

Paper Summary

<!--META_START-->

Title: Implementing evidence-based assertions of clinical actionability in the context of secondary findings

Authors: Christine M. Pak, Marian J. Gilmore, Joanna E. Bulkley, Pranesh Chakraborty, Orit Dagan-Rose

DOI: <https://doi.org/10.1016/j.gim.2024.101164>

Year: 2024

Publication Type: Journal

Discipline/Domain: Genomic Medicine / Clinical Genetics

Subdomain/Topic: Clinical actionability, secondary genomic findings, evidence-based frameworks

Eligibility: Eligible

Overall Relevance Score: 98

Operationalization Score: 95

Contains Definition of Actionability: Yes

Contains Systematic Features/Dimensions: Yes

Contains Explainability: Yes

Contains Interpretability: Yes

Contains Framework/Model: Yes

Operationalization Present: Yes

Primary Methodology: Conceptual with pragmatic evaluation

Study Context: Development and implementation of an assertion rubric for clinical actionability in second

Geographic/Institutional Context: Primarily U.S.-based with contributions from Canada

Target Users/Stakeholders: Clinical laboratories, geneticists, policy makers, genomic medicine implemen

Primary Contribution Type: Framework/methodology for actionability assessment and assertion

CL: Yes

CR: Yes

FE: Yes

TI: Partial

EX: Yes

GA: Yes

Reason if Not Eligible: N/A

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****Year:**** 2024

****Publication Type:**** Journal

****Discipline/Domain:**** Genomic Medicine / Clinical Genetics

****Subdomain/Topic:**** Clinical actionability, secondary genomic findings, evidence-based frameworks

****Contextual Background:**** The paper addresses the gap in standardized, evidence-based assessment of

****Geographic/Institutional Context:**** Primarily U.S.-based research institutions and clinical genetics organiza

****Target Users/Stakeholders:**** Clinical laboratories, geneticists, health policy makers, genomic medicine

****Primary Methodology:**** Conceptual framework development with iterative refinement and pragmatic ev

****Primary Contribution Type:**** Framework/methodology for actionability assessment and assertion.

General Summary of the Paper

This article presents the ClinGen AWG's development of an evidence-based "assertion rubric" to generat

Eligibility

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

How Actionability is Understood

The authors define clinical actionability as the potential for an intervention, informed by genetic findings, t

> "Clinical actionability in this context includes interventions that could be implemented to mitigate or prev

> "The assertion process allows the AWG to capture... effectiveness of medical interventions... penetranc

What Makes Something Actionable

- Severity of health outcome
- Likelihood (penetrance) of outcome
- Effectiveness of intervention in preventing/mitigating outcome
- Nature/burden of intervention
- Strength and quality of supporting evidence
- Contextual adoption in clinical practice
- Ethical or feasibility constraints on gathering more evidence

How Actionability is Achieved / Operationalized

- **Framework/Approach Name(s):** ClinGen Actionability Assertion Rubric
 - **Methods/Levers:** 4-domain SQM scoring → preliminary assertion → expert discussion → consensus
 - **Operational Steps / Workflow:**
 1. Score outcome–intervention pairs in four domains (0–3 each).
 2. Identify highest-scoring O/I pair for each gene–condition pair.
 3. Generate preliminary assertion using score thresholds.
 4. Discuss in AWG meetings; consider additional predefined factors.
 5. Document rationale for final assertion.
 - **Data & Measures:** Evidence from systematic reviews, meta-analyses, clinical guidelines; penetrance
 - **Implementation Context:** Applied to both adult and pediatric gene–condition pairs across 350+ cases
- > “The total score is the sum of the four domain scores... used to generate the preliminary assertion of a
- > “The assertion level can be changed based on... poor-quality evidence... interventions widely used... c
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Dimensions and Attributes of Actionability (Authors’ Perspective)

- **CL (Clarity):** Yes — Clear, structured scoring and definition of levels.
 - **CR (Contextual Relevance):** Yes — Context-specific scoring (adult/pediatric frameworks).
 - **FE (Feasibility):** Yes — Consideration of real-world clinical adoption and feasibility of interventions.
 - **TI (Timeliness):** Partial — Timeliness implied via secondary finding reporting priorities.
 - **EX (Explainability):** Yes — Rationale documented for each assertion.
 - **GA (Goal Alignment):** Yes — Focus on preventing/mitigating health outcomes aligned with patient health
 - **Other Dimensions Named by Authors:** Burden of intervention, ethical considerations for evidence co
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Theoretical or Conceptual Foundations

- Builds on ACMG recommendations for secondary finding reporting.
 - Extends the existing ClinGen semi-quantitative metric framework.
 - Incorporates evidence hierarchies (systematic review, meta-analysis, guidelines).
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Indicators or Metrics for Actionability

- Total domain score (0–12) for highest-scoring O/I pair
- Effectiveness score thresholds
- Tier 1 evidence for “definitive” designation

Barriers and Enablers to Actionability

- **Barriers:** Limited/poor-quality evidence; rare/pediatric conditions with limited trial feasibility.
- **Enablers:** Established clinical use; strong guidelines; high-penetrance variants.

Relation to Existing Literature

Positions the rubric as a standardization advance over prior ad hoc practices in secondary finding reporting

Summary

The paper describes the creation and implementation of the ClinGen Actionability Assertion Rubric, a sta

Scores

- **Overall Relevance Score:** 98 — Offers explicit definition, detailed dimensions, and a fully developed
- **Operationalization Score:** 95 — Provides clear step-by-step process, criteria, and integration into pra

Supporting Quotes from the Paper

- “Clinical actionability in this context includes interventions that could be implemented to mitigate or prev
- “The total score is the sum of the four domain scores... used to generate the preliminary assertion of ac
- “The assertion level can be changed based on... interventions widely used... high-quality evidence not
- “The assertion process allows the AWG to capture... effectiveness of medical interventions... penetranc

Actionability References to Other Papers

- ACMG SF v2.0, v3.0, v3.1 policy statements
- Hunter et al. (2016, 2018, 2022) on clinical actionability assessment protocols
- Saelaert et al. (2019) on professional perspectives in reporting secondary findings