sufficiently reliable and informative to support this specified decision. Evidence outside that statement may remain scientifically valuable, but it should not inherit the same decision authority automatically.

CONCLUSION

Biomarkers should be judged by the decisions they are capable of supporting, not by the visual persuasiveness of a correlation, the novelty of an assay, or mechanistic plausibility alone. Context of use determines what must be measured, target engagement identifies only one level of pharmacological evidence, pharmacodynamic response does not automatically establish patient benefit, and predictive interpretation requires treatment-specific evidence rather than prognosis alone.

The proposed decision-utility framework therefore separates decision specification, measurement fitness, pharmacological relevance, action thresholds, evidence convergence, consequences of error, and transferability. Its purpose is not to impose a universal qualification pathway. It is to prevent evidence from silently crossing boundaries it has not actually resolved.

A biomarker becomes translationally consequential when its result changes a named decision and when the evidence supporting that change is appropriate to the cost of being wrong. Until then, even an elegant and reproducible correlate should be described for what it is: informative evidence whose decision authority remains to be established.

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REFERENCES

1. Schuck RN, Sekar V. Use of biomarkers in drug development for regulatory purposes. *Clin Transl Sci.* 2025;18(10). doi:10.1111/cts.70377
2. Menetski JP, Hoffmann SC, Cush SS, Nayak Kamphaus T, Austin CP, Herrling PL, et al. The Foundation for the National Institutes of Health Biomarkers Consortium: Past accomplishments and new strategic direction. *Clin Pharmacol Ther.* 2019;105(4):829-43. doi:10.1002/cpt.1362
3. Marshall S, Ahamadi M, Chien J, Iwata D, Farkas P, Filipe A, et al. Model-informed drug development: Steps toward harmonized guidance. *Clin Pharmacol Ther.* 2023;114(5):954-9. doi:10.1002/cpt.3006
4. Van Calster B, Wynants L, Verbeek JFM, Verbakel JY, Christodoulou E, Vickers AJ, et al. Reporting and interpreting decision curve analysis: A guide for investigators. *Eur Urol.* 2018;74(6):796-804. doi:10.1016/j.eururo.2018.08.038
5. Pascual J, Attard G, Bidard FC, Curigliano G, De Mattos-Arruda L, Diehn M, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: A report from the ESMO Precision Medicine Working Group. *Ann Oncol.* 2022;33(8):750-68. doi:10.1016/j.annonc.2022.05.520
6. Bayle A, Belcaid L, Aldea M, Vasseur D, Peyraud F, Nicotra C, et al. Clinical utility of circulating tumor DNA sequencing with a large panel: A National Center for Precision Medicine (PRISM) study. *Ann Oncol.* 2023;34(4):389-96. doi:10.1016/j.annonc.2023.01.008
7. Sanz-Garcia E, Genta S, Chen X, Ou Q, Araujo DV, Abdul Razak AR, et al. Tumor-naïve circulating tumor DNA as an early response biomarker for patients treated with immunotherapy in early phase clinical trials. *JCO Precis Oncol.* 2023;7. doi:10.1200/PO.22.00509
8. Bakker E, Hendrikse NM, Ehmann F, van der Meer DS, Llinares Garcia J, Vetter T, et al. Biomarker qualification at the European Medicines Agency: A review of biomarker qualification procedures from 2008 to 2020. *Clin Pharmacol Ther.* 2022;112(1):69-80. doi:10.1002/cpt.2554
9. Huber C, Zinserling J, Benda N, Vetter T, Rueckbeil M. Methodological insights on biomarker-based patient selection: A review of Scientific Advice procedures at the European Medicines Agency. *Clin Pharmacol Ther.* 2025;117(5):1226-35. doi:10.1002/cpt.3558
10. Benatar M, Ostrow LW, Lewcock JW, Bennett F, Shefner J, Bowser R, et al. Biomarker qualification for neurofilament light chain in amyotrophic lateral sclerosis: Theory and practice. *Ann Neurol.* 2024;95(2):211-6. doi:10.1002/ana.26860
11. Bartelink IH, Jones EF, Shahidi-Latham SK, Lee PRE, Zheng Y, Vicini P, et al. Tumor drug penetration measurements could be the neglected piece of the personalized cancer treatment puzzle. *Clin Pharmacol Ther.* 2019;106(1):148-63. doi:10.1002/cpt.1211
12. Huynh C, Henrich A, Strasser DS, Boof ML, Al-Ibrahim M, Meyer Zu Schwabedissen HE, et al. A multipurpose first-in-human study with the novel CXCR7 antagonist ACT-1004-1239 using CXCL12 plasma concentrations as target engagement biomarker. *Clin Pharmacol Ther.* 2021;109(6):1648-59. doi:10.1002/cpt.2154
13. Sadiq MW, Yu H, Åstrand M, Scott IC, Williams A, Hewitt L, et al. Population pharmacokinetic/target engagement modelling of tozorakimab in healthy volunteers and patients with chronic obstructive pulmonary disease. *Br J Clin Pharmacol.* 2024;90(12):3286-95. doi:10.1111/bcp.16195
14. Pantel AR, Gitto SB, Makvandi M, Kim H, Medvedv S, Weeks JK, et al. [18F]FluorThanatrace PET imaging of PARP-inhibitor drug-target engagement as a biomarker of response in ovarian cancer, a pilot study. *Clin Cancer Res.* 2023;29(8):1515-27. doi:10.1158/1078-0432.CCR-22-1602
15. Mummery CJ, Börjesson-Hanson A, Blackburn DJ, Vijverberg EGB, De Deyn PP, Ducharme S, et al. Tau-targeting antisense oligonucleotide MAPTRx in mild Alzheimer's disease: A phase 1b, randomized, placebo-controlled trial. *Nat Med.* 2023;29(6):1437-47. doi:10.1038/s41591-023-02326-3
16. Li J, Florian J, Campbell E, Schrieber SJ, Bai JPF, Weaver JL, et al. Advancing biosimilar development using pharmacodynamic biomarkers in clinical pharmacology studies. *Clin Pharmacol Ther.* 2020;107(1):40-2. doi:10.1002/cpt.1653

17. Sheikhy M, Schrieber SJ, Sun Q, Gershuny V, Matta MK, Bai JPF, et al. Considerations for use of pharmacodynamic biomarkers to support biosimilar development—(I) A randomized trial with PCSK9 inhibitors. *Clin Pharmacol Ther.* 2023;113(1):71-9. doi:10.1002/cpt.2769
18. Florian J, Gershuny V, Sun Q, Schrieber SJ, Matta MK, Hazel A, et al. Considerations for use of pharmacodynamic biomarkers to support biosimilar development—(III) A randomized trial with interferon beta-1a products. *Clin Pharmacol Ther.* 2023;113(2):339-48. doi:10.1002/cpt.2784
19. Gershuny V, Sun Q, Schrieber SJ, Matta MK, Weaver JL, Ji P, et al. Considerations for use of pharmacodynamic biomarkers to support biosimilar development—(II) A randomized trial with IL-5 antagonists. *Clin Pharmacol Ther.* 2023;113(1):80-9. doi:10.1002/cpt.2760
20. Mok TSK, Lopes G, Cho BC, Kowalski DM, Kasahara K, Wu YL, et al. Associations of tissue tumor mutational burden and mutational status with clinical outcomes in KEYNOTE-042: Pembrolizumab versus chemotherapy for advanced PD-L1-positive NSCLC. *Ann Oncol.* 2023;34(4):377-88. doi:10.1016/j.annonc.2023.01.011
21. Sechidis K, Papangelou K, Metcalfe PD, Svensson D, Weatherall J, Brown G. Distinguishing prognostic and predictive biomarkers: An information theoretic approach. *Bioinformatics.* 2018;34(19):3365-76. doi:10.1093/bioinformatics/bty357
22. Soo RA, Martini JF, van der Wekken AJ, Teraoka S, Ferrara R, Shaw AT, et al. Early circulating tumor DNA dynamics and efficacy of lorlatinib in patients with treatment-naïve, advanced, ALK-positive NSCLC. *J Thorac Oncol.* 2023;18(11):1568-80. doi:10.1016/j.jtho.2023.05.021
23. Wilbaux M, Yang S, Jullion A, Demanse D, Graus Porta D, Myers A, et al. Integration of pharmacokinetics, pharmacodynamics, safety, and efficacy into model-informed dose selection in oncology first-in-human study: A case of roblitinib (FGF401). *Clin Pharmacol Ther.* 2022;112(6):1329-39. doi:10.1002/cpt.2752
24. Guo C, Liao KH, Li M, Wang IM, Shaik N, Yin D. PK/PD model-informed dose selection for oncology phase I expansion: Case study based on PF-06939999, a PRMT5 inhibitor. *CPT Pharmacometrics Syst Pharmacol.* 2023;12(11):1619-25. doi:10.1002/psp4.12882
25. Lu Y, Liang S, Hong Y, Tajima N, Patel K, Li H, et al. Application of the model-informed drug development paradigm to datopotamab deruxtecan dose selection for late-stage development. *CPT Pharmacometrics Syst Pharmacol.* 2024;13(1):23-8. doi:10.1002/psp4.13058
26. Samineni D, Venkatakrishnan K, Othman AA, Pithavala YK, Poondru S, Patel C, et al. Dose optimization in oncology drug development: An International Consortium for Innovation and Quality in Pharmaceutical Development white paper. *Clin Pharmacol Ther.* 2024;116(3):531-45. doi:10.1002/cpt.3298
27. Zhao Y, Sanghavi K, Roy A, Murthy B, Bello A, Aras U, et al. Model-based dose selection of subcutaneous nivolumab in patients with advanced solid tumors. *Clin Pharmacol Ther.* 2024;115(3):488-97. doi:10.1002/cpt.3148
28. Thakre N, Goebel A, Winzenborg I, Suleiman AA, D'Cunha R, Mensing S, et al. Population pharmacokinetic and exposure-response modeling to inform risankizumab dose selection in patients with ulcerative colitis. *Clin Pharmacol Ther.* 2024;116(3):847-57. doi:10.1002/cpt.3330
29. Sadatsafavi M, Khakban A, Mohammadi T, Gupta S, Bansback N, IMPACT Study Team. Stakeholder-informed positivity thresholds for disease markers and risk scores: A methodological framework and an application in obstructive lung disease. *J Clin Epidemiol.* 2024;175:111509. doi:10.1016/j.jclinepi.2024.111509
30. Oni-Orisan A, Srinivas N, Mehta K, Das JL, Nguyen TT, Tison GH, et al. Leveraging innovative technology to generate drug response phenotypes for the advancement of biomarker-driven precision dosing. *Clin Transl Sci.* 2021;14(3):784-90. doi:10.1111/cts.12973
31. Bakker JP, Izmailova ES, Clement A, Hoffmann S, Leptak C, Menetski JP, et al. Regulatory pathways for qualification and acceptance of digital health technology-derived clinical trial endpoints: Considerations for sponsors. *Clin Pharmacol Ther.* 2025;117(1):56-72. doi:10.1002/cpt.3398