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Routine Laboratory Tests and Artificial Intelligence in Pre-Marital Screening: A Systematic Review for the Prevention of Hereditary Hemolytic Anemia

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REVIEW TITLE AND BASIC DETAILS

Review title

Routine Laboratory Tests and Artificial Intelligence in Pre-Marital Screening: A Systematic Review for the Prevention of Hereditary Hemolytic Anemia

Condition or domain being studied

Population-based healthcare; Non-Pharmacological Interventions; Screening Procedure; Clinical Outcome

Rationale for the review

This systematic review addresses a critical gap in pre-marital screening programs for hereditary hemolytic anemias (e.g., thalassemia, sickle cell disease). While routine lab tests (CBC, blood smear, ESR) are widely used for initial carrier detection, their interpretation relies heavily on manual analysis, which may lack sensitivity or scalability. The integration of artificial intelligence (AI) offers transformative potential to: 1. Enhance accuracy by detecting subtle patterns in routine test data that humans might miss. 2. Improve accessibility in resource-limited settings where advanced diagnostics (e.g., genetic testing) are unavailable. 3. Standardize screening across diverse populations, reducing variability in test interpretation. Despite promising pilot studies, no comprehensive review has evaluated the real-world effectiveness of AI in this context or synthesized implementation challenges (e.g., data diversity, infrastructure needs). This review will: - Provide evidence on whether AI-augmented routine tests can replace or triage costly confirmatory testing. - Guide policymakers on feasible AI integration into existing screening programs. - Identify

research gaps to prioritize future AI model development. By bridging these gaps, the review aims to optimize prevention strategies for hereditary anemias globally, aligning with WHO goals for genetic disease reduction. Key Additions to Existing Knowledge: - First systematic evaluation of AI + routine tests for pre-marital carrier screening. - Practical insights into barriers/facilitators for AI adoption in public health programs. - Evidence-based recommendations to update screening guidelines.

Review objectives

Primary Objective: To evaluate the diagnostic accuracy of AI-assisted routine laboratory tests (CBC, blood smear, ESR) for detecting carriers of hereditary hemolytic anemia in pre-marital screening programs. Secondary Objectives: 1. To compare the performance of AI models versus conventional interpretation methods. 2. To identify implementation challenges (e.g., cost, infrastructure) of AI integration. 3. To assess clinical utility (e.g., reduction in unnecessary confirmatory testing). Research Questions: 1. How does AI improve sensitivity/specificity of routine tests for carrier detection? 2. What are the key barriers to adopting AI in real-world screening programs? 3. Can AI reduce disparities in access to effective screening?

Keywords

Premarital screening; Hereditary hemolytic anemia; Artificial intelligence; Routine laboratory tests; Thalassemia; Sickle cell disease; Complete blood count CBC; Peripheral blood smear; Erythrocyte Sedimentation Rate ESR; Machine learning; Diagnostic accuracy; Sensitivity and specificity; Carrier detection; Predictive modeling; Screening programs; Public health; Resource-limited settings; Cost-effectiveness; Neural networks; Clinical decision support systems

Country

Saudi Arabia; Iran (Islamic Republic of); Greece; India; United Arab Emirates; Türkiye; Pakistan; Bangladesh; Malaysia; United States of America; United Kingdom; Italy; Yemen

ELIGIBILITY CRITERIA

Population

Included

• Asymptomatic individuals undergoing premarital screening • Couples of reproductive age (typically 18-45 years) • Populations with high prevalence of hereditary hemolytic anemias (thalassemia, sickle cell disease) • Studies using routine blood tests (CBC, blood smear, ESR) as initial screening

Excluded

• Symptomatic patients or those with diagnosed hemolytic anemia • Studies focusing exclusively on genetic testing without routine lab correlates • Non-reproductive age groups (pediatric/elderly populations) • General population screenings without premarital/preconception context

Intervention(s) or exposure(s)

Included

Artificial intelligence; Machine learning; Laboratory procedure; Urine Blood Test; Diagnostic Procedure

• AI/ML models analyzing routine lab tests (CBC, blood smear, ESR) for carrier detection • Hybrid approaches combining AI with manual review • Studies validating AI tools in real-world screening settings • Both supervised and unsupervised learning models

Excluded
• AI systems using only advanced tests (e.g., HPLC, genetic sequencing) without routine lab inputs • Non-AI decision tools (e.g., simple rule-based algorithms) • Theoretical models without clinical validation • AI applications focused solely on treatment/disease management

Comparator(s) or control(s)

Included
PICO tags selected: Diagnostic Procedure; Laboratory Data Interpretation; Hematologic test; Screening Procedure

• Non-AI methods of interpreting routine lab tests (CBC, blood smear, ESR)• Manual hematologist/clinician interpretation• Conventional automated analyzer results without machine learning• Rule-based decision algorithms (non-ML computerized systems)

Excluded
• Advanced diagnostic methods (HPLC, genetic testing) without routine lab correlation• AI-assisted interpretation (even if partial)• Theoretical/untested interpretation approaches• Studies where comparator methodology is unspecified

Study design
Only nonrandomized study types will be included.

Included
• Diagnostic accuracy studies (prospective/retrospective) • Clinical validation studies of AI models • Comparative studies (AI vs. conventional interpretation) • Implementation research on AI-integrated screening programs • High-quality cohort studies with outcome data

Excluded
• Case reports or case series (<10 participants) • Review articles (systematic reviews will be hand-searched) • Conference abstracts without full methodology • Opinion pieces/editorials without original data • Animal or pure in vitro studies

Context
This systematic review evaluates the integration of artificial intelligence (AI) with routine laboratory tests (complete blood count, peripheral blood smear, erythrocyte sedimentation rate) in global pre-marital screening programs for hereditary hemolytic anemias (thalassemia, sickle cell disease). Why this matters: 1. Public health urgency: 5-7% of global populations are carriers of hemoglobinopathies, with high prevalence in Mediterranean, Middle Eastern, and South Asian regions. 2. Diagnostic gap: Current programs rely on manual interpretation of basic tests, risking missed carriers due to subjective analysis. 3. AI opportunity: Machine learning can enhance accuracy, standardize results, and improve accessibility in resource-limited settings. Unique focus: First synthesis of both diagnostic performance and implementation challenges of AI-augmented screening.

TIMELINE OF THE REVIEW

Date of first submission to PROSPERO
12 June 2025

Review timeline
Start date: 12 June 2025. End date: 31 December 2025.

Date of registration in PROSPERO
12 June 2025

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol
A full protocol has been written but is not available because:

Protocol is being finalized for institutional approval prior to publication.

SEARCHING AND SCREENING

Search for unpublished studies
Only published studies will be sought.

Main bibliographic databases that will be searched
The main databases to be searched are *CENTRAL - Cochrane Central Register of Controlled Trials*, *CINAHL - Cumulative Index to Nursing and Allied Health Literature*, *Embase.com*, *MEDLINE*, *PubMed* and *Scopus*.

Other important or specialist databases that will be searched
✔ Other specialist databases: "GulfBase" or "IMEMR" (for Middle Eastern screening programs)

LILACS (If including Latin American studies) IEEE Xplore (Key for AI/ML algorithms in medicine)

Search language restrictions
The review will only include studies published in English and Arabic.

Search date restrictions
Databases will be searched for articles published from 1 January 2010, there are no search end date restrictions.

Other methods of identifying studies
Other studies will be identified by: *contacting authors or experts*, *looking through all the articles that cite the papers included in the review ("snowballing")*, *reference list checking*, *searching conference proceedings* and *searching trial or study registers*.

Additional information about identifying studies
Handsearching WHO/CDC reports and national screening program guidelines

Link to search strategy
A full search strategy is available in the full protocol as described in the *Availability of full protocol* section

Selection process
Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

Other relevant information about searching and screening
Manual screening via shared spreadsheets (Excel/Google Sheets) with dual-independent review. Non-English studies translated via certified bilingual team members.

DATA COLLECTION PROCESS

Data extraction from published articles and reports
Data will be extracted independently by at least two people (or person/machine combination) with a process to resolve differences.

Authors will not be contacted for further information.

Study risk of bias or quality assessment
Risk of bias will be assessed using: *QUADAS-2*

Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.

Additional information will **not** be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment
QUADAS-2 Domain 4 (Flow/Timing) will evaluate attrition bias. Funnel plots/Egger's test applied if ≥10 studies pooled.

Certainty assessment
The certainty of evidence will be evaluated using the GRADE approach (Grading of Recommendations, Assessment, Development, and Evaluations). Key domains include: 1. Risk of bias (QUADAS-2 assessments) 2. Inconsistency (I^2 statistic >50% indicating heterogeneity) 3. Indirectness (e.g., population or test applicability) 4. Imprecision (confidence interval width around sensitivity/specificity estimates) 5. Publication bias (funnel plots if ≥10 studies). Evidence will be graded as high, moderate, low, or very low certainty.

OUTCOMES TO BE ANALYSED

Main outcomes
1. Diagnostic accuracy of AI-assisted routine tests: - Sensitivity, specificity, AUC for detecting carriers of hereditary hemolytic anemia (primary). 2. Comparative performance: - Difference in accuracy (AI vs. conventional interpretation). 3. Clinical utility: - Reduction in unnecessary

confirmatory testing (e.g., genetic tests). 4. Implementation metrics: - Feasibility, cost, turnaround time (secondary).

Additional outcomes

1. Ethical/legal challenges: - Data privacy concerns, algorithmic bias, or consent issues in AI-driven screening. 2. Population-specific performance: - Variation in AI accuracy by ethnicity/region (e.g., Mediterranean vs. Southeast Asian cohorts). 3. User acceptance: - Healthcare provider/patient trust in AI results (if reported in studies). 4. Model transparency: - Frequency of explainable AI (XAI) techniques used in included studies.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

If sufficient homogeneous data (≥3 studies reporting compatible outcomes) are available: 1. Primary Meta-Analysis: - Bivariate random-effects models will pool sensitivity, specificity, and AUC values across studies, accounting for between-study variance. - Summary receiver operating characteristic (SROC) curves will visualize diagnostic performance. 2. Secondary Analyses: - Subgroup meta-analyses by: - AI model type (e.g., traditional ML vs. deep learning) - Routine test combination (CBC alone vs. CBC + smear) - Geographic region (high vs. low prevalence areas) 3. Heterogeneity Assessment: - Quantified using I^2 statistic (thresholds: <25% low, 25-75% moderate, >75% high). - Explored via meta-regression if substantial heterogeneity exists. 4. Narrative Synthesis: - For non-quantifiable outcomes (e.g., implementation barriers), findings will be thematically organized using SWIFT-Review or similar tools. Software: R (metafor, mada), Stata, or RevMan.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work		
Formal searching/study identification		
Screening search results against inclusion criteria		
Data extraction or receipt of IPD		
Risk of bias/quality assessment		
Data synthesis		

Review status

The review is currently planned or ongoing.

Publication of review results

Results of the review will be published in English and Arabic.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

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No conflict of interest declared.

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No conflict of interest declared.

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Funding source

Review has no specific/external funding but is supported by guarantor/review team (non-commercial) institutions.

Additional information about funding

No external funding; team members contribute time as part of academic roles.

Peer review

The final manuscript will undergo independent peer review by experts in hematology, diagnostic AI, and public health prior to journal submission. Reviewers will assess methodological rigor, data synthesis validity, and clinical relevance per PRISMA-AI guidelines.

ADDITIONAL INFORMATION

Additional information

This review aligns with WHO recommendations on hereditary anemia prevention. If meta-analysis is unfeasible, a SWiM-guided narrative synthesis will highlight AI's role in reducing screening disparities. Updates will be documented if protocol amendments occur post-registration.

Review conflict of interest

Declared individual interests are recorded under team member details.. No additional interests are recorded for this review.

Medical Subject Headings

Premarital Examinations; Anemia, Hemolytic, Congenital; alpha-Thalassemia; beta-Thalassemia; Anemia, Sickle Cell; Artificial Intelligence; Machine Learning; Diagnostic Tests, Routine; Clinical Laboratory Techniques

SIMILAR REVIEWS

Check for similar records already in PROSPERO

PROSPERO identified a number of existing PROSPERO records that were similar to this one (last check made on 12 June 2025). These are shown below along with the reasons given by that the review team for the reviews being different and/or proceeding.

- Artificial Intelligence-Driven Prediction of Free Flap Failure in Microsurgery A Systematic Review and Meta-Analysis [published 7 May 2025] [CRD420251047313]. The review was judged **not to be similar**
- AI-based detection and measurement of marginal bone loss around dental implants in periapical radiographs - a systematic review. [published 14 March 2025] [CRD420251009693]. The review was judged **not to be similar**
- Screening Mammography and Artificial Intelligence: A Comprehensive Systematic Review [published 17 January 2025] [CRD42025634360]. The review was judged **not to be similar**
- Comprehensive Systematic Review and Meta-Analysis: Evaluating Artificial Intelligence (AI) Effectiveness and Integration Obstacles within Anesthesiology [published 6 December 2024] [CRD42024618865]. The review was judged **not to be similar**
- Real-World Clinical Validation of AI-Powered Clinical Decision Support Systems in Hospitals: A Systematic Review of Their Impact on Patient Safety and Quality of Care [published 2 June 2025] [CRD420251038285]. The review was judged **not to be similar**
- The Role of Artificial Intelligence and Machine Learning in the Diagnosis and Management of Temporomandibular Disorders: A Systematic Review [published 17 April 2025] [CRD420251035080]. The review was judged **not to be similar**
- Artificial Intelligence in Acute Stroke Management: A Systematic Review & Meta-analysis [published 24 February 2025] [CRD420250652390]. The review was judged **not to be similar**
- Artificial Intelligence in Temporomandibular Disorders: Part I – Diagnostic Accuracy and Clinical Utility (Systematic Review and Meta-analysis); Part II – AI Treatment Planning, Preoperative Decision Support, and Postoperative Outcome Prediction [published 7 May 2025] [CRD420251047311]. The review was judged **not to be similar**
- Artificial Intelligence in Cerebrovascular Diseases: A Comprehensive Systematic Review of Revolutionary Innovations in Risk Prediction, Diagnosis, and Management [published 27 January 2025] [CRD42025638869]. The review was judged **not to be similar**

PROSPERO version history

- Version 1.0, published 12 Jun 2025

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Any enquiries about the record should be referred to the named review contact