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Systematic Review and Meta-Analysis on Diagnostic Test of Biomarkers for Classical Galactosaemia

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Abstract

Classical galactosaemia (CG) is an autosomal recessive inherited disorder caused by deficiency of galactose-1-phosphate uridyl transferase (GALT) enzyme resulting in accumulation of galactose and galactose-1-phosphate. Affected children develop severe illness with feeding difficulties, liver failure, septicaemia, and cataracts following ingestion of galactose from breast milk or infant formula in the first weeks of life[1]. A galactose-restricted diet has proven effective in treating the neonatal life-threating manifestations[2]. Diagnosis of CG is aided by screening tests measuring either total galactose (TG) and/or enzyme activity assay of GALT[3]. This study aimed to evaluate the analytical and diagnostic test for TG and GALT as clinical biomarkers for CG.

This systematic review was conducted according to the criteria in PRISMA guidelines. Selection of relevant manuscripts, risk of bias assessment, and data extraction were performed independently by three investigators. Three databases were searched: Medline, PubMed and Science Direct. The electronic search keywords were used for systematic review were: (1) Specificity; (2) Sensitivity; and (3) Classical Galactosemia or Classical Galactosaemia. The inclusion criteria were: (1) Classical galactosaemia (2) Results of diagnostic test at least two parameters of specificity and sensitivity (3) English articles (4) Study published > 1980. The exclusion criteria were: (1) Other type of galactosaemia (e.g. galactokinase deficiency and galactose epimerase deficiency) (2) Diagnostic test result not available or insufficient data (3) Non-english articles (4) Study published < 1979. The flow chart according to the PRISMA guideline is presented in Figure 1. The risk of bias was evaluated using the QUADAS-2 assessment, conducted independently and in duplicate by two authors experienced in using the QUADAS-2 tools (Figure 2).

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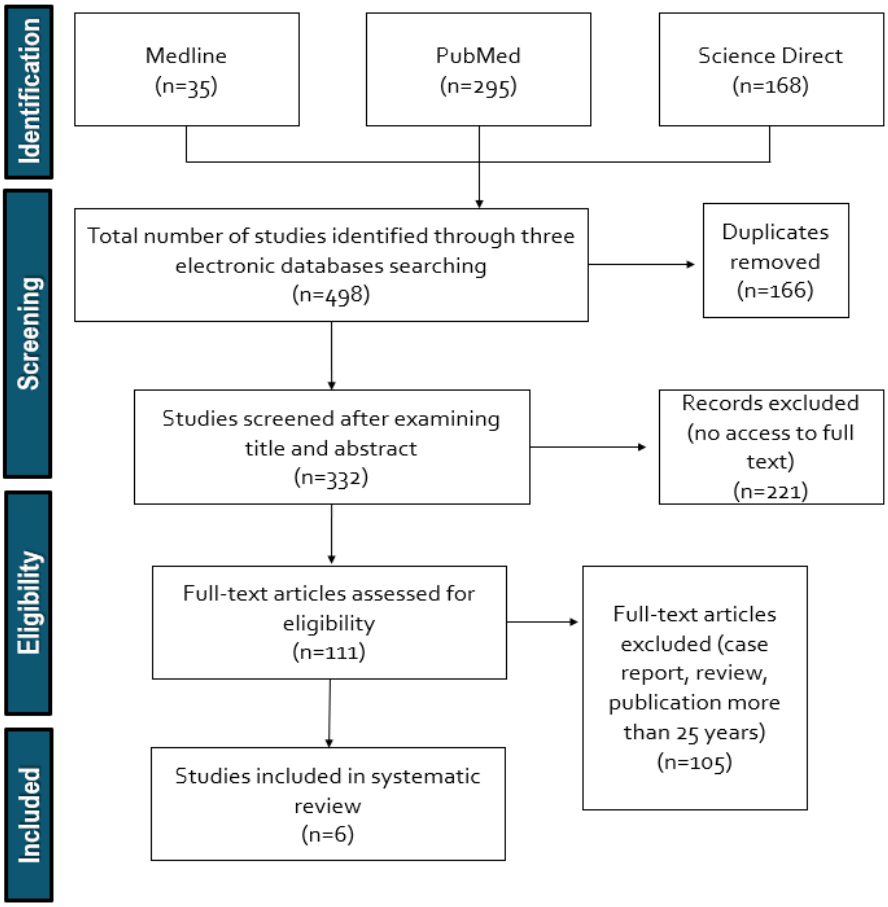

Figure 1: PRISMA Flow Chart

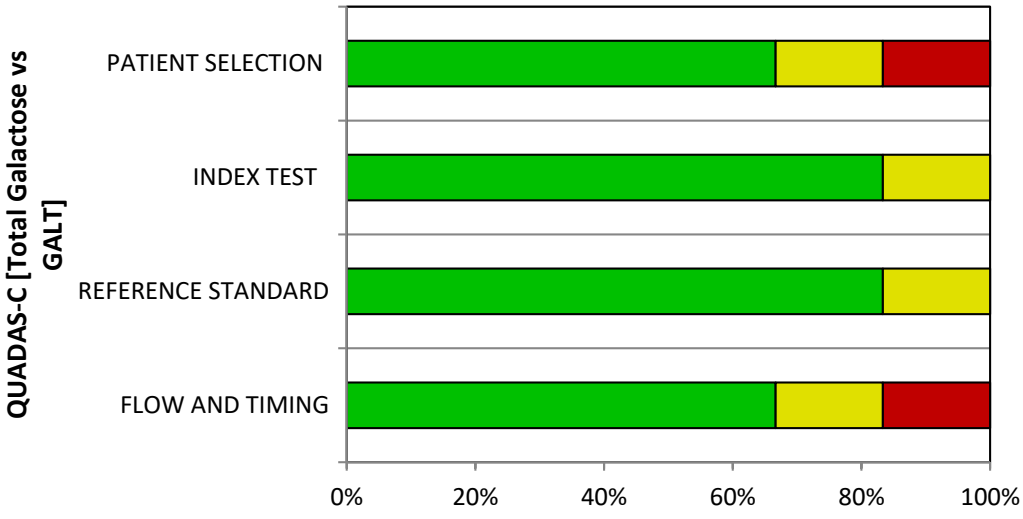

Figure 2: Risk of bias using QUADAS-2 assessment

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Diagnostic tests of sensitivity and specificity were determined and translated to receiver operating curve (ROC) and area under curve (AUROC) while Fisher's exact test was performed to analyse the contingency table.

Four approaches were identified through this study. Approach A for screening of CG using TG only, approach B for screening of CG using GALT only, approach C for screening of CG using TG as first tier and GALT as second tier, and approach D for screening of CG using GALT as first tier and TG as second tier. Five studies were included in the meta-analysis. Diagnosis of CG was divided based on approach A (TG; 4 studies; n=241,365), approach B (GALT; 2 studies; n=791), approach C (TG as first tier and GALT as second tier; 1 study; n=139) and approach D (GALT as first tier and TG as second tier; 4 studies; n=1,593,586).

Table 1 shows comparison of diagnostics parameters and area under the curve for all approaches. Figure 3 and 4 show Forest plot and Receiver Operating Curve (ROC) for each approach, respectively.

Table 1 Summary of diagnostic test and area under the curve for different approaches

Parameter	Approach A	Approach B	Approach C	Approach D
Sensitivity	100%	100%	100%	100%
Specificity	91.8%	100%	67.4%	99.9%
Positive predictive value (PPV)	0.5%	100%	2.2%	4.8%
Negative predictive value (NPV)	100%	100%	100%	100%
Area under curve (95% CI)	1.0 (1 to 1)	0.625 (0 to 1)	1.0 (1 to 1)	1.0 (1 to 1)
p-value	<0.01	<0.01	> 0.05	<0.01

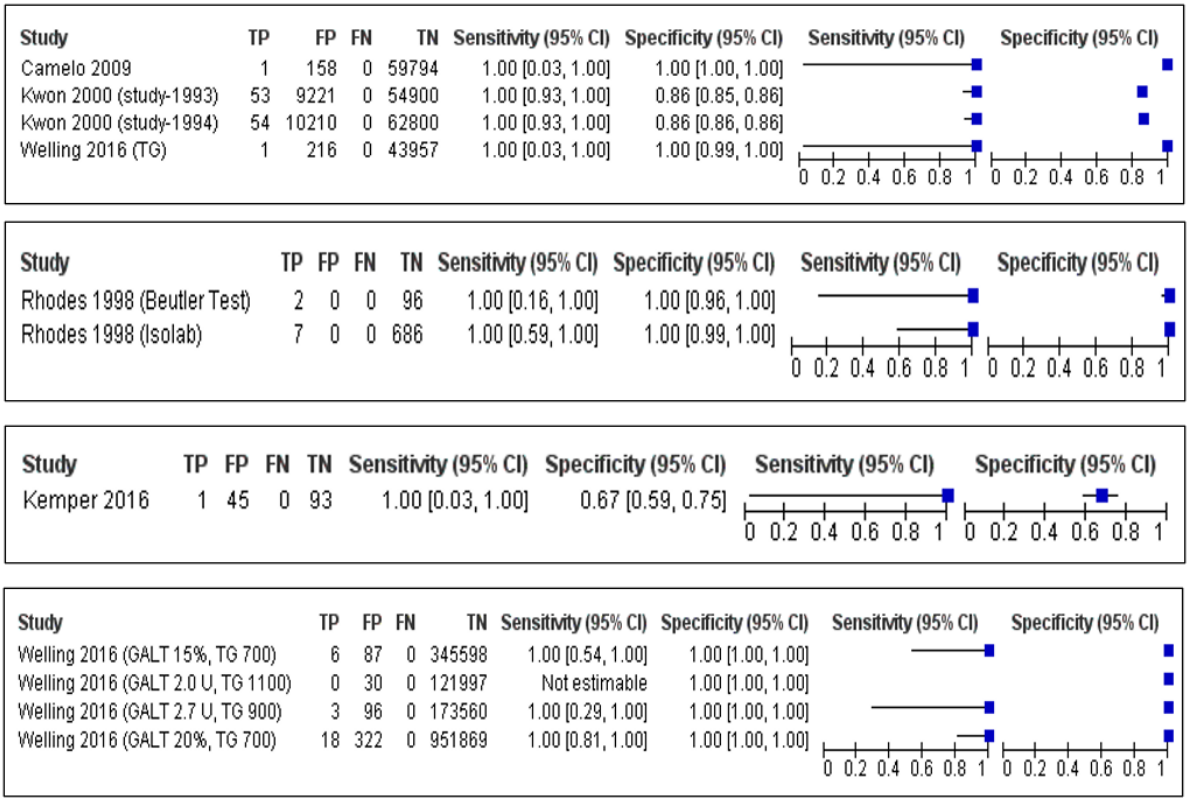

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Figure 3: Forest plot for different approaches (from up to down: Approach A, Approach B, Approach C and Approach D). TP: true positive, FP: false positive, FN: false negative, TN: true negative.

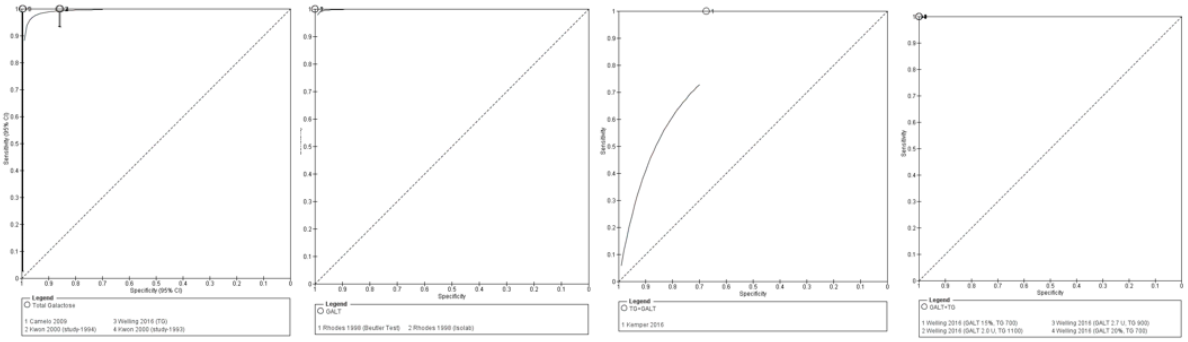

Figure 4: Receiver Operating Curve for different approaches (from left to right: Approach A, Approach B, Approach C and Approach D).

Approach A gave 90-100% in sensitivity and specificity but had very poor positive predictive value. Approach B gave both 100% sensitivity and specificity, however it has a poor area under the curve. Approach C gave 100% in sensitivity but moderate in specificity. Approach D is suggested to be used as screening for CG as it showed high sensitivity, specificity and area under the curve. Therefore, laboratories in Malaysia may consider using GALT assay as first tier of screening and TG assay as second tier of screening for CG diagnosis. Additional studies are needed to establish more efficient strategies for newborn screening to reduce false-positive diagnosis as well as to assess the efficacy of the new diagnostic strategies.

Keywords
Classical galactosaemia, galactose-1-phosphate uridyl transferase, meta-analysis, systematic review, total galactose

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