Clinical Utility of Genomic Testing: A Measurement Toolkit

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THE MEDICAL GENOME INITIATIVE

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

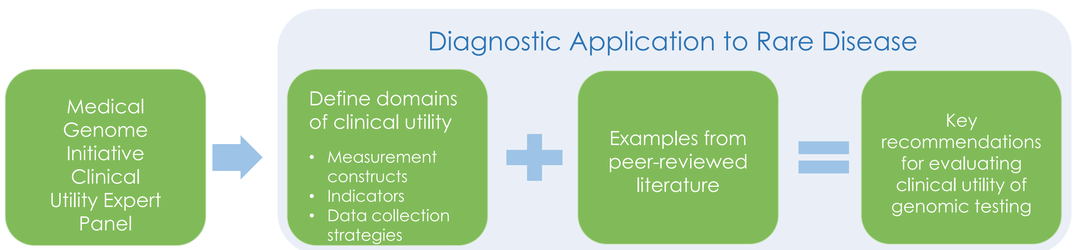
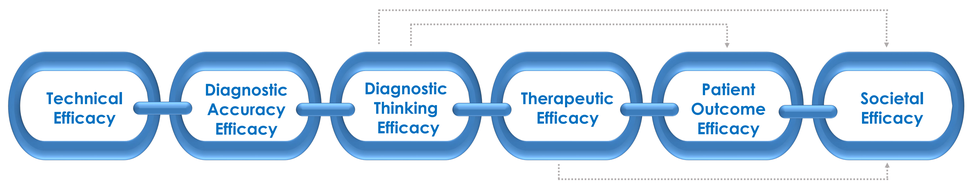


Table 1: Application of the Fryback and Thornbury Model of Efficacy[1] to Genome Sequencing

Domain	Key Questions	Measurement construct	Indicator	Data Source/Strategy	Reference
1: Technical efficacy	In the laboratory, does the test measure what it purports to measure?	Analytic validity	Sensitivity (recall), specificity, precision (technical positive predictive value) when "gold standard" reference available	Laboratory reports	Marshall et el (submitted)
			Positive percent agreement (PPA), negative percent agreement (NPA) when only standard technical result available		FDA[23]
2: Diagnostic accuracy efficacy	Does the test result distinguish patients with and without the target disorder?	Clinical Validity	Variant classification accuracy	Laboratory reports	
			Gene-phenotype matching		Rehm[20]; Strande[21]
			Test outcome (positive, negative, inconclusive)		Rehm[20]; Richards[22]
3: Diagnostic thinking efficacy	Does the test help a clinician to come to a diagnosis or discover a previously unrecognized phenotype or risk factor?	Understanding disease etiology and prognosis	Diagnostic classification (complete, partial, possible, dual diagnosis); prognostic clarity	Case report forms, medical records, clinician interviews, C-GUIDE	Lionel[2] Posey[3] French[4] Chandler[5] Scocchia[6] Dragojlovic[7] Kingsmore[8] Hayeems[9]
			Diagnostic error (false positive, false negative, misdiagnosis, overdiagnosis)		
		Timeliness	Time to diagnosis		
		Diagnostic investigation intensity	Initiated or averted diagnostic investigations		
4: Therapeutic efficacy	Does the test aid in planning treatment? Does the test change or avert planned treatment?	Medical management changes triggered by test result	Initiation of referral to sub-specialist	Case report forms, medical records, clinician interviews, C-GUIDE	Petrikin[10] Stark[11] Clark[12] Hayeems[9]
			Initiation/alteration/cessation of intervention (medication, diet, surveillance, rehabilitation, supportive care) for patient or family member		
5: Patient outcome efficacy	Do patients who have the test fare better than similar patients who do not?	Health outcomes	Phenotype-specific clinical outcomes, morbidity, mortality, QALY, DALY	Case report forms, medical records, patient reported	WHO ICF Denny[13] Farnaes[14] Robinson[15]
		Non-health outcomes	Knowledge and understanding, psychosocial response/personal utility, decision quality	Validated patient reported outcome measures	Kohler[24] Grant[25]
6: Societal efficacy	Does the test demonstrate value for money and societal acceptability?	Family, community, society impacts	Family member risk identification, cascade testing, management implications, personal/public values and preferences	Case report forms, medical records, administrative data, patient/parent surveys, patient/public engagement	Marshall[16] Kulchak- Rahm[17] Anderson[18]
		Value for money	Direct and indirect costs, endpoints described in levels 3-5		Stark [11] Schwarze[19]

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



Case examples[14] Key Questions:	In the lab, does the test measure what it purports to measure?	Does it distinguish between patients with and without the disorder?	Does the test help the clinician establish a diagnosis? Does the test influence the diagnostic pathway?	Does the test aid in planning treatment? Does the test change or avert planned treatment?	Do patients who have the test fare better than similar patients who do not?	Is it acceptable to society? Is it cost effective?
Patient 6019 (causal gene GABRA1) [14]	N/A	N/A	Avoided repeat EEG, increased clinician confidence in therapy when readmitted	Steroids weaned; discontinuation of inappropriate anti-epileptic at next admission		
Patient 6026 (causal gene JAG1) [14]	N/A	N/A		Avoided Kasai hepatoportoenterostomy	83-94% decreased mortality	Costs avoided: $131,795*
Data collection tools	N/A	N/A	←EMR Review, interviews with clinicians→			Comparison between actual healthcare utilization and counterfactual diagnostic trajectory

*compared to historical matched control ····· Indicates an alternate route

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/actions 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

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