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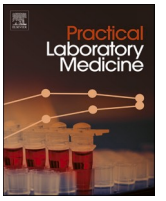

Feasibility of using real-world free thyroxine data from the US and Europe to enable fast and efficient transfer of reference intervals from one population to another

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ABSTRACT

Objectives: The direct approach for determining reference intervals (RIs) is not always practical. This study aimed to generate evidence that a real-world data (RWD) approach could be applied to transfer free thyroxine RIs determined in one population to a second population, presenting an alternative to performing multiple RI determinations.

Design and methods: Two datasets (US, n = 10,000; Europe, n = 10,000) were created from existing RWD. Descriptive statistics, density plots and cumulative distributions were produced for each data set and comparisons made. Cumulative probabilities at the lower and upper limits of the RIs were identified using an empirical cumulative distribution function. According to these probabilities, estimated percentiles for each dataset and estimated differences between the two sets of percentiles were obtained by case resampling bootstrapping. The estimated differences were then evaluated against a pre-determined acceptance criterion of ≤7.8% (inter-individual biological variability). The direct approach was used to validate the RWD approach.

Results: The RWD approach provided similar descriptive statistics for both populations (mean: US = 16.1 pmol/L, Europe = 16.4 pmol/L; median: US = 15.4 pmol/L, Europe = 15.8 pmol/L). Differences between the estimated percentiles at the upper and lower limits of the RIs fulfilled the pre-determined acceptance criterion and the density plots and cumulative distributions demonstrated population homogeneity. Similar RI distributions were observed using the direct approach.

Conclusions: This study provides evidence that a RWD approach can be used to transfer RIs determined in one population to another.

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1. Introduction

Measurement of free thyroxine (FT4), in combination with other thyroid hormones, is used to diagnose and manage many thyroid disorders [1]. To determine whether an individual's FT4 levels are outside of the expected, non-pathologic range it is necessary to determine an appropriate reference interval (RI) in a healthy reference population [2,3]. Ideally, RIs are determined using a direct approach, as set out by the Clinical and Laboratory Standards Institute (CLSI) EP28-A3c guidelines [4]. This involves collecting ≥120 samples from carefully selected, disease-free volunteers whose baseline characteristics reflect the population in question [3–6]. Data are collected from the volunteers with the sole purpose of defining the RI [7]. It is recognised that this approach is time consuming and often impractical, particularly given that RIs should be established for each population subgroup (e.g. according to age, ethnicity, biological sex, geographic region or certain clinical conditions) [2–4,8,9].

Using an indirect approach may streamline the process of determining various RIs to be used for the interpretation of laboratory test results. For example, the refineR algorithm has been applied to a range of analytes and produced similar RIs when using real-world data (RWD) to those established by direct methods [10,11]. However, while determining RIs using pre-existing measurements already stored in a database may be less time consuming than the direct approach, steps should be taken to limit confounding factors and ensure accurate RI determination [7,12]. These may include limiting the number of people with possible disease in the dataset by excluding data from specific populations or settings [7].

The aim of this study was to generate evidence that a RWD approach could be applied to transfer FT4 RIs determined in a US population to a European population, enabling the use of the same universal RIs for populations in different geographical locations and presenting an alternative to multiple RI determination studies using the direct approach. More generally, the approach described might be applicable to a variety of other biomarkers and populations, reflecting different subgroups.

2. Methods

This study was designed following the US Food and Drug Administration (FDA) 'Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices' Guidance [13] and 'Framework for the FDA's Real-World Evidence Program' [14].

2.1. Equivalency of FT4 RI distributions determined using RWD from the US vs. Europe

Two datasets were created from a large database of existing RWD collected from the US and Europe during routine clinical care. One dataset comprised n = 10,000 FT4 measurements (Elecsys® FT4 II assay, Roche Diagnostics International Ltd, Rotkreuz, Switzerland) from 11 sites in the US (Supplementary Table 1). The other dataset comprised n = 10,000 FT4 measurements (Elecsys FT4 III assay, Roche Diagnostics International Ltd, Rotkreuz, Switzerland) from two sites in Europe: Hospital Universitario Fundación Jimenez Diaz, Madrid, Spain, n = 5000 and MVZ Labor Dr. Limbach Heidelberg, Germany, n = 5000. To avoid selection bias, samples were randomly selected according to the FDA Guidance and Framework [13,14], and were selected from each region equally. Supplementary Table 2 provides a breakdown of samples according to the assay and analyser used. All FT4 immunoassay generations are traceable to each other.

Descriptive statistics, density plots and cumulative distributions were produced for both datasets and comparisons made. The cumulative probabilities at the lower and upper limits of the RI were identified using an empirical cumulative distribution function (R Core Team software, version 4.1.0). According to these probabilities, estimated percentiles for each dataset, estimated differences between the two sets of percentiles and associated 95% confidence intervals (CIs) were obtained using case resampling bootstrapping methods with n = 1000 replicates. Bootstrapping involved resampling the data with replacement, with the size of the resample set equal to the size of the original dataset, and computing percentiles from the resample set. This process was repeated 1000 times to improve precision. A statistically sufficient sample size of 10,000 was established through this analysis.

The estimated differences between the lower and upper limits of the RIs from the US vs. Europe were permitted to differ by a predetermined acceptance criterion of ≤7.8%, the inter-individual biological variability [15].

2.2. RWD management

The RWD database comprised anonymised data that were not associated with patient details (e.g. disease status, demographic information), other than location and date of testing. RWD were transferred via a connectivity protocol that enabled bidirectional data exchange between Roche and external collaborators. This allowed Roche to monitor performance and quality in real time and offer support such as remote troubleshooting, software updates or security patches. It also provided access to an electronic data repository (e-Library), allowing external laboratories to download up-to-date product information. The data transfer process is validated for accuracy, reliability, consistent and intended performance and the ability to discern invalid or altered records, to ensure that transferred data are complete and correct. Raw data were retrieved from the RWD database; no filtering was applied for sample data transfer.

2.3. Validation of the RWD approach using the direct approach in a US and European population

The direct approach was used to determine FT4 RIs in the US and Europe, to validate the RWD approach. FT4 RIs were determined using FT4 measurements from apparently healthy volunteers from the US (n = 150) and Europe (n = 150). Inclusion and exclusion

criteria are provided in Supplementary Table 3. FT4 concentrations were measured at Roche Diagnostics GmbH, Penzberg, Germany using the Elecsys FT4 IV assay on the cobas® e 411 analyser (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) to ensure all samples were analysed consistently and avoid bias. Descriptive statistics and percentiles were generated for the two populations and comparisons made, focusing on the lower and upper RI limits. Boxplots showing distribution summaries for the US and European populations were produced.

3. Results

3.1. Equivalency of FT4 RI distributions determined using RWD from the US vs. Europe

Descriptive statistics for FT4 data from existing RWD from people in the US and Europe are shown in Fig. 1A. Similar descriptive statistics were observed for both populations (mean: US = 16.1 pmol/L, Europe = 16.4 pmol/L; median: US = 15.4 pmol/L, Europe = 15.8 pmol/L).

The estimated percentiles for each dataset and the estimated absolute differences between the two at the upper and lower limits of the RIs are shown in Fig. 1B. The differences between the estimated US and European percentiles at the upper and lower limits of the RIs fulfilled the pre-determined acceptance criterion of ≤7.8%, meaning the two RIs are comparable.

The distribution of FT4 measurements from existing RWD from the US and Europe are shown in Fig. 1C and D. The density plots and

A

Descriptive Statistics, pmol/L	US (Elecsys FT4 II) n = 10,000	Europe (Elecsys FT4 III) n = 10,000
Mean	16.1	16.4
Median	15.4	15.8
Minimum[a]	1.30	0.5
Maximum[b]	100	100
SD	5.96	4.33

B

Percentiles	Estimated Values, pmol/L			Pre-determined Acceptance Criterion[c] Met?
	US (95% CI)	Europe (95% CI)	Absolute Difference (95% CI)	
2.5%	9.37 (9.08–9.68)	10.7 (10.6–10.9)	NA	NA
9.76%	11.9 (11.8–12.0)	12.5 (12.4–12.6)	0.600 (0.500 to 0.800)	Yes
25%	13.6 (13.5–13.6)	14.0 (14.0–14.1)	NA	NA
50%	15.4 (15.3–15.6)	15.8 (15.8–15.9)	NA	NA
75%	17.6 (17.5–17.8)	18.0 (17.9–18.0)	NA	NA
93.03%	21.6 (21.2–21.8)	21.7 (21.5–21.9)	0.200 (–0.100 to 0.500)	Yes
97.5%	25.1 (24.6–25.6)	25.0 (24.5–25.4)	NA	NA

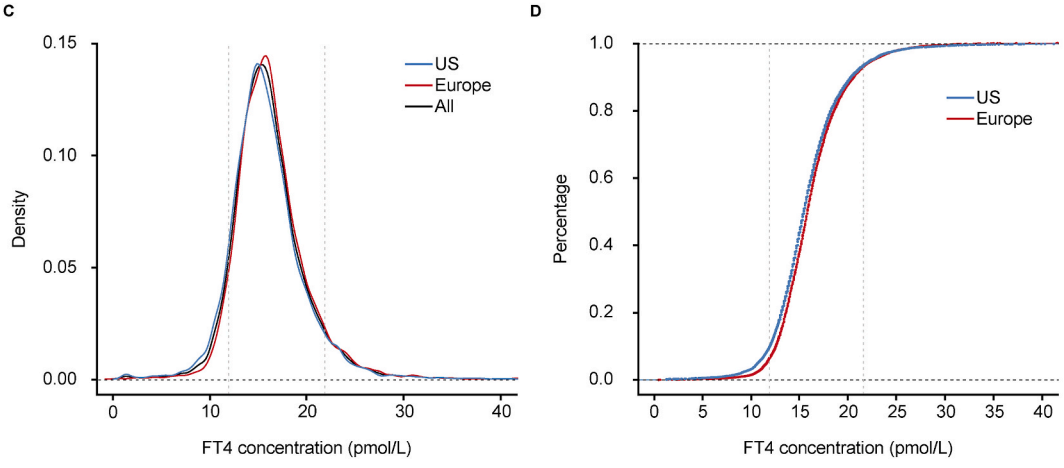

Fig. 1. FT4 data from existing RWD sources according to site. A) descriptive statistics of FT4 values (US, n = 10,000; Europe, n = 10,000 samples); B) absolute estimated FT4 values (US, n = 1000; Europe, n = 1000 bootstrapped samples); C) density plots showing distribution of FT4 values (US, n = 10,000; Europe, n = 10,000 samples); D) cumulative distributions of FT4 values (US, n = 10,000; Europe, n = 10,000 samples). [a]The minimum value measured in the European dataset has been rounded up from 0.499 pmol/L to 0.5 pmol/L to reflect the lower end of the measuring range of the Elecsys FT4 III, which is 0.5 pmol/L [16,17]. The minimum value measured in the US dataset was 1.3 pmol/L, which is the lower end of the measuring range of the Elecsys FT4 II [18]. [b]The maximum values measured in the European and the US datasets have been rounded down from 101 pmol/L to 100 pmol/L to reflect the upper end of the measuring ranges of the Elecsys FT4 II and the Elecsys FT4 III, both of which are 100 pmol/L [16–18]. [c]The pre-determined acceptance criterion only applied to the 9.76th and the 93.03rd percentiles; the percentiles closest to the lower and upper end of the RI. CI, confidence interval; FT4, free thyroxine; NA, not applicable; RI, reference interval; RWD, real-world data; SD, standard deviation; US, United States.

cumulative distributions demonstrate population homogeneity between the US and Europe, particularly at the lower and upper limits, indicating a similar RI distribution for the two populations. A small peak observed on the left-hand side of the density plot for the US population was not present for the European population. This arises because the lower end of the measuring range for the Elecsys FT4 II assay used in the US is 1.3 pmol/L (the limit of quantification) [18], whereas the lower end of the measuring range for the Elecsys FT4 III assay globally (excluding the US) is 0.5 pmol/L (the limit of detection) [16,17], so samples from the US dataset with a concentration of <1.3 pmol/L are reported as having a concentration of 1.3 pmol/L.

3.2. *Validation of the RWD approach using the direct approach in a US and European population*

Fig. 2A provides the descriptive statistics and percentiles for FT4 measurements from samples collected from the US and Europe. Similar descriptive statistics were observed for the two populations. The CIs of the percentiles overlapped, demonstrating population homogeneity, particularly at the lower and upper limits (2.5% [95% CI]: US = 11.5 [9.43–12.0] pmol/L, Europe = 11.8 [8.98–12.6] pmol/L; 97.5% [95% CI]: US = 20.4 [18.8–24.4] pmol/L, Europe = 20.0 [19.1–21.4] pmol/L).

Fig. 2B is a boxplot showing the distribution of FT4 measurements in the US and Europe. A slightly lower measurement distribution was observed in data collected from the US vs. Europe (mean 15.0 vs. 15.9 pmol/L; median 14.8 vs. 16.1 pmol/L, respectively).

4. Discussion

This study aimed to generate evidence that a RWD approach could be used to transfer FT4 RIs determined in the US to Europe. The percentiles corresponding to cumulative probabilities of the two populations at the upper and lower RI limits differed by less than the inter-individual biological variability of ≤7.8% [15]; therefore, the pre-determined acceptance criterion was met, showing that the variability between the two populations examined was less than the pre-determined variability between individuals. As such, we have shown that RIs determined in the US using RWD may be transferrable to Europe. The pre-determined acceptance criterion applied was conservative; the allowable total error of 9.5% (the tolerable limit of the combined imprecision and bias) could have been applied instead [15]. In addition, different inter- and intra-individual biological variability are reported [15,19], which could also have been applied.

To validate our findings, the direct approach, as per CLSI EP28-A3c [4], was used and comparable distributions and RI limits were observed for the US and Europe. This reinforces the concept that RIs determined in one population can be transferred to another. Furthermore, these results indicate that additional sample collection required for the direct approach can be replaced by pre-existing RWD.

Similar results were obtained for both populations using RWD, which were generated using the Elecsys FT4 II assay in the US and the Elecsys FT4 III assay in Europe. These findings are supported by a method comparison study that reported high comparability between the US when using the Elecsys FT4 II assay and Europe when using the Elecsys FT4 III assay [20]. Similar FT4 upper and lower RI limits have also been measured (using the Elecsys FT4 III assay on cobas 6000 and 8000 analysers) in a Swiss population using the direct method (2.5% [95% CI]: 11 [10.7–11.1] pmol/L, 97.5% [95% CI]: 22.2 [21.7–22.6] pmol/L) and an alternative method using data collected during routine clinical practice (2.5% [95% CI]: 11 [10.1–11.3] pmol/L, 97.5% [95% CI]: 21.5 [19.2–21.8] pmol/L) [17]. For the direct method, RIs were determined using measurements from patients with normal thyroid-stimulating hormone (TSH) results, whereas the alternative method used measurements from patients with normal and abnormal TSH results. This study provides

A

Descriptive Statistics	US n = 150	Europe n = 150
Mean, pmol/L	15.0	15.9
Minimum, pmol/L	9.43	8.98
Maximum, pmol/L	24.4	21.4
Range, pmol/L	15.0	12.4
SD, pmol/L	2.18	2.15
CV, %	14.5	13.6
Percentiles (95% CI), pmol/L		
2.5%	11.5 (9.43–12.0)	11.8 (8.98–12.6)
5%	11.9 (10.8–12.2)	12.4 (11.4–12.9)
10%	12.4 (11.9–12.9)	13.2 (12.4–13.5)
25%	13.6 (13.1–13.9)	14.1 (13.7–14.7)
50% (median)	14.8 (14.4–15.3)	16.1 (15.6–16.5)
75%	16.0 (15.7–16.8)	17.2 (16.9–17.8)
90%	17.2 (16.9–18.8)	18.8 (18.1–19.3)
95%	18.8 (17.6–22.0)	19.3 (18.9–20.4)
97.5%	20.4 (18.8–24.4)	20.0 (19.1–21.4)

B

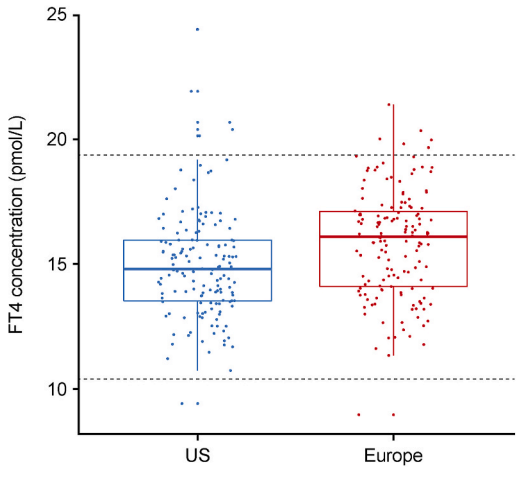

Fig. 2. FT4 concentrations measured in samples from the US (n = 150) and Europe (n = 150) using the Elecsys FT4 IV assay. A) descriptive statistics and percentiles for FT4 measurements; B) boxplots showing distribution of FT4 measurements. CI, confidence interval; CV, coefficient of variation; FT4, free thyroxine; SD, standard deviation; US, United States.

evidence that RIs can be transferred from one population to another However, differing RI distributions in the US and Europe have been reported for insulin-like growth factor-I using similar methods to those described in our study [21]. This highlights the importance of verifying the transferability of RIs to different populations.

A strength of this study is that a large dataset (n = 20,000) was used, which increases its reliability and robustness. The study was also designed following the FDA Guidance and Framework [13,14], which again increases reliability and robustness. To strengthen the findings, the results of the RWD method were validated using the direct method; however, further studies investigating additional markers and verifying the broader validation of this approach are needed to generalise the findings.

A limitation of this study is that certain demographic factors were not considered. The samples collected for the direct approach were from adults only (22[US]/18[Europe]–79 years). Whilst FT4 concentrations vary between babies, children and adults [22], there is no evidence that FT4 concentrations vary substantially amongst adults of different ages [23], therefore, the direct approach findings should be largely unaffected by the age of the adults in each population. The exact age of the people in the RWD database is unknown and, for the purposes of this study, it was assumed that the age distribution was similar in both populations examined. This study also did not record the biological sex of the people included, as evidence suggests that biological sex has no significant effect on FT4 levels [23]; additionally, pregnant women were not excluded from the RWD database, and seasonal changes were not accounted for. Where information such as age, biological sex, ethnicity and geographic region are available, meaningful filters could be applied to the RWD [7]. A further limitation is that the European RWD were only collected from two sites, whereas the US RWD were collected from 11 sites around the US. This was for practical reasons and is reflective of the real-world nature of the study.

In summary, this study supports that RIs determined in one population using RWD may be transferrable to a second population. This RWD approach could be a valuable tool and may negate the need for additional sample collections to determine population-specific RIs for some biomarker assays. This approach does not require active sampling so is less burdensome for patients and enables faster determination of RIs, which may in turn reduce the costs associated with determining RIs. Similar approaches could be used to validate RIs for specific sub-populations such as age, ethnicity, biological sex or certain clinical conditions. Future work should look to validate the RWD approach in other populations and biomarkers.

Ethical approval

Data collected from the RWD database were fully anonymised so informed consent was not required; exemption was received from the Western Copernicus Group institutional review board. Local ethics committee approval (Ethik-Kommission der BLÄK, Ethik-Kommission Nr_ 20083) and institutional review board approval (Advarra Institutional Review Board, Pro00047458) was obtained for samples collected for the direct approach.

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CRediT authorship contribution statement

Hedwig Kurka: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Peter Dilba:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Carlos Castillo Perez:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Peter Findeisen:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Ignacio Gadea Gironés:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Alex Katayev:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Laura Rodríguez Alonso:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **André Valcour:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Thorsten Rehberg:** Data curation, Writing – review & editing. **Benedikt Weber:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Horst Donner:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Anja Thorenz:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing..

Declaration of competing interest

Hedwig Kurka, Peter Dilba, Thorsten Rehberg, Benedikt Weber, Horst Donner and Anja Thorenz are employees of Roche Diagnostics GmbH. Alex Katayev and André Valcour are employees of Laboratory Corporation of America Holdings (Labcorp). Ignacio Gadea Gironés, Carlos Castillo Perez, Peter Findeisen and Laura Rodríguez Alonso have no conflict of interest to declare.

Data availability

Requests concerning the data supporting the findings of this study can be directed to rotkreuz.datasharingrequests@roche.com for consideration.

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The Elecsys FT4 IV assay on the cobas e 411 analyser was not FDA-cleared in the US at the time of study development, but it was cleared by the FDA effective 7 April 2023, shortly before manuscript submission.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plabm.2024.e00382.

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