
Robin Z. Hayeems1, David P. Dimmock2, David P. Bick3, John W. Belmont4, Robert C. Green5, Brendan Lanpher6, Vaidhevi Jobanputra7, Roberto Mendoza1, Shashikant Kulkarni8, Megan E. Grove9, Stacie L. Taylor4, and Euan Ashley9 on behalf of the Medical Genome Initiative.

1The Centre for Genetic Medicine, The Hospital for Sick Children, Toronto, ON, Canada. 2Rady Children’s Institute for Genomic Medicine, San Diego, CA, USA. 3HudsonAlpha Institute for Biotechnology, Huntsville, Alabama, USA. 4llumina Inc., San Diego, CA, USA. 5Brigham and Women’s Hospital, Broad Institute and Harvard Medical School, Boston, MA, USA. 6Mayo Clinic, Rochester, MN, USA. 7New York Genome Center, New York, New York, USA. 8Baylor Genetics and Baylor College of Medicine, Houston, TX, USA. 9Stanford Medicine, Stanford, CA, USA

*Presenting author

BACKGROUND

- Whole genome sequencing (WGS) is emerging as the most robust strategy for achieving timely diagnoses in undiagnosed rare disease populations
- Evidence of clinical utility and cost-effectiveness is required for WGS to be accepted into practice, commissioned in a health system, or receive reimbursement
- Defining and measuring clinical utility is complex and context specific
- Purpose: Develop a standardized framework and define measurement best practices to optimize the evidence base for decision makers and health care systems invested in providing high quality genome diagnostics

METHODS

Diagnostic Application to Rare Disease

Table 1: Application of the Fryback and Thornbury Model of Efficacy1 to Genome Sequencing

<table>
<thead>
<tr>
<th>Domain</th>
<th>Key Questions</th>
<th>Measurement construct</th>
<th>Indicator</th>
<th>Data Source/Strategy</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>1. Technical efficacy</td>
<td>In the laboratory, does the test measure what it purports to measure?</td>
<td>Analytic validity</td>
<td>Sensitivity (recall), specificity, precision (technical positive predictive value) when 'gold standard' reference available</td>
<td>Laboratory reports, Marshall et al (submitted)</td>
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<td>2. Diagnostic accuracy efficacy</td>
<td>Does the test result distinguish patients with and without the target disorder?</td>
<td>Clinical Validity</td>
<td>Gene-phenotype matching</td>
<td>Laboratory reports, Rabinovitch et al</td>
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<td>3. Diagnostic thinking efficacy</td>
<td>Does the test help a clinician to come to a diagnosis or discover a previously unrecognized phenotype or risk factor?</td>
<td>Understanding disease etiology and prognosis</td>
<td>Diagnostic classification [complete, partial, possible, dual diagnosis]; prognostic clarity</td>
<td>Case report forms, medical records, clinician interviews, C-GUIDE, Lione6, Posey8, French4, Chandle3, Scocciali21, Dragojlovic20, Kugnapora17, Hayeems9</td>
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<td>4. Therapeutic efficacy</td>
<td>Does the test aid in planning treatment? Does the test change or alter planned treatment? Initiation/alteration/cessation of therapy when triggered by test result</td>
<td>Medical management</td>
<td>Initiation or alteration of diagnostic investigations; Initiation of referral to sub-specialist care</td>
<td>Case report forms, medical records, clinician interviews, C-GUIDE, Petitti21, Park19, Hayeems9</td>
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<td>5. Patient outcome efficacy</td>
<td>Do patients who have the test fare better than similar patients who do not?</td>
<td>Health outcomes</td>
<td>Phenotype-specific clinical outcomes, morbidity, mortality, QALY, DALY</td>
<td>Case report forms, medical records, patient reported, WHO-ICF, Penny9, Famosi15, Robinson13, Kugnapora17, Grant13</td>
<td></td>
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<tr>
<td>6. Societal efficacy</td>
<td>Does the test demonstrate value for money and societal acceptability?</td>
<td>Value for money</td>
<td>Direct and indirect costs, endpoints described in levels 3-5</td>
<td>Case report forms, medical records, administrative data, patient/parent surveys, patient/public engagement, Marcus19, Kulchik-Rahm17, Anderson16, Stark11, Schwartz10</td>
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</table>

Figure 1: Clinical Utility Chain of Evidence Applied to Case Examples

RECOMMENDATIONS FOR EVALUATING CLINICAL UTILITY OF GENOMIC TESTING

1. Assessment of clinical utility should consider four dimensions: diagnostic thinking, medical management, patient health and non-health outcomes, and societal impacts.
2. Assessing diagnostic thinking includes actively tracking changes in differential diagnosis, influences on/along related to diagnostic journey, changes in prognostic certainty, and timeliness of diagnosis.
3. Assessing therapeutic efficacy includes medical recommendations/interventions that follow from WGS. Interventions can include therapies targeted to underlying disease mechanisms, supportive therapies, disease-specific monitoring plans, sub-specialist referrals, and other changes in management.
4. Assessing patient outcomes should include health and non-health impacts. Health impacts include morbidity, mortality, service utilization, quality of life, etc. Non-health outcomes include knowledge, psychosocial response, perceived utility, decision quality, etc.
5. Assessing societal efficacy should relate to family impacts, societal acceptability, and value for money. Benefits of information generated by WGS must be balanced against individual, community, and societal level costs and consequences.

FUTURE DIRECTIONS

- Harmonize efforts to apply toolkit to WGS-based studies to generate clinical utility evidence
- Incorporate study design principles into the toolkit to optimize evidence quality
- Link with health technology assessment agencies to synergize endpoints for economic evaluation
- Modify toolkit as -omic technologies and applications evolve

CONTACT

Website: https://medgenomeinitiative.org/
Email: info@medgenomeinitiative.org
Twitter: @medical_genome
Corresponding author: Robin Z. Hayeems (robin.hayeems@sickkids.ca)

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