Paper Summary

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Title: An Age-Based Framework for Evaluating Genome-Scale Sequencing Results in Newborn Screenin

Authors: Laura V. Milko, Julianne M. O'Daniel, Daniela M. DeCristo, Stephanie B. Crowley, Ann Katherin

DOI: https://doi.org/10.1016/j.jpeds.2018.12.027

Year: 2019

Publication Type: Journal Article

Discipline/Domain: Medical Genetics, Pediatrics, Genomic Medicine

Subdomain/Topic: Newborn Screening, Clinical Actionability, Next-Generation Sequencing (NGS)

Eligibility: Eligible

Overall Relevance Score: 95

Operationalization Score: 90

Contains Definition of Actionability: Yes (explicit and implicit)

Contains Systematic Features/Dimensions: Yes

Contains Explainability: Yes

Contains Interpretability: Partial

Contains Framework/Model: Yes (ASQM – Age-based Semiquantitative Metric)

Operationalization Present: Yes

Primary Methodology: Conceptual + Comparative Validation Study

Study Context: Evaluation of gene–disease pairs for genomic newborn screening using a standardized ac

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

Target Users/Stakeholders: Policy-makers, clinicians, genetic counselors, parents, newborn screening pr

Primary Contribution Type: Conceptual framework with validation against existing panels

CL: Yes

CR: Yes

FE: Yes

TI: Partial

EX: Yes

GA: Partial

Reason if Not Eligible: N/A

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Contextual Background:

The study is grounded in the public health context of newborn screening (NBS) in the United States, spec

General Summary of the Paper

This paper introduces and validates the Age-based Semiquantitative Metric (ASQM), a framework for ass

Eligibility

Eligible for inclusion: **Yes**

The paper explicitly defines clinical actionability, operationalizes it through a standardized scoring system

How Actionability is Understood

The authors define actionability through five explicit criteria: severity, likelihood (penetrance), efficacy of i

> “Each gene–disease pair was scored (0–3 points) on 5 criteria: severity… likelihood… efficacy… accep

> “Gene–disease pairs were placed into… pediatric conditions with high actionability… pediatric condition

What Makes Something Actionable

- High severity of potential outcome
- High likelihood of disease manifestation
- Highly effective interventions available
- Interventions are acceptable in terms of burden and risk
- Strong knowledge base and clinical consensus on gene–disease relationship

How Actionability is Achieved / Operationalized

- **Framework/Approach Name:** Age-based Semiquantitative Metric (ASQM)
- **Methods/Levers:** Structured scoring (0–3) for five actionability criteria; consensus review by multidis
- **Operational Steps / Workflow:** Literature curation → preliminary scoring → consensus meetings → c
- **Data & Measures:** Severity, penetrance, intervention efficacy, intervention acceptability, knowledge b
- **Implementation Context:** Newborn genomic screening; policy and parental decision-making

> “The ASQM allows a priori categorization… to facilitate decision-making about incorporating genomic s

> “Gene–disease pairs… placed into 1 of 4 categories…” (p. 69)

Dimensions and Attributes of Actionability (Authors’ Perspective)

- **CL (Clarity):** Yes – explicit scoring rubric with defined terms (p. 70)
- **CR (Contextual Relevance):** Yes – pediatric onset and intervention timing central to classification (p.
- **FE (Feasibility):** Yes – considers intervention efficacy and acceptability (p. 70)
- **TI (Timeliness):** Partial – age-of-onset and age-at-intervention incorporated (p. 69)
- **EX (Explainability):** Yes – transparent scoring and rationale for classification (p. 70, Fig. 1B)
- **GA (Goal Alignment):** Partial – implicit in alignment with NBS goals
- **Other Dimensions Named by Authors:** Knowledge base strength; ethical principle of preserving futur

Theoretical or Conceptual Foundations

- Builds on prior Semiquantitative Metric (Berg et al., 2016)
- Aligns with public health screening principles (Wilson and Jungner, updated for genomics)
- Compares to RUSP and BabySeq frameworks

Indicators or Metrics for Actionability

- Total ASQM score (0–15) across five criteria
- Cut-offs for automatic category assignment (≥12 for high actionability, <9 for low)

Barriers and Enablers to Actionability

- **Barriers:** Lack of effective interventions, insufficient knowledge base, controversial evidence
- **Enablers:** Strong clinical evidence, existing practice guidelines, early intervention potential

Relation to Existing Literature

Positions ASQM as a more integrated and age-aware framework compared to BabySeq's validity/onset/p

Summary

Milko et al. (2019) present the ASQM, an evidence-based, age-sensitive framework for scoring and class

Scores

- **Overall Relevance Score:** 95 – Provides explicit, multidimensional definition of actionability, systema
- **Operationalization Score:** 90 – Offers fully articulated scoring system, workflow, and validation, thou

Supporting Quotes from the Paper

- "[Each gene–disease pair was scored… on 5 criteria: severity… likelihood… efficacy… acceptability… k
- "[Gene–disease pairs were placed into… 4 categories… based on final ASQM score, age of onset/actio
- "[Lack of effective intervention and/or insufficient knowledge… common reasons… not meet criteria for
- "[Validated our framework against the… RUSP… high ASQM scores assigned to most RUSP conditions

Actionability References to Other Papers

- Berg et al., 2016 – Semiquantitative Metric for Evaluating Clinical Actionability
- Wilson & Jungner screening criteria updates (Andermann et al., 2008)
- Ceyhan-Birsoy et al., 2017 – BabySeq curated gene list
- RUSP methodology references (Kemper et al., 2014)