EPH201

Systematic review of the accuracy of T-cell receptor excision circle (TREC)-based newborn screening for severe combined immunodeficiency (SCID)

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(1) Objectives

- Screening for SCID is possible through the quantification of TRECs. Samples below a given cut-off represent T-cell lymphopenia (TCL) and are referred for confirmatory testing. TREC testing identifies both SCID and other forms of TCL.
- This study aimed to quantify the test accuracy of TREC-based screening for SCID to inform population-level screening decision-making. This aim was structured according to the PIRD framework for test accuracy reviews (**Table 1**).
- Secondary measures included programme uptake rates, detection of non-SCID TCLs, and repeat dried bloodspot requests, uptake, retest and referral rates.

(2) Methods

- Systematic review, with search up to 1 November 2021 in electronic databases, supplemented with grey literature and hand-searching. A preference was given to studies of real-world screening programmes.
- Primary outcomes were positive predictive value (PPV) and false positivity rates. Secondary outcomes included operational measures such as rates of retest, resampling and referral.

(3) Results

- The review identified 19 unique cohorts across 15 studies that reported the outcomes of TREC-based screening in isolation.
- There was notable heterogeneity in terms of screening algorithms, test methodologies, TREC cut-offs, and diagnostic criteria used.
- Incidence of SCID and non-SCID TCLs varied considerably.
- PPV for SCID alone ranged from 0.80% to 20.00% (**Table 2**). PPV for all TCL (including SCID) ranged from 20.29% to 89.36%. PPV is presented according to TREC cut-off groupings for SCID only (**Figure 1**) and all TCL (including SCID) (**Figure 2**) for 12 studies with appropriate measurements.
- Rates of retest (range 0.24 to 2.03%), repeat sample requests (range 0.02 to 0.61%) and onward referral (range 0.02 to 0.11%) varied. Incidence of SCID and non-SCID TCLs varied considerably across the included cohorts.

(4) Conclusions

- International screening programmes for SCID are heterogeneous, with noted variability in the thresholds, methods and screening algorithms used.
- The PPV of the TREC-test varies considerably depending on whether the focus is restricted to SCID only (low PPV) or all TCL (higher, widely varied PPV).
- As a proportion of the total population screened, the false positivity rates for all TCLs (including SCID) are low, but are considerably higher when restricted to SCID.
- Screening algorithm structure and TREC-test thresholds influence false positivity and the number of samples requiring confirmatory testing, as SCID and non-SCID conditions will require further work-up once identified by the TREC test, thereby impacting organisational and budget impact considerations relevant to implementing population-level screening.

Table 1. PIRD framework for systematic review

Population	Newborn infants
Index test	TREC assay using dried bloodspot
Ref. standard	Flow cytometry, T-cell proliferation, genetic testing, clinical diagnosis
Diagnosis	SCID

Table 2. TREC analysis results presented as ranges

Ranges	Percentage (%)
PPV SCID	0.80 to 20.00
PPV TCL	20.29 to 89.36
Rate of retest	0.24 to 2.03
Repeat sample requests	0.02 to 0.61
Rate of onward referral	0.02 to 0.11

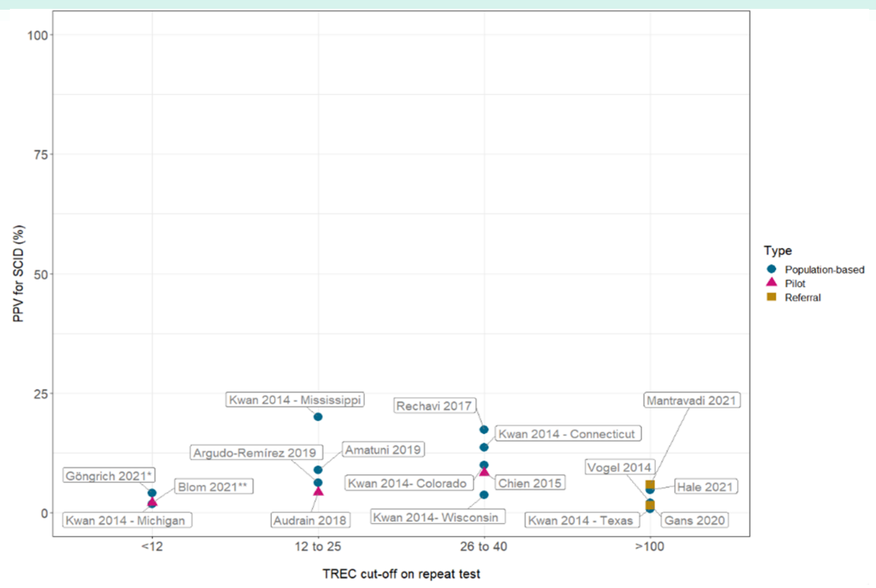

Figure 1. PPV for SCID by TREC cut-off

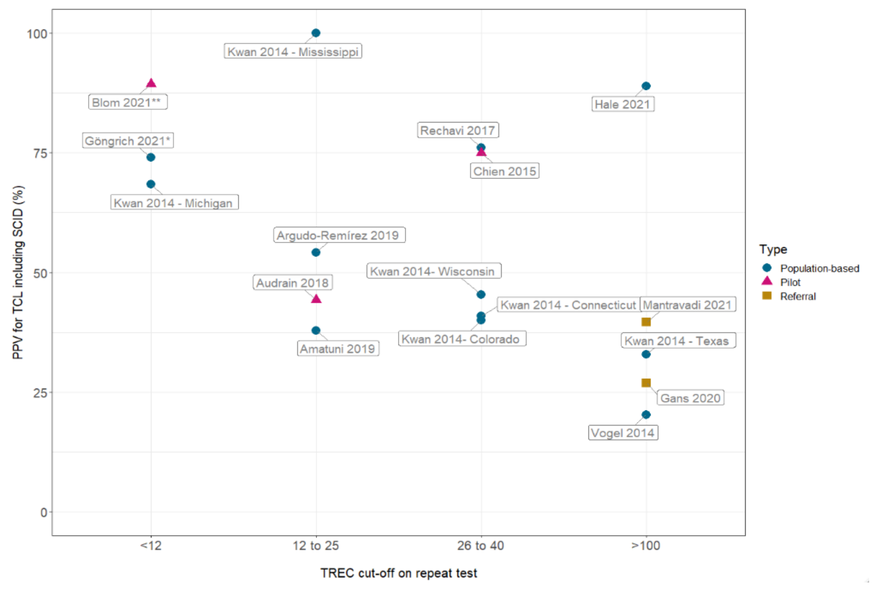

Figure 2. PPV for all TCL (incl. SCID) by TREC cut-off

Related HIQA Activities

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