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Fifty years of newborn screening for congenital hypothyroidism: current status in Australasia and the case for harmonisation

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Abstract

Objectives: Since its implementation 50 years ago in Quebec, Canada, newborn screening for congenital hypothyroidism has become one of the most successful public health measures worldwide. Screening programmes across Australia and New Zealand are characterised by significant commonalities in screening algorithms, and a high degree of regional cooperation in harmonisation efforts. We aimed to conduct a comprehensive survey of current performance and practices related to the total testing process for congenital hypothyroidism screening and provide recommendations for harmonisation priorities within our region.

Methods: A survey was conducted involving the six newborn screening laboratories which provide complete geographic coverage across Australasia. Approximately 360,000 newborns are screened annually. Survey questions incorporated pre-analytical, analytical, and post-analytical aspects of the screening programmes and an extensive 5-year (2016–2020) retrospective analysis of individual programme performance data. Responses from individual screening programmes were collated.

Results: The uptake of newborn screening was over 98% for the six major jurisdictions. All programmes have adopted a single-tier thyroid stimulating hormone (TSH) strategy using the Perkin Elmer GSP instrument. Significant similarities exist between programmes for recommended age of collection and recollection protocols for low birthweight newborns. The process for the determination of TSH cutoffs varies between programmes. TSH lower cut-offs for borderline-positive and positive notifications between 12–15 and 12–25 mIU/L blood, respectively. Recall rates vary between 0.08 and 0.20%. The case definition for congenital hypothyroidism generally includes biochemical and radiological parameters in addition to the commencement of thyroxine. All programmes reported collecting biochemical and clinical data on infants with positive screening tests, and positive predictive values vary between 23.6 and 77.3%. Variation in reported incidence (1:1,300–2,000) cannot be entirely explained by cutoff or recall rate (although one programme reporting fewer cases includes only permanent disease).

Conclusions: Despite similarities between newborn screening algorithms for congenital hypothyroidism across Australia and New Zealand, differences in reported

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programme performance provide the basis for further harmonisation. Surveillance of a large population offers the potential for the ongoing development of evidence-based screening guidelines.

Keywords: congenital hypothyroidism; harmonisation; newborn screening.

Introduction

Congenital hypothyroidism (CH) is the most common cause of preventable intellectual disability worldwide [1]. Early detection of CH through newborn screening (NBS) followed by early thyroid hormone replacement and close monitoring of affected babies promotes normal growth and development [2–6].

Mass NBS for CH was first introduced in Quebec, Canada, in 1972 [7] following the development by Professor Jean Dussault of a radioimmunoassay for T4 in blood dried on paper. Screening used the samples initially collected for PKU screening. CH screening programmes commenced across three jurisdictions in Australia in 1977 [8] (New South Wales, Victoria, and South Australia), then nationwide in New Zealand in 1978. Queensland and Western Australia implemented programmes in 1980 [9] and 1981 [10], respectively. Locally, the 20-year impact of NBS on CH outcomes has been eloquently demonstrated [11, 12]. Today, NBS programmes in Australasia remain voluntary and provide complete geographical coverage in both countries.

Initial moves towards harmonisation of newborn screening programmes have been regional initiatives around the conditions on the screening panel [13–15] and terminology [16] but with the increasing realisation of the importance of evidence in decision-making in medicine, harmonisation of screening protocols (pre-analytical, laboratory and follow-up) is occurring through published guidelines [17–19]. Use of guidelines and harmonised terminology will provide comparable and consistent screening outcomes and allow refinement of evidence-based guidelines through the surveillance of a larger collective population.

All CH NBS programmes in Australasia follow a common strategy of single-tier testing of thyroid stimulating hormone (TSH) with the principle aim of identifying primary thyroid disorders through an elevated TSH concentration measured on dried blood spots (DBS). Healthcare systems across Australia and New Zealand are broadly similar, and CH is the most common disorder detected on NBS. However, substantive differences may exist between the CH NBS performance and algorithms and, as in other countries, present a major barrier to standardised case reporting and performance evaluation across programmes [20]. With the aim of identifying priorities for regional co-operation, we conducted a comprehensive survey of current practices in the various CH NBS programmes.

Methods

Participants and cooperating organisations

The Laboratory and Newborn Screening (LNBS) subcommittee, of the Australasian Paediatric Endocrine Group (APEG) developed and coordinated the CH NBS survey. The survey was distributed in word format to the six NBS laboratories in Australia and New Zealand (Sydney, New South Wales; Melbourne, Victoria; Adelaide, South Australia; Brisbane, Queensland; and Perth, Western Australia; and Auckland, New Zealand), which provide complete geographical coverage across the region.

Performance data is routinely collected and reported by the screening laboratories. This project compares practices and already reported performance data, and was considered a quality audit by each of the NBS programmes. Each jurisdiction obtained the appropriate ethics approval necessary for their data to be included for publication. No identifying information was collected for individual patients.

Questionnaire

The Australasian CH NBS algorithm and the survey questions are detailed in Figure 1. The survey consisted of 30 questions divided into four sections to cover the total testing process (TTP) and programme statistical data. For some questions, respondents were asked to provide information related to the last 5 years (2016–2020). Each section aimed to elucidate specific important aspects of the CH NBS programme and included:

(1) Pre-analytical questions (n=7) related to the geographical coverage, timing of collection and specific protocols in place for birth weight or gestational age;
(2) Analytical questions (n=12), related to the analytical platform used, processes for checking new immunoassay kits, screening strategy, and quality assurance.
(3) Post-analytical questions (n=11), this extensive section related to the interpretation (specifically cut-offs applied), reporting practices of screen positive and screen negative results, programme governance, and NBS programme performance data.

Annual birth rates were rounded to the nearest 1,000 for those <10,000 and to the nearest 5,000 for those ≥10,000. The positive predictive value of CH screening was calculated as the proportion of screen-detected cases divided by the total number of screened babies with a screen-positive (including borderline-positive) CH screen result.

Results

All six (100%) Australasian newborn screening laboratories completed and returned the questionnaire. Together approximately 360,000 babies each year are screened for CH.

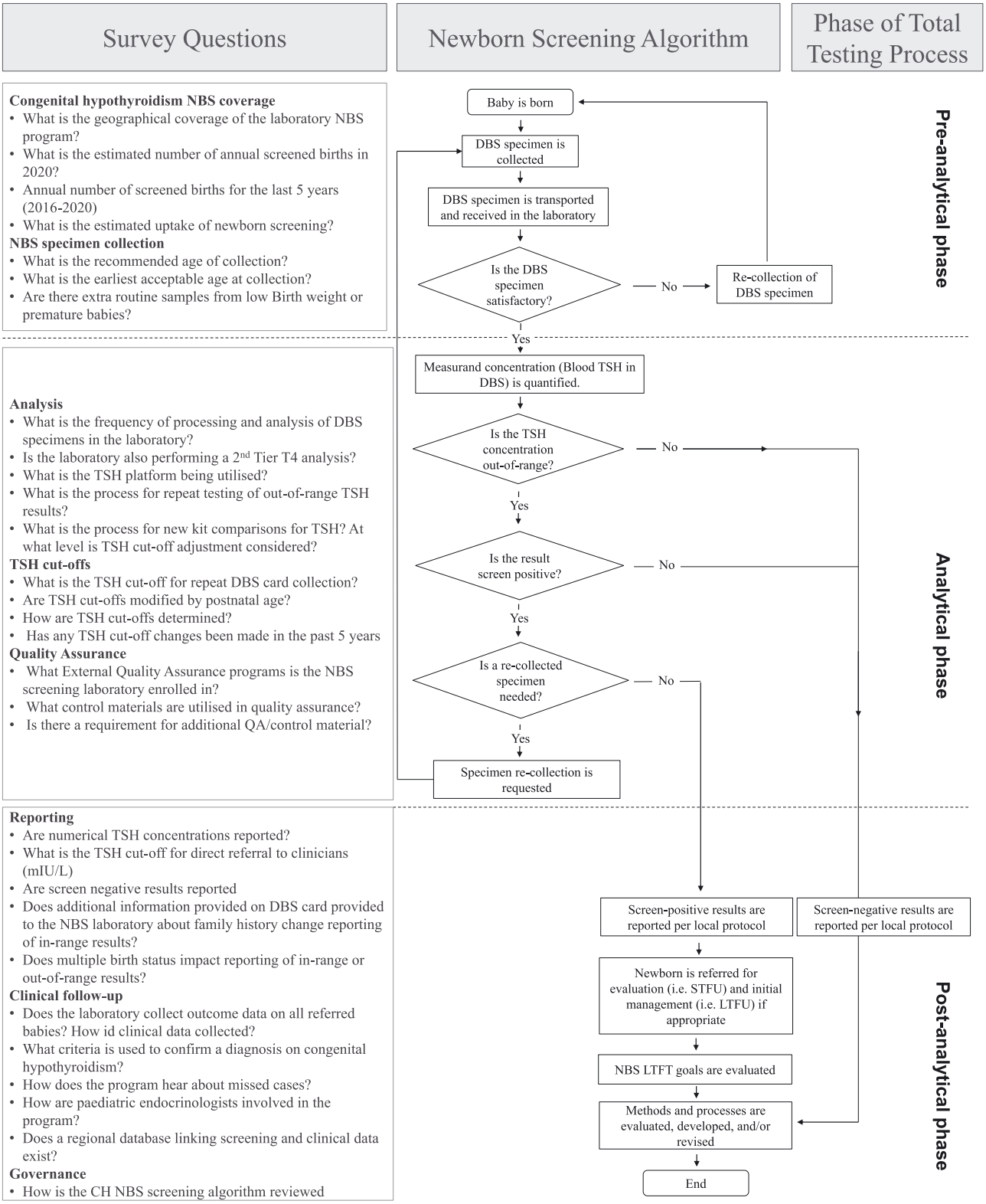

Figure 1: Newborn screening algorithm for congenital hypothyroidism adopted in Australia and New Zealand with survey questions related to pre-analytical, analytical, and post-analytical phases of the total testing process.

Pre-analytical

The geographical coverage of the NBS programmes, the estimated number of screens performed in 2020, and the percentage uptake of the programmes in Australasia are shown in Figure 2. Determination of the percentage coverage of the Australian programmes is reliant on the completion of birth registrations by parents and, therefore, the availability of accurate data can be delayed. Over-counting can occur through unrecognised repeat screens, and there is also variable practice between programmes as to whether reported coverage includes known parental decline of participation in newborn screening.

Five programmes have a recommended age of collection for the initial sample of 48–72 h, and one as close to 48 h of age as possible. No programmes report valid complete screening results from samples collected before 24 h of age however, all programmes test these in order to report significantly out-of-range results, and request a recollect after the baby is 48 h of age. Extra routine samples are requested by all programmes from premature and/or low birth weight babies. Three programmes recommend recollection at 14 days for babies ≤1,500 g birthweight and a further recollect at 28 days for those weighing ≤1000 g, and the others vary in frequency and timing (Table 1).

Analytical

All programmes process and analyse screening cards 5 days a week (Monday to Friday) and two (South Australia and Victoria) also process samples on Saturday. A TSH only strategy (all measured on the Perkin Elmer GSP platform) has been adopted by all programmes, although a T4 assay is currently being validated as a second-tier strategy in New South Wales. All programmes confirm out-of-range TSH results in duplicate or triplicate prior to reporting except for Queensland who immediately report the initial abnormal result then confirm the result by repeating in singlicate.

All of the Australasian NBS laboratories transitioned from AutoDELFIA to Perkin Elmer GSP TSH platforms between 2010 and 2020, and report making minor adjustments to TSH cutoffs around the time of the transition period. All routinely consider further TSH cut-off adjustments when a new kit lot is introduced. There is universal participation in External Quality Assurance

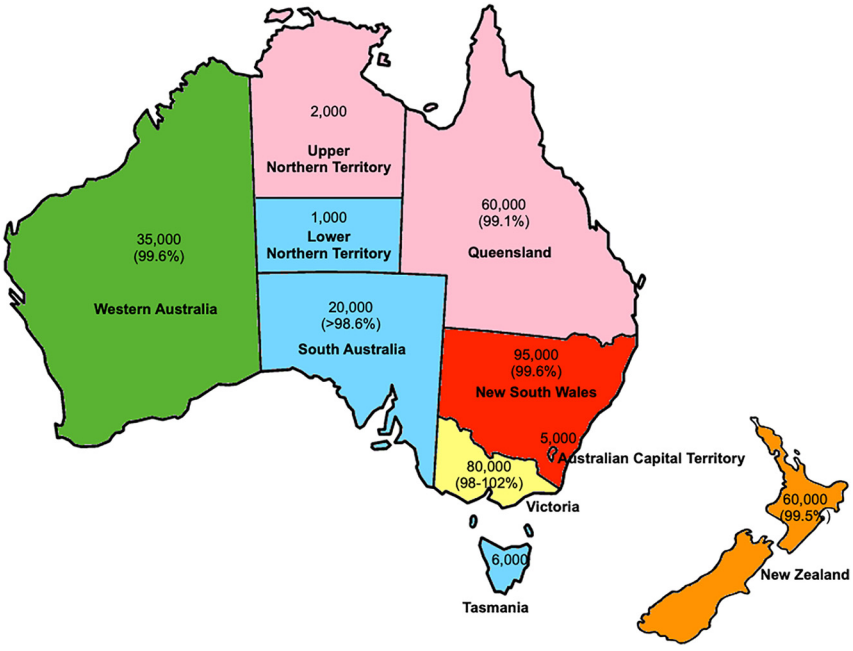

Figure 2: Numbers of newborn screens performed in the year 2020 in the various states and territories of Australia and New Zealand. Estimated rates of uptake of each primary newborn screening programme are included in brackets. Colours indicate the geographical coverage of the primary newborn screening laboratory.

Table 1: Sample collection times and TSH cutoffs for the Australasian NBS programmes.

NBS programme	Pre-analytical			Post analytical			
	Recommended age at collection, h	Earliest acceptable age at collection[a], h	Extra routine samples from LBW or premature babies	TSH cutoff for direct referral (mIU/L blood, GSP)	TSH cutoff for repeat card (mIU/L blood, GSP)	Are TSH cutoffs (mIU/L) modified by postnatal age?	How are cutoffs determined?
New Zealand	48–72	24	≤1,500 g repeat screen 14 days ≤1,000 g repeat again 28 days	≥ 20.0	≥13–19.9	>240 h and 2nd cards (≥6.0)	Historical, validated by a local outcome study for children with TSH below screening cutoff
Queensland	48–72	48	<1,500 g repeat at 14 days <1,000 g repeat again at 28 days	≥12	No repeat cards	No	99.9% of newborn population 48–72 h of age
New South Wales	48–72	24	<1,500 g or <30/40 have repeat at 1 month	≥25.0	≥15–24.9	>120 h (≥6.0)	Annual analyte review meeting; assessment of centiles, missing cases, confirmed cases
Victoria	48–72	36	<1,000 g repeat 3 weeks 1,000–1,499 g repeat 2 weeks	≥25.0	≥13–24.9	>120 h and 2nd cards (≥10.0)	Historically included comparison to expected CH population frequency
South Australia	At or near 48	36	<1,500 g repeat 10 and 30 days (or at discharge)	≥20.0	≥12–14.9 request routine recollection ≥15–19.9 immediate recollection	>120 h (≥8.0)	Historical calculation of centiles values and monthly monitoring TSH values of confirmed cases
Western Australia	48–72	24	≤1,500 g repeat screen 14 days ≤1,000 g repeat again 28 days	≥20.0	≥12.0–19.9	24–72 h (≥12.0) 72–96 h (≥9.0) ≥96 h (≥7.0)	Repeat card cutoff aim 0.1% CH repeat card rate, overall PPV 40% Direct referral cutoff aim 90% abnormal TFTs at referral

[a]Samples are tested by the screening laboratories at all ages but repeat cards are requested if collected prior to the earliest acceptable age.

Table 2: Participation in quality assurance programmes by Australasian NBS programmes for congenital hypothyroidism.

Screening programme	External quality assurance programme enrolment	Internal quality control materials	Need for additional EQA/IQC material
New Zealand	CDC, RfB, RCPAQAP	Kit controls and CDC samples	No
Queensland	CDC, RCPAQAP	Kit, in-house controls and CDC samples	No
New South Wales	CDC, RCPAQAP	Kit controls and CDC samples	No
Victoria	CDC, RCPAQAP	Kit controls	Yes, third party QC at decision level 10–20 mIU/L blood
South Australia	CDC	Kit and in-house controls	No
Western Australia	CDC, RCPAQAP	Kit controls and CDC samples	No

CDC, Centre for Disease Control and Prevention (Proficiency and QC); RfB, Reference Institute for Bioanalytics; RCPAQAP, Royal College of Pathologists of Australasia Quality Assurance Programs (bloodspot programme); EQA, external quality assurance; IQC, internal quality control.

Programmes (EQA) (Table 2), with the majority enrolled in both the Centers for Disease Control and Prevention (CDC) and Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP) schemes.

Post-analytical

All programmes report a TSH value above which the baby is referred for clinical assessment and collection of formal thyroid function tests (TSH cutoff, Table 1). In addition, five programmes (excepting Queensland) have a lower cutoff; whereby a second dried blood sample is requested from babies with TSH levels between the lower and higher cutoffs (sometimes referred to as a borderline-positive screen result). Five programmes modify TSH cutoffs for postnatal age (excepting Queensland), such that lower cutoffs are used when interpreting TSH levels on samples collected from older babies. The determination of the TSH cutoffs by programmes varies significantly with adopted strategies including historical review of clinical outcome data, statistical analysis of newborn cohorts, and the integration of both these strategies.

All programmes include the numerical TSH concentration in the written report, with the exception of New Zealand which may provide this verbally at the time of

Table 3: Reporting protocols and outcome review mechanisms in Australasian NBS programmes for congenital hypothyroidism.

Screening programme	Are numerical TSH concentrations reported?	Are screen-negative results reported?	How does the laboratory collect clinical outcome data on referred babies?	What criteria are used to confirm a diagnosis of CH?
New Zealand	Not reported numerically in written reports	Yes, reported to individual requestor	Send outcome form to referred doctor	Biochemistry, imaging (if available) and whether levothyroxine treatment commenced
Queensland	Yes, reported as mIU/L blood	No	Email treating doctor to request follow-up TFT results, scan results and information on treatment	Biochemistry, imaging (if available) and whether levothyroxine treatment commenced
New South Wales	Yes, reported as mIU/L blood	Yes, fortnightly summary report sent to birth hospital	Send outcome form to referred doctor	Biochemistry, imaging (if available) and whether levothyroxine treatment commenced
Victoria	Yes, reported as mIU/L blood	Yes, weekly summary report sent to birth hospital	Send outcome form to referred doctor	Biochemistry, imaging (if available)
South Australia	Yes, reported as mIU/L blood	Yes, summary report sent to birth hospital	Report requests notification of additional testing to confirm CH outcome	Biochemistry, imaging (if available)
Western Australia	Yes, reported as mIU/L blood	Yes, fortnightly summary report to birthing centre	Referrals followed to initial TFT outcome (same laboratory) Annual review with paediatric endocrinologists to determine final clinical outcome	Counted as CH case if ongoing levothyroxine requirement age 2 years

notification of screen-positive results (Table 3). Screen-negative results are notified as for other laboratory test results by all programmes except Queensland (not reported).

Although all NBS programmes collect clinical outcome data, the mechanism to achieve this – including form type, data fields, and collaboration with clinicians – varies between programmes. The criteria used by the programmes to confirm a diagnosis of CH includes a combination of clinical data such as commencement on levothyroxine, formal confirmatory thyroid function tests, and radiological evidence of thyroid abnormalities (Table 3). All programmes define cases based on information available after the initial clinical assessment, with the exception of Western Australia where the definition is dependent on on-going levothyroxine treatment at age 2 years. Missed CH cases (screen-negative but subsequently identified to have congenital hypothyroidism) are generally reported back to the NBS programme by clinicians, though there is some uncertainty about whether all missed cases are identified and reported. When informed of missed CH cases, all regional NBS laboratories retrieve and re-test original samples.

Five-year screening performance metrics are summarised in Table 4. Over this period, screening TSH cutoffs have remained broadly consistent but did include minor adjustments to align with population centiles, in particular with the transition from AutoDELFIA to Perkin Elmer GSP TSH platforms. CH incidence, based on the local case definition, varies from approximately 1:1,300 to 1:2,000 babies screened and is highest in New South Wales, despite a relatively low recall rate (0.10%). CH incidence is lowest in Western Australia where the case definition excludes transient disease, despite a relatively high recall rate (0.20%). The reported rate of borderline-positive TSH results leading to second card request varies fivefold, although for the two programmes with the lowest rates of second card request this count excluded borderline-positive results in babies following low birth-weight collection protocols and from whom further samples were expected. The rate of screen-positive results leading to direct referral is highest (0.11%) in Queensland where there is no separate borderline-positive protocol. CH screen positive predictive values vary between 38.3 and 77.1% (Table 4) for programmes that count CH cases based on clinical information available in the newborn period and was lowest (23.6%) in Western Australia where only permanent disease is counted.

Overall, paediatric endocrinologists are highly involved in CH NBS, including programme governance (for example, membership of advisory committees), with the exception of South Australia where the follow-up care of babies with CH is instead provided by metabolic physicians (Table 5). However, in general the approach to review of the CH screening algorithm (including frequency of review and criteria to initiate changes) is not well specified or consistent between programmes.

Discussion

The practice of NBS is well-established in Australia and New Zealand. Six screening laboratories provide testing as outlined in Figure 1 and there is close to 100% acceptance by the population. CH NBS is evaluated by regular monitoring of screening metrics. As part of this comparative project, all regional screening laboratories provided CH summary data over a 5-year period (Table 4). The current incidence of screen-detected primary CH varies amongst the programmes from approximately 1:1,300 to 1:2,000. There is no *a priori* reason for this difference (for example regional iodine supply or genetic susceptibility) although

Table 4: Australasian CH newborn screening programme metrics 2016–2020.

Screening programme	No. babies screened	CH borderline-positive (second card requests, %)	CH screen-positive direct referrals, %	Screen-detected CH cases	Screen-negative CH cases	Recall rate %	PPV %	CH incidence
New Zealand	293,218	144[a] (0.05%)	88 (0.03%)	146	2	0.08	62.9	1:2,008
Queensland	316,856	92 (0.10%)[c]	355 (0.11%)	171	1	0.11	38.3	1:1,853
New South Wales	509,859	148[a] (0.03%)	354 (0.07%)	388	3	0.10	77.3	1:1,314
Victoria	393,365	305 (0.08%)	369 (0.09%)	246	3	0.17	67.0	1:1,599
South Australia	136,281	89 (0.07%)	49 (0.04%)	71	0	0.11	51.4	1:1,919
Western Australia	167,779	267 (0.15%)	85 (0.05%)	83[b]	0	0.20	23.6	1:2,021

[a]Count excludes borderline-positive results in babies following low birth-weight collection protocols and from whom a further sample is expected. [b]CH cases defined as those remaining on thyroxine treatment aged 2 years, differing to the other programmes which define cases based on clinical information available in the newborn period. [c]Requests for second cards occurred only from January 2016 to August 2017, the number is the total requests but percentage calculated for the number of babies screened during this time interval only.

Table 5: Involvement of Paediatric Endocrinology (PE) in newborn screening for CH in Australasia.

Screening programme	How are paediatric endocrinologists (PEs) involved in the screening programme?	How is the CH screening algorithm reviewed?
New Zealand	PE on NBS technical working group, national screening programme communicates with regional paediatricians through regular meetings and updates. All disease-probable referrals referred with direct input of PE, directed (as possible) to nominated paediatrician at regional hospitals or PE as available.	3 yearly protocol review based on screening metrics plus feedback from clinicians. Approval for change comes from Ministry of Health, as advised by technical working group.
Queensland	PE copied into every notification to clinicians. The PE is contacted to clarify an uncertain diagnosis and when follow-up data is not available.	Reviewed on an ad hoc basis.
New South Wales	Refer possible CH to general paediatricians rather than PEs. PEs on expert Ministry of Health advisory group. Liaise with PEs periodically as required.	Annual analyte review meeting of screening metrics, feedback from clinicians, new research and recommendations. Changes adopted by consensus.
Victoria	Annual CH report generated and sent to PEs at the two major children's hospitals.	No set frequency.
South Australia	PE not directly involved in CH screening.	Review of reference intervals and action limits require sign-off by genetic pathologist and clinical scientist.
Western Australia	Single tertiary PE service – directly involved in recall, assessment and outcome review all referred babies with possible CH. PEs represented on NBS committee.	Annually and as required. Changes to direct referral cutoff discussed with and authorised by PE service.

the lowest prevalence is reported by a programme (Western Australia) which only counts permanent disease as determined by a trial off levothyroxine therapy at about 2 years of age. Other clinical centres follow similar rationales for trialling children off levothyroxine therapy at 2–3 years of age [17] – for example low maintenance levothyroxine dose – but this information is not systematically collected by the screening programme. The difference in incidence is significant and suggests either that some infants are missing out on the benefit of screening or some are treated unnecessarily. It should be noted that screening programmes are principally designed to detect clinically significant biochemical disease in the newborn period and not necessarily to differentiate transient from permanent forms of congenital hypothyroidism. The contribution from environmental and ethnic factors (amongst others) to the higher reported incidence rate from the New South Wales screening programme cannot be excluded. Lower thresholds for levothyroxine treatment (and therefore case counting), may also be a factor.

The difference in incidence may be partly due to the use of different screening cutoffs. The cutoff is the TSH level above which an additional action is requested on the baby. This includes both direct clinical referral and request for a repeat sample (sometimes called a borderline result, but counted as a positive screen by all programmes). Cutoffs are selected to detect as much clinically significant disease as possible whilst minimising harms caused by false positive results and possible over-diagnosis. TSH cutoffs vary worldwide and have generally decreased over time [21, 22], despite uncertain benefit associated with the detection of increasingly mild and subclinical cases [1, 23].

Australasian screening TSH cutoffs are relatively high as compared with reported international values [24]. Several non-Australasian programmes have demonstrated increased detection of permanent CH – with an acceptable recall rate for the programme – associated with a lower TSH cut-off [25, 26]. Furthermore some (but not all) programmes adjust cutoffs dependent on the age of the baby, reflecting lower normal values as the TSH surge at birth subsides. Numeric TSH values within our region are directly comparable between laboratories as not only is the same platform used but also the same External Quality Assurance Programmes in which all laboratories exhibit consistently good performance. Whilst the range (TSH ≥12–15 mIU/L blood) may not appear great, it would be anticipated to impact screening metrics, that is, lower TSH cutoffs associated with a higher recall rate and increased

incidence at the expense of a worse positive predictive value. However, the expected associations were not consistently observed.

Cutoff values for programmes are determined in a variety of ways including historical values, local outcome studies [27, 28], alignment with population centiles and adjustment to other monitoring parameters (for example, repeat card rates). Alignment of cutoff values to defined metrics – for example centiles, and multiples of the median (MoM) – would allow programmes to easily determine cutoff levels at different ages and monitor for drift while also facilitating regional comparison.

The difference in incidence is also at least partially caused by differences in disorder definition, most notably whether permanent disease only is counted or, more commonly babies treated for the condition from birth. In addition, clinicians may utilise a variable diagnostic and treatment threshold for screen-detected babies with mildly elevated serum TSH levels. There is an argument to be made for programmes to adopt a single clear disorder case definition for the purpose of regional and international comparison while potentially using another definition for local purposes. In particular, an agreed screen positive case definition would facilitate meaningful comparison of programme screen positive predictive values.

Screening pathways must suit local circumstances. The direct referral threshold for term newborns under 1 week of age varies between TSH concentrations ≥12–25 mIU/L blood across regional laboratories, with all but one programme utilising an additional (lower) borderline-positive cutoff leading to request of a repeat screening specimen. This practice is designed to reduce referral and medicalisation of babies with false-positive screen results. However, risk of loss to follow-up may mean that it is preferable to refer babies at a lower TSH level.

All Australasian screening programmes have protocols for routine repeat sample collection in low birth weight or premature babies, which increase the reliability of CH detection where hypothalamic-pituitary immaturity limits detection at 48 h [29]. Although broadly similar, recommended re-collection intervals and the maximum number of routine samples vary between Australasian screening programmes. These protocols have been adapted and implemented separately by screening laboratories over the past decade however the practice has not been comprehensively evaluated. Healthcare professionals move around the region and harmonisation of protocols would minimise confusion in neonatal units and give a larger data set for outcome studies.

Laboratory reporting practice of screen-positive and screen-negative CH results is similar across the region. All laboratories include numerical TSH concentrations in whole blood units when reporting screen-positive results, either verbally or in the written report. This can give clinicians an indication of likely disease severity and can assist with planning the urgency of review, especially if the report provides the clinician with an approximate serum equivalent value. Most laboratories also report screen-negative results, most often to the birth hospital, which can provide an opportunity to identify babies in whom screening has not occurred. Matching screens to a denominator of national or state-wide births to identify unscreened babies can be challenging dependent on the timeframe of birth notification and can be more efficient and effective at the birth facility level.

Local healthcare factors mean that screen-positive results are referred to a variety of clinicians, including paediatricians and paediatric endocrinologists working across both public and private health systems. Provision and use of guidelines and/or the inclusion of a paediatric endocrinologist in the referral process can support the consistency of care provided. Locally produced clinical guidelines are available as are international consensus guidelines produced with local input [17, 19, 30]. Two such guidelines covering the screening, investigation, management, and therapeutic monitoring of children with CH, principally focused on the follow-up of affected babies, have recently been published [17, 30]. The Clinical and Laboratory Standards Institute (CLSI) is a global leader in laboratory standardisation and is currently finalising a CH NBS guidance document (NBS10 – Newborn Screening for Congenital Hypothyroidism). This will include greater detail of newborn screening laboratory processes, but should be interpreted in the context of local technical, logistical and regulatory requirements.

Clinical services have knowledge of missed cases, the utility of screening amongst those seen in clinic, as well as the overall impact on families, and can therefore add great value to screening performance review [31, 32]. Most Australasian screening programmes involve nominated paediatric endocrinologists in advisory groups or invite review of monitoring reports. Clinicians are routinely asked to provide follow-up information on referred babies with possible CH, although the level of detail collected varies between NBS programmes. To address this, the APEG LNBS subcommittee is currently developing a regional "CH outcome form." Likewise, knowledge of missed cases is a key component of monitoring screen performance but it is unclear whether these are comprehensively reported to screening programmes. Within our region, there is an opportunity to link NBS data to existing dynamic patient registries, which could enhance the feedback process for

individual cases as well as provide information on long-term outcomes.

Evaluation of screening programmes for rare disorders is problematic and requires sufficient numbers to draw valid conclusions. Most programmes in the region do not have sufficient numbers in a reasonable time period hence the ability to aggregate data from programmes would facilitate such studies. To make valid aggregations and comparisons the following is necessary: comparability of numeric results (currently true due to use of the same analytical platform and rigorous quality assurance); harmonisation of baby age at sample collection (largely true for newborns); harmonisation of cutoffs to a statistical metric e.g. centile and use of the metric to calculate different cutoffs for different ages; consideration to inclusion or otherwise of low birthweight babies in studies, or not, and if so harmonisation of protocols for sample collection in this group; harmonisation of disorder definition; and harmonisation of outcome data collection including disorder aetiology where known.

Conclusions

Overall, NBS for CH across Australasia is performed to a high standard with the same fundamental approach and goals. The outcome of this comprehensive survey demonstrates the significant commonality and also areas for improvements in harmonisation of CH NBS. The pre-analytical and analytical areas demonstrate significant harmonisation but the post analytical phase demonstrates discordance in the decision limits and action applied between the screening programs. Furthermore, reported screening performance metrics should be interpreted with caution in the absence of an agreed CH case definition. To our knowledge this is the first report demonstrating the state of harmonisation of NBS for CH in the region and provides a framework for discussion moving forward. In this, the 50th anniversary of NBS for CH, it is important to reflect on the significant contribution that this public health initiative has made to paediatric medicine. Laboratory-clinician cooperation, and harmonisation efforts such as this are essential for the full benefits of screening to be realised.

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The local Institutional Review Board deemed the study exempt from review.

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