Paper Summary

<!--META_START-->

Title: A semiquantitative metric for evaluating clinical actionability of incidental or secondary findings from

Authors: Jonathan S. Berg, Ann Katherine M. Foreman, Julianne M. O'Daniel, Jessica K. Booker, Lacey I

DOI: 10.1038/gim.2015.104

Year: 2016

Publication Type: Journal Article

Discipline/Domain: Genomic Medicine / Medical Genetics

Subdomain/Topic: Clinical Actionability Assessment in Genomic Sequencing

Eligibility: Eligible

Overall Relevance Score: 95

Operationalization Score: 100

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 Framework Development and Application

Study Context: Evaluation of incidental/secondary findings in clinical genome-scale sequencing

Geographic/Institutional Context: University of North Carolina at Chapel Hill, USA

Target Users/Stakeholders: Clinical geneticists, genomic testing laboratories, healthcare providers, policy

Primary Contribution Type: Framework/method for assessing clinical actionability of gene–disease pairs

CL: Yes

CR: Yes

FE: Yes

TI: Partial

EX: Yes

GA: Partial

Reason if Not Eligible: N/A

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A semiquantitative metric for evaluating clinical actionability of incidental or secondary findings from geno

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Publication Type:

Journal Article

Discipline/Domain:

Genomic Medicine / Medical Genetics

Subdomain/Topic:

Clinical Actionability Assessment in Genomic Sequencing

Contextual Background:

The paper addresses the challenge of systematically evaluating the clinical actionability of genomic varia

Geographic/Institutional Context:

University of North Carolina at Chapel Hill, USA

Target Users/Stakeholders:

Clinical geneticists, genetic counselors, genomic laboratories, healthcare providers, professional organiza

Primary Methodology:

Conceptual framework and scoring metric development, applied analysis of multiple gene lists

Primary Contribution Type:

Development and validation of a semiquantitative scoring framework for clinical actionability

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General Summary of the Paper

This paper presents a semiquantitative metric for evaluating the clinical actionability of incidental or secon

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Eligibility

Eligible for inclusion: **Yes**

How Actionability is Understood

Actionability is conceptualized as a **continuum** rather than a binary state, integrating the potential seve

> “The LVBC developed a semiquantitative metric for determining the clinical actionability of gene–diseas

> “The subcategories… approximate the clinical utility of revealing incidental/secondary findings in a pres

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What Makes Something Actionable

- High severity of the potential health outcome
- Moderate to high likelihood of disease manifestation
- Availability of effective preventive or therapeutic interventions
- Low burden or acceptable risk of intervention
- Substantial and reliable knowledge base supporting decision-making

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How Actionability is Achieved / Operationalized

- **Framework/Approach Name(s):** Semiquantitative Metric for Clinical Actionability
- **Methods/Levers:** Five criteria scored 0–3 (severity, likelihood, efficacy, burden, knowledge base)
- **Operational Steps / Workflow:** Evidence review → Assign scores for each criterion → Consensus sc
- **Data & Measures:** Literature from OMIM, GeneReviews, PubMed, clinical guidelines
- **Implementation Context:** NCGENES project and ACMG incidental findings recommendations

> “All five criteria are scored on a scale of 0–3… The outcome and intervention are defined in advance…

> “The LVBC chose to consider genes with a score ≥11… as meeting the threshold of actionability.” (p. 4

Dimensions and Attributes of Actionability (Authors’ Perspective)

- **CL (Clarity):** Yes — Clarity through structured scoring definitions (Table 1)
- **CR (Contextual Relevance):** Yes — Explicit to presymptomatic, incidental/secondary findings contex
- **FE (Feasibility):** Yes — Evaluated through “burden of intervention” score
- **TI (Timeliness):** Partial — Implied in presymptomatic intervention consideration
- **EX (Explainability):** Yes — Transparent, evidence-based scoring with defined criteria
- **GA (Goal Alignment):** Partial — Implicit alignment with clinical utility and patient benefit
- **Other Dimensions Named by Authors:** Knowledge base strength

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Theoretical or Conceptual Foundations

- Clinical utility concepts from genomic medicine
- Evidence-based assessment models
- Prior ACMG deliberative consensus recommendations

Indicators or Metrics for Actionability

- Total score (0–15)

- Threshold ≥11 for high actionability

- Subscores for severity, likelihood, efficacy, burden, and knowledge base

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Barriers and Enablers to Actionability

- **Barriers:** Limited evidence base; subjective burden assessment; rare diseases with insufficient pene

- **Enablers:** Structured metric; multidisciplinary consensus; adaptability to different contexts

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Relation to Existing Literature

The paper builds on and critiques earlier expert consensus models like the ACMG recommendations, add

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Summary

This paper delivers a rigorous, transparent framework for assessing the clinical actionability of incidental

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Scores

- **Overall Relevance Score:** 95 — Clear conceptualization of actionability as multidimensional, detailed

- **Operationalization Score:** 100 — Fully developed metric with applied examples and scoring workflow

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Supporting Quotes from the Paper

- “Actionability is a continuum, not a binary state.” (p. 468)

- “The LVBC established five core characteristics of clinical actionability…” (p. 469)

- “The LVBC chose to consider genes with a score ≥11… as meeting the threshold of actionability.” (p. 47

Actionability References to Other Papers

- ACMG Recommendations for Reporting of Incidental Findings (Green et al., 2013)

- Evidence-based Genomic Applications in Practice and Prevention Working Group (Goddard et al., 2013

- NCGENES project preliminary outputs (Berg et al., 2013)