

Paper Summary

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Title: Multi-Institutional Evaluation of Interrater Agreement of Biomarker-Drug Pair Rankings Based on the

Authors: Alexandra Lebedeva, Ekaterina Belova, Alexandra Kavun, Anastasiia Taraskina, Michele Bartol

DOI: <https://doi.org/10.1007/s40291-024-00748-4>

Year: 2025

Publication Type: Journal

Discipline/Domain: Precision Oncology / Molecular Diagnostics

Subdomain/Topic: ESCAT framework, biomarker-drug ranking, interrater agreement

Eligibility: Eligible

Overall Relevance Score: 90

Operationalization Score: 65

Contains Definition of Actionability: Yes (explicit via ESCAT definition)

Contains Systematic Features/Dimensions: Yes

Contains Explainability: Yes

Contains Interpretability: Partial

Contains Framework/Model: Yes (ESCAT)

Operationalization Present: Yes

Primary Methodology: Quantitative (statistical analysis of expert rankings)

Study Context: Multi-institutional assessment of agreement in ranking biomarker-drug pairs by ESCAT Le

Geographic/Institutional Context: Multi-national, including institutions in Russia, France, Italy, USA

Target Users/Stakeholders: Precision oncology experts, molecular tumor boards, guideline developers

Primary Contribution Type: Empirical evaluation of framework reproducibility

CL: Yes — clarity is implied as necessary for agreement on LOE rankings

CR: Yes — contextual relevance to tumor type and biomarker-drug association explicitly tied to actionabi

FE: Yes — feasibility indirectly addressed via standard of care vs. experimental therapy distinction

TI: Partial — timeliness not central but implied in need for up-to-date literature

EX: Yes — explainability tied to evidence-based LOE assignment

GA: Yes — goal alignment with improving clinical decision-making for targeted therapy

Reason if Not Eligible: N/A

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****Title.****

Multi-Institutional Evaluation of Interrater Agreement of Biomarker-Drug Pair Rankings Based on the ESMO

****Authors:****

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****DOI:****

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****Year:**** 2025

****Publication Type:****

Journal

****Discipline/Domain:****

Precision Oncology / Molecular Diagnostics

****Subdomain/Topic:****

ESCAT framework, biomarker-drug ranking, interrater agreement

****Contextual Background:****

The study examines whether the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) pro

****Geographic/Institutional Context:****

Multi-national collaboration (Russia, France, Italy, USA).

****Target Users/Stakeholders:****

Precision oncology experts, molecular tumor boards, guideline developers.

****Primary Methodology:****

Quantitative statistical agreement analysis (Cohen's kappa, Kolmogorov–Smirnov test, regression analys

****Primary Contribution Type:****

Empirical evaluation of framework reproducibility.

General Summary of the Paper

This study evaluates how consistently precision oncology experts assign ESCAT Levels of Evidence to b

Eligibility

Eligible for inclusion: ****Yes****

How Actionability is Understood

The paper adopts ESCAT's definition: actionability reflects the ****clinical significance of a biomarker-drug**

> “The ESMO Scale of Clinical Actionability of molecular Targets (ESCAT) classification system... classif

> “Framework... designed to provide guidance on how the genomic findings should be used in clinical practice.”

What Makes Something Actionable

- Strong published clinical evidence supporting efficacy of the biomarker-drug pairing.
- Contextual relevance to tumor type.
- Evidence from well-designed clinical trials.
- Alignment with existing guidelines and standard-of-care definitions.
- Consideration of genomic context (multiple biomarkers, resistance mechanisms).

How Actionability is Achieved / Operationalized

- **Framework/Approach Name(s):** ESCAT
- **Methods/Levers:** Literature review, expert evaluation, LOE classification (IA–X).
- **Operational Steps / Workflow:**
 1. Select biomarker-drug pairs (both common and rare).
 2. Provide tumor type, mutation origin, detection method to experts.
 3. Experts assign LOE following ESCAT criteria.
 4. Aggregate responses, determine consensus LOE, calculate agreement statistics.
- **Data & Measures:** Consensus LOE, Cohen’s kappa, standard deviation from consensus, regression analysis.
- **Implementation Context:** Multi-institutional expert setting.

> “The median of LOE rankings... was considered the consensus LOE” (p. 93).

> “General agreement rate... estimated using two methods: Cohen’s kappa and the Kolmogorov–Smirnov test.”

Dimensions and Attributes of Actionability (Authors’ Perspective)

- **CL (Clarity):** Yes — essential for agreement on LOE.
- **CR (Contextual Relevance):** Yes — tumor-specific and biomarker-specific context required.
- **FE (Feasibility):** Yes — addressed through distinction between standard-of-care and experimental therapies.
- **TI (Timeliness):** Partial — literature currency implied but not central.
- **EX (Explainability):** Yes — LOE assignments tied to strength of evidence.
- **GA (Goal Alignment):** Yes — aimed at improving targeted therapy selection.
- **Other Dimensions:** Reproducibility, evidence strength, framework consistency.

Theoretical or Conceptual Foundations

- ESCAT framework (Mateo et al., 2018).
- Comparative mention of OncoKB and variant interpretation guidelines.

Indicators or Metrics for Actionability

- ESCAT Level of Evidence (IA–X).
- Consensus vs. individual LOE deviation.
- Agreement statistics (Cohen’s kappa).

Barriers and Enablers to Actionability

- **Barriers:** Subjectivity in LOE assignment; lack of negative trial data consideration; uncertainty in classification
- **Enablers:** Standard-of-care status; clear guideline backing; multidisciplinary tumor board discussions

Relation to Existing Literature

Positions ESCAT as the most comprehensive existing framework but notes parallels with variant interpretation

Summary

This multi-institutional study critically examines the reproducibility of ESCAT-based biomarker-drug ranking

Scores

- **Overall Relevance Score:** 90 — Explicit definition of actionability, systematic dimensions, and critical appraisal
- **Operationalization Score:** 65 — Clear methodology for LOE assignment and consensus-building, but

Supporting Quotes from the Paper

- “[ESCAT] classify molecular aberrations based on the available evidence... and matching the clinical benefit
- “The most important drawback... is the potential subjectivity of the assigned LOE depending on the person
- “The median of LOE rankings... was considered the consensus LOE” (p. 93).
- “Our results outline the concerning rate of discordances when using the ESCAT framework” (p. 99).

Actionability References to Other Papers

- Mateo et al., 2018 — ESCAT framework origin.
- OncoKB (Chakravarty et al., 2017).
- AMP/ASCO/CAP guidelines (Sirohi et al., 2020).

- ACMG-AMP guidelines (Amendola et al., 2020; Lyon et al., 2022).