Paper Summary

<!--META_START-->

Title: Next-generation sequencing, should I use anti-HER2 therapy for HER2-amplified tumors off-label? I

Authors: Doah Cho, Sarah J. Lord, John Simes, Wendy Cooper, Michael Friedlander, Susie Bae, Chee K

DOI: 10.1177/17588359221112822

Year: 2022

Publication Type: Journal

Discipline/Domain: Oncology / Precision Medicine

Subdomain/Topic: HER2-targeted therapy; Off-label treatment decision frameworks

Eligibility: Eligible

Overall Relevance Score: 95

Operationalization Score: 90

Contains Definition of Actionability: Yes (implicit and explicit in biomarker–treatment context)

Contains Systematic Features/Dimensions: Yes

Contains Explainability: Yes

Contains Interpretability: Yes (biological rationale, biomarker testing validity)

Contains Framework/Model: Yes (seven-question extrapolation framework)

Operationalization Present: Yes (detailed framework and application example)

Primary Methodology: Conceptual / Framework development with illustrative application

Study Context: Clinical decision-making for off-label HER2-targeted therapy in HER2-amplified cancers w

Geographic/Institutional Context: Australia; University of Sydney and collaborating institutions

Target Users/Stakeholders: Oncologists, molecular tumor boards, clinical researchers, policymakers

Primary Contribution Type: Conceptual framework + practical guidance for extrapolation in precision onco

CL: Yes — clarity in biomarker definition and testing necessary for actionability

CR: Yes — explicitly ties contextual relevance to extrapolation appropriateness

FE: Yes — feasibility linked to cost/access and biomarker testing capability

TI: Partial — timeliness implied in using current testing and treatment options before disease progression

EX: Yes — explainability through step-wise rationale and biological plausibility

GA: Yes — alignment with clinical goals of improved patient outcomes and informed consent

Reason if Not Eligible: N/A

<!--META_END-->

Title:

Next-generation sequencing, should I use anti-HER2 therapy for HER2-amplified tumors off-label? Illustra

Authors:

Doah Cho, Sarah J. Lord, John Simes, Wendy Cooper, Michael Friedlander, Susie Bae, Chee Khoon Lee

DOI:

10.1177/17588359221112822

Year:

2022

Publication Type:

Journal

Discipline/Domain:

Oncology / Precision Medicine

Subdomain/Topic:

HER2-targeted therapy; Off-label treatment decision frameworks

Contextual Background:

This paper addresses the growing clinical challenge of whether targeted cancer therapies—proven in spe

Geographic/Institutional Context:

Australia; National Health and Medical Research Council Clinical Trials Centre, University of Sydney; coll

Target Users/Stakeholders:

Oncologists, molecular tumor boards, precision oncology decision-makers, clinical researchers, and polic

Primary Methodology:

Conceptual framework development with illustrative clinical application.

Primary Contribution Type:

Decision-making framework for extrapolating biomarker–treatment evidence to off-label contexts.

General Summary of the Paper

The paper presents a structured framework for deciding whether to use targeted therapies off-label when

---

Eligibility

Eligible for inclusion: **Yes**

How Actionability is Understood

Actionability is defined as the co-dependency between a biomarker and a targeted treatment—where sele

> “A biomarker is ‘actionable’ if treatment selection based on biomarker status improves clinical outcomes

> “Actionability may differ between cancers due to differences in intratumoral heterogeneity, tumor microe

---

What Makes Something Actionable

- Reliable and validated biomarker testing (analytical validity)
- Clearly defined biomarker positivity criteria for the cancer type
- Strong evidence from clinical trials or high-quality non-randomized studies linking biomarker presence to
- Biological plausibility and consistency across tumor types
- Distinction between prognostic and predictive value
- Consideration of surrogate endpoint validity
- Comparable safety profile in new cancer context

How Actionability is Achieved / Operationalized

- **Framework/Approach Name(s):** Seven-question extrapolation framework
- **Methods/Levers:** Analytical validity check, biomarker criteria validation, evidence tiering (ESCAT), na
- **Operational Steps / Workflow:** Sequential question-based evaluation; uncertainty scoring for each do
- **Data & Measures:** Concordance metrics (NGS vs. evidentiary standard tests), prevalence data, prec
- **Implementation Context:** Applied by clinicians and molecular tumor boards when trial data are lackin

> “Questions 1 to 6 should be considered individually, and judgment for the level of uncertainty for extrap

> “Recommendations should be individualized and consider the estimated benefit versus risks of off-labe

---

Dimensions and Attributes of Actionability (Authors’ Perspective)

- **CL (Clarity):** Yes — need for transparent, validated biomarker definition.
- **CR (Contextual Relevance):** Yes — extrapolation must consider tumor-specific biology.
- **FE (Feasibility):** Yes — feasibility tied to cost, access, and testing capabilities.
- **TI (Timeliness):** Partial — urgency implied to decide before disease progression.
- **EX (Explainability):** Yes — framework explicitly explains rationale for decisions.
- **GA (Goal Alignment):** Yes — focused on aligning treatment with patient outcome goals.
- **Other Dimensions Named by Authors:** Safety similarity, surrogate endpoint validity, cost and equity i

---

Theoretical or Conceptual Foundations

- ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

- GRADE Evidence-to-Decision (EtD) frameworks
- PICO model for framing clinical questions

Indicators or Metrics for Actionability

- Concordance rates between NGS and standard HER2 testing
- Sensitivity, specificity, PPV, and NPV of biomarker assays
- Survival and response outcomes from RCTs or high-quality observational studies
- Surrogate endpoint validation status in the cancer type of interest

---

Barriers and Enablers to Actionability

- **Barriers:** Biological heterogeneity; lack of validated criteria in new tumor type; unvalidated surrogate
- **Enablers:** Strong biomarker–treatment evidence in analogous cancers; validated testing; patient willi

---

Relation to Existing Literature

Positions the framework within ongoing discussions about precision oncology actionability, building on ES

Summary

This paper develops and illustrates a structured seven-question framework to guide off-label targeted the

---

Scores

- **Overall Relevance Score:** 95 — Strong explicit/implicit definition of actionability, comprehensive feat
- **Operationalization Score:** 90 — Detailed and actionable framework with clear application steps, thou

---

Supporting Quotes from the Paper

- “A biomarker is ‘actionable’ if treatment selection based on biomarker status improves clinical outcomes
- “Have the criteria used to define HER2 positivity been assessed in the cancer type for off-label trastuzu
- “Questions 1 to 6 should be considered individually, and judgment for the level of uncertainty for extrapo
- “Off-label therapy may be justified if sufficient evidence exists to support a positive benefit-risk assessm

---

Actionability References to Other Papers

- ESCAT (Mateo et al., 2018)
- Wolff et al., 2018 HER2 testing guidelines

- Multiple RCTs: Slamon et al., 2001; Bang et al., 2010; Fader et al., 2020
- Haslam et al., 2019 surrogate endpoint correlation study