CH-C patients who were missed in the screening, some unrecognized cases with isolated hypothyroidism may be present, and early death of patients with multiple pituitary hormone deficiencies may have been ignored. Thus, we cannot directly compare the performance of our system to that used in The Netherlands.

Setting a higher cutoff for FT_4 has both advantages and disadvantages. At a cutoff of 0.9 ng/dl instead of 0.7 ng/dl, the estimated sensitivity rises to 81.8%; it may increase three times more considering the requests for a second filter paper test (retesting ratio, 0.50%). In Sapporo city, the FT_4 cutoff has been set to 1.0 ng/dl (7); six CH-C patients were identified through the screening over 4 years, and the prevalence of CH-C was reported to be 1 in 13 872 live births (Table 3). If a cutoff of 0.7 ng/dl were to be applied to their cohort, only one of six CH-C patients would have been detected by screening. Thus, resetting the cutoff value to 0.9 ng/dl (or higher) may be necessary. This level is in accordance with the FT_4 cutoff 0.93 ng/dl used in The Netherlands for the diagnosis of CH-C (5) and is ~ -2 S.D. of both the reported cord blood values (23) and our FT_4 values (Fig. 3) for normal newborns.

Adequacy of the retesting ratio depends on many factors including population size, system performance parameters such as sensitivity and PPV, and local economic conditions. The retesting ratio was as high as 0.76% in Sapporo city, due to a higher cutoff value and inclusion of low-birth weight newborns. This ratio may be acceptable in a smaller city but may not be suitable for Kanagawa prefecture. The estimated retesting ratio of 0.50% (3735 samples during 10 years) resulting from a cutoff of 0.9 ng/dl may be more acceptable than a ratio of 0.76%. A comparative figure for retesting for congenital adrenal hyperplasia in Kanagawa prefecture is 0.3%. Because FT_4 determinants did not change significantly according to collection dates (Fig. 4), as shown also in normal newborns (13), differential cutoff values according to the sampling dates are not expected to reduce the retesting ratio.

Another problem is the introduction of an immediate evaluation system to facilitate early treatment of CH-C patients, especially for those with multiple pituitary hormone deficiencies. As stated in the Subjects and methods section, unless two consecutive tests reveal low FT_4 values, newborns will not be subject to a thorough evaluation in our system. The aim of performing a second sampling is to exclude false positives. Indeed, during the study period, second samples were requested for 1220 newborns, but only 113 of these newborns were sent for thorough evaluation and 1107 false-positive cases were eliminated (Table 3). Even with a cutoff of 1.0 ng/dl, the number of newborns sent for evaluation will increase minimally (79 additional cases across 10 years). We retrospectively analyzed the impact of introduction of an immediate evaluation system in which newborns with FT_4 lower than 0.5 ng/dl (6.4 pmol/l) will be immediately evaluated. Seven CH-C patients, including three patients in group M, would have been diagnosed without delay. However, according to our simulation, this strategy will create a false-positive number of more than 200 over 10 years, with a PPV of 2.8%. The question of whether this figure is reasonable is beyond the scope of our study. Nevertheless, we plan to improve our screening strategy by considering scientific, economical, ethical, and political issues.

In conclusion, measurement of FT_4 in dried blood spots on filter paper is suitable for newborn screening for CH-C; moreover, the combined primary TSH–FT_4 system applied in Kanagawa prefecture identified a significant number of CH-C patients before they manifested clinical symptoms. The survey identified 24 CH-C patients, 14 of whom had multiple pituitary hormone deficiencies, yielding an incidence rate of CH-C of 1 in 30 833 live births. Screening sensitivity was calculated to be 59.1%, based on 13 true-positive cases and nine false-negative cases, with a cutoff of 0.7 ng/dl of FT_4. A more appropriate (higher) FT_4 cutoff value and proper implementation of the screening would facilitate early detection of CH-C cases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

M Adachi, Y Yamagami, and F Hirahara conceptualized and designed the study. M Adachi and A Soneda contributed to the data collection, analysis, and writing of the manuscript. Y Asakura and K Muroya contributed to preparation of the manuscript by critically analyzing it.

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