Evidence Review of The Use of First-Line Genome Sequencing to Diagnose Rare Germline Disorders

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BACKGROUND

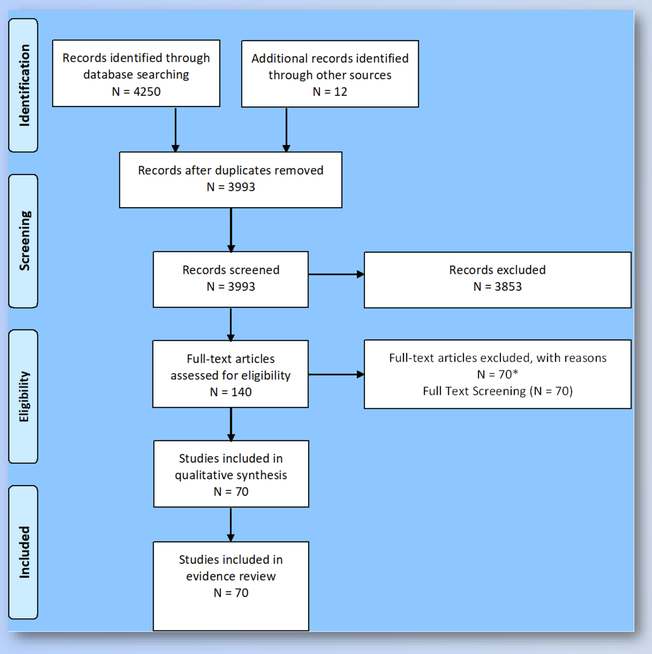
- Genome sequencing (GS) has evolved as a clinically validated assay with robust capabilities to identify rare genetic disorders.
- Recently published guidelines and health technology assessments have sought to identify patient populations that would benefit most from exome or genome sequencing (Smith HS et al, 2019; Malinowski et al, 2020 Manicknam et al, 2021; Shickh et al 2021, Souche et al 2022).
- Questions remain, however, regarding when to apply GS as a first-line diagnostic test for rare germline disorders.
- To address this questions, the Medical Genome Initiative conducted a focused literature review as part of a framework to develop patient selection recommendations.
- The purpose of the literature review was to appraise the evidence focused on the use of first-line GS for the diagnosis of rare germline disorders.

APPROACH

- Inclusion Criteria
  - -GS for diagnosis of rare germline disorders published January 2011-August 2022
  - -Report either diagnostic yield (DY) or clinical utility of GS
- Exclusion Criteria
  - -Case reports or secondary publications
  - -Fetal, microbiology, oncology and healthy cohorts
- Studies were reviewed by 2 independent reviewers who abstracted metrics study characteristics and outcome measures including DY and clinical utility
- Study quality assessed using adapted criteria for diagnostic studies from the American College of Radiology which grades study design and measures to reduce sources of bias. Studies graded on a 4 point scale (1= highest quality, 4=lowest quality) (Kurth et al, 2021)

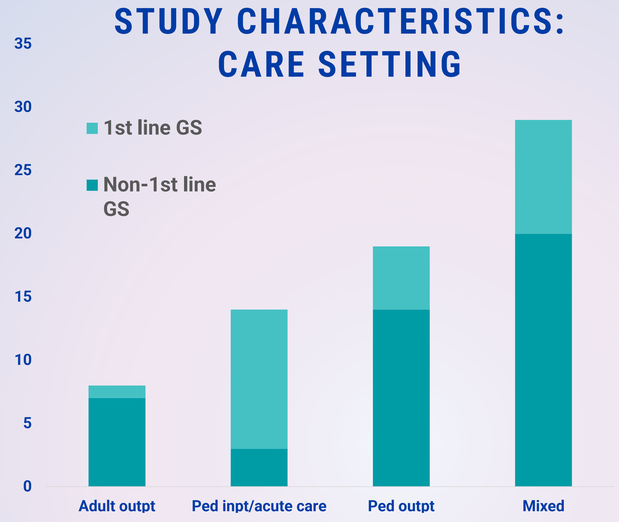
RESULTS

PRISMA DIAGRAM



- 70 studies met inclusion criteria, comprising over 22,834 patients who received GS in one of the following settings: acute care pediatric inpatients, pediatric outpatients, adult outpatients, or mixed cohorts.

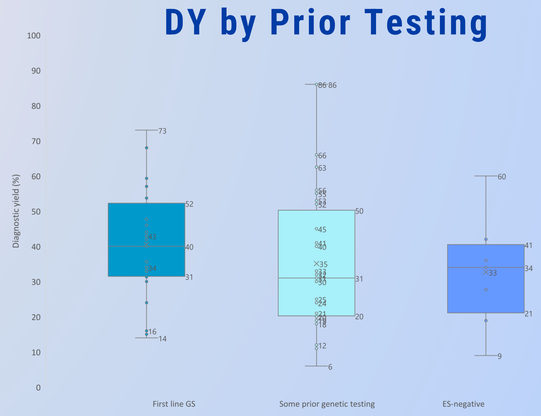
STUDY CHARACTERISTICS: CARE SETTING



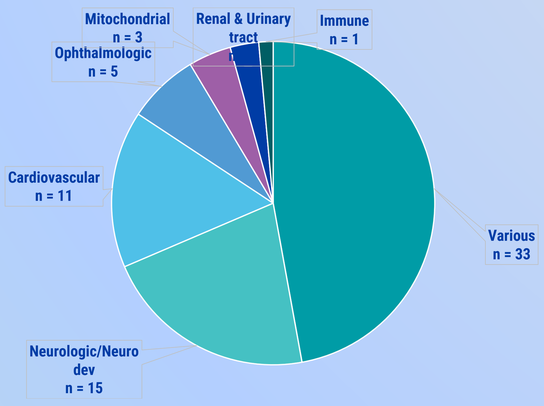
- GS was the first-line genetic test in 37.1% (26/70) of studies analyzed.
- GS as a first line test was most frequently applied in pediatric acute care/hospitalized patients (11/14 or 78.5%)
- In addition to differences in study design, studies showed substantial variability in GS analysis approach, variant types reported, and turn around times
- Turn around time was reported for 18 studies and ranged from 3 to 73 days (median 12.9 days).
- Measures of clinical utility were reported in 23 studies and often focused on changes where GS was diagnostic.

	No. studies (%)	Diagnostic yield (range)	No. high quality studies (%)	Clinical utility measures reported (%)
First-line GS	26 (38.5%)	40.5% (14-73)	13 (50%)	13 (21.4%)
ES-negative (>80%)	8 (11.4%)	32.9% (9-60)	15 (35.7%)	1 (1%)
Some prior genetic tests (ES in <80%)	34 (48.5%)	35.1 (6-86)		9 (12.8%)

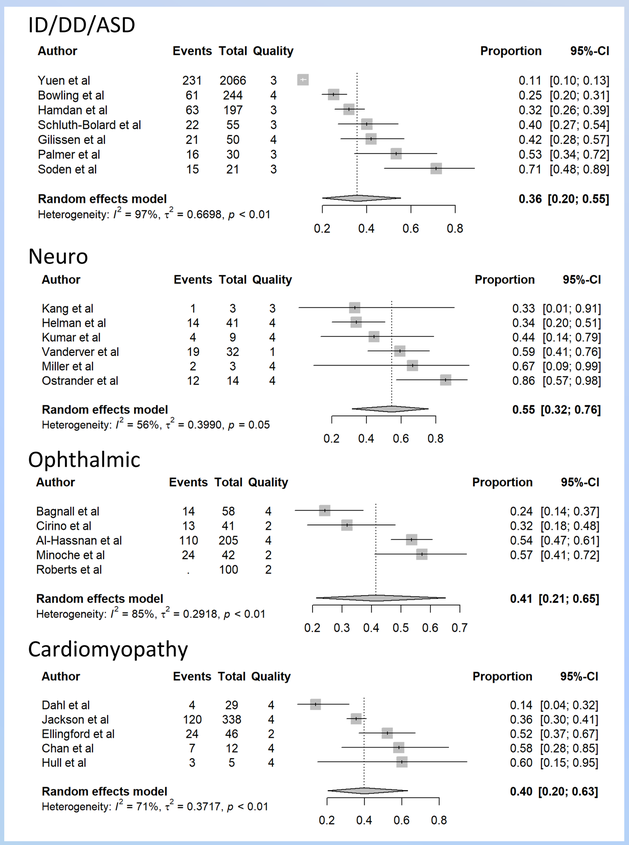
STUDY CHARACTERISTICS: DY by Prior Testing



PHENOTYPE CATEGORIES



Forest Plots Reveal Substantial Heterogeneity in DY for both Selected and Mixed Phenotypes



DISCUSSION

- This focused literature review highlights the diagnostic capabilities of GS across diverse phenotypes, age groups and care settings. Data specifically studying GS with adult-onset conditions remains limited.
- These studies suggest that first-line GS is appropriate in certain patient populations, but additional high-quality studies are needed to further assess the use of first-line GS for indications beyond pediatric acute care/hospitalized patients.
- Diagnostic yield of GS differed among study cohorts and varied based on degree of prior genetic testing. Additional unmeasured factors likely also contribute to DY in any given study including analysis strategy, variant types analyzed, selectivity of inclusion criteria, as well as phenotype itself. Individual phenotypic factors including family history and suspected pattern of inheritance, severity, complexity and specificity of phenotype may also play a role.
- Heterogeneity among study design and variant reporting limits comparability of DY across studies. This underscores the need for additional metrics to assess utility of GS.

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