Levothyroxine prescribing and laboratory test use after a minor change in reference range for thyroid-stimulating hormone

Christopher Symonds MD, Gregory Kline MD, Inelda Gjata BSc, Marianne Sarah Rose PhD, Maggie Guo MSc, Lara Cooke MD, Christopher Naugler MD

Cite as: *CMAJ* 2020 May 4;192:E469-75. doi: 10.1503/cmaj.191663

See related article at www.cmaj.ca/lookup/doi/10.1503/cmaj.200511

ABSTRACT

BACKGROUND: Prescribing of levothyroxine and rates of thyroid function testing may be sensitive to minor changes in the upper limit of the reference range for thyroid-stimulating hormone (TSH) that increase the proportion of abnormal results. We evaluated the population-level change in levothyroxine prescribing and TSH testing after a minor planned decrease in the upper limit of the reference range for TSH in a large urban centre with a single medical laboratory.

METHODS: Using provincial administrative data, we compared predicted volumes of TSH tests with actual TSH test volumes before and after a planned change in the TSH reference range. We also determined the number of new levothyroxine prescriptions for previously untreated patients and the rate of changes to the prescribed dose for those on previously stable, long-term levothyroxine therapy before and after the change in the TSH reference range.

RESULTS: Before the change in the TSH reference range, actual and predicted monthly volumes of TSH testing followed an identical course. After the change, actual test volumes exceeded predicted test volumes by 7.3% (95% confidence interval [CI] 5.3%–9.3%) or about 3000 to 5000 extra tests per month. The proportion of patients with newly "abnormal" TSH results almost tripled, from 3.3% (95% CI 3.2%–3.4%) to 9.1% (95% CI 9.0%–9.2%). The rate of new levothyroxine prescriptions increased from 3.24 (95% CI 3.15–3.33) per 1000 population in 2013 to 4.06 (95% CI 3.96–4.15) per 1000 population in 2014. Among patients with preexisting stable levothyroxine therapy, there was a significant increase in the number of dose escalations ($p < 0.001$) and a total increase of 500 new prescriptions per month.

INTERPRETATION: Our findings suggest that clinicians may have responded to mildly elevated TSH results with new or increased levothyroxine prescriptions and more TSH testing. Knowledge translation efforts may be useful to accompany minor changes in reference ranges.

Subclinical hypothyroidism, defined as an increase in serum thyroid-stimulating hormone (TSH) with normal levels of free thyroxine, is common. This biochemical phenotype does not have a matching clinical phenotype by which a clinical diagnosis can be recognized.[1] This entity is referred to as biochemical subclinical hypothyroidism, whereby the TSH lies between the upper limit of the reference range and 10 mIU/L in individuals younger than 65 years of age.[2]

Controversy exists as to the merits of treating biochemical subclinical hypothyroidism.[3–5] Some cross-sectional studies have reported links to a risk of vascular events in subsets of patients with this condition.[6,7] However, the largest prospective studies and pooled data do not support an association with coronary events or with cardiac or total mortality.[8,9] Among larger randomized controlled trials, none have shown that levothyroxine therapy in biochemical subclinical hypothyroidism meaningfully affects clinical end points.[10–12] Furthermore, many patients who initially display biochemical subclinical hypothyroidism will have spontaneous normalization without intervention.[13–15] A recent guideline[16] and a Cochrane systematic review[17] have cautioned against routine use of levothyroxine in such cases, particularly when the TSH is below 10 mIU/L. Clinicians may be reassured about the indication for levothyroxine therapy in patients with serum TSH above 10 mIU/L, given that 97.5% of patients who are free of thyroid disease have a TSH value below this level.[18] Initiation of levothyroxine in

biochemical subclinical hypothyroidism is not always benign, as a substantial proportion of patients are eventually overtreated to the point of causing hyperthyroidism,[19] which may have adverse clinical consequences.[20,21]

The normal range for TSH measurements has previously lacked standardization, but recent harmonization efforts have permitted the adoption of common, assay-independent reference ranges.[22] Population studies excluding people with signs of thyroid dysfunction have suggested that the healthy upper reference limit for TSH is between 3.0 and 4.0 mIU/L.[23] Expert opinion has suggested that a more accurate TSH reference range, with reduced upper limits, be implemented.[18] In cases where the laboratory-specific TSH reference limit historically exceeded 4.0 mIU/L, a change to the new limit of 4.0 mIU/L effectively creates a "new" segment of the population with an abnormal TSH result, whose results would have been considered normal if interpreted in relation to the previous reference range.[24] Apparent clinical effects that are purely artifacts of reference range changes were previously seen in a study of sperm counts, in which an adjustment in the reference range produced the spurious appearance of a population decline in fertility.[25] A similar effect on vitamin D deficiency rates was seen with a change in reference definitions of normality.[26]

We hypothesized that lowering the upper limit of the reference range for TSH (without changing the assay) would lead to an increase in the number of patients receiving levothyroxine, reflecting the tendency of clinicians to offer more levothyroxine prescriptions solely on the basis of a new biochemical abnormality. We also hypothesized that this increase in levothyroxine treatment would result in a secondary increase in the use of thyroid laboratory testing as clinicians began to follow up borderline results or new treatments.

Methods

Study setting

Our sampling frame was the Calgary site of Alberta Precision Laboratories, which is the sole provider of laboratory tests to the Calgary region (estimated catchment area 1.4 million persons) as part of the government-provided health system.

On May 1, 2014, our laboratory changed the upper limit of the reference range for TSH from 6.0 to 4.0 mIU/L as part of a provincial initiative to harmonize reference ranges across laboratories in Alberta. The previous upper reference limit had been unchanged in the preceding 20 years. We determined the monthly rate of TSH testing by the Calgary laboratory in the 4 years before the change in upper reference limit for comparison with the frequency of TSH testing in the 12 months after the change. Because of underlying seasonality in laboratory test volumes,[27] we used historic test volumes to predict TSH volumes using an interrupted time-series approach with the Holt–Winters additive model, presented as stationary R^2 with a mean absolute percentage of error. This model is especially useful in assessing changes in laboratory test-ordering volumes over short periods (< 1 yr) because it controls for both the underlying slope of change in volumes that may be associated with an aging population or with population growth and the marked but predictable monthly variation in test volumes.[28] Using this method, our team has previously investigated the impact of changes in our laboratory's test-ordering practices at monthly time scales.[29,30]

Data sources

To assess the possible change in physician prescribing behaviour related to the change in upper reference limit for TSH, we interrogated the Alberta Health Pharmaceutical Information Network to determine the number and dose of levothyroxine prescriptions recorded in Calgary Zone city pharmacies for the 6-month period from May 1 to Oct. 31 in each of 3 calendar years (2011, 2012 and 2013, when the historical upper limit of the TSH reference range was in effect) for comparison with the same time frame immediately after implementation of the new upper limit in 2014. The Pharmaceutical Information Network is a provincial program that requires all pharmacists working in community locations to report drug dispensing data to the Alberta Ministry of Health for inclusion in a central database. This database has been updated on a daily basis since 2007 and has been estimated to capture 95% of the drugs dispensed outside of the hospital setting, regardless of patients' insurance status[31] (unpublished electronic health record usage statistics, Alberta Ministry of Health, 2016). We subdivided levothyroxine prescriptions after May 2014 into 2 groups: new prescriptions (for patients with no thyroxine prescriptions recorded in the previous 12 mo) and dose increases (for patients with a stable, lower-dose thyroxine prescription recorded repeatedly for at least 24 mo before the date of the upper limit change).

Statistical analysis

To examine changes in the rates of new prescriptions (with 95% confidence intervals [CIs]) within and between each year, we used a Poisson regression model with the number of new prescriptions as the outcome variable and the month (May to October) and year (2011 to 2014) as the predictor variables. We included the population in each year as an offset, to allow estimation of the rate of new and also higher-dose prescriptions per 1000 population. We examined the consistency of monthly prescribing patterns over study years with the likelihood ratio statistic to assess for evidence against overdispersion. We estimated predicted rates from the model with 95% CIs and performed statistical calculations using Stata 11.0 (StataCorp) with $p < 0.05$ set as the level of statistical significance.

Ethics approval

This study was approved by the Calgary Regional Health Ethics Board (approvals REB13-1271 and REB13-0459).

Results

Over the study time frame, between 45 000 and 65 000 TSH tests were performed each month at the Calgary laboratory (Figure 1). In the 4-year period before May 2014, the actual and predicted monthly test volumes followed a tightly correlated pattern. The

high volume of TSH tests and the stability of test numbers over 4 years strengthens this correlation. However, in the year after the change in reference range, a sharp and persistent separation emerged, with actual TSH test volumes exceeding those predicted by 7.3% (95% CI 5.3%–9.3%), or between 3000 and 5000 extra tests per month, as shown graphically in the Holt–Winters time-series model in Figure 1. The time-series model showed a good fit with the data, with stationary R^2 of 0.74 and mean absolute percent error of 2.62 (where a mean absolute percent error less than 10 generally indicates a highly accurate forecast model).

Within the year after the change in reference limit, the prevalence of TSH-defined biochemical subclinical hypothyroidism increased threefold. From January to April 2014, there were 198 797 TSH tests, of which 6611 had results above 6.0 but less than 10.0 mIU/L, for a prevalence of biochemical subclinical hypothyroidism of 3.3% (95% CI 3.2%–3.4%). From May to December 2014, there were 315 432 TSH tests, with 28 632 having a result greater than the new upper reference limit of 4.0 mIU/L but less than 10.0 mIU/L, for a prevalence of 9.1% (95% CI 9.0%–9.2%).

There was a significant difference in the rate of new levothyroxine prescriptions per 1000 population over the 4 years of the study, potentially related to the change in the upper limit of the reference range. For the 6-month period of May to October in each year from 2011 to 2013, new prescriptions of levothyroxine remained stable. However, after the upper limit change, the number of new prescriptions dispensed rose by 25.3%, from 3.24 (95% CI 3.15–3.33) per 1000 population in 2013 to 4.06 (95% CI 3.96–4.15) per 1000 population in 2014 (Table 1).

The numbers of new and increased-dose prescriptions are shown in Figure 2 and the rates of levothyroxine dose increases per 1000 population in Figure 3, according to month of prescription. There was no significant difference in the rate of increased-dose prescriptions across the years 2011 to 2013 ($p = 0.1$) (Figure 3A), so these data were collapsed for comparison with the 2014 data (Figure 3B). There was a significant interaction between month and year (2 categories, $p < 0.001$; Figure 3A). This interaction is further illustrated in Figure 3B, where for May alone, there was no significant difference between 2014 and 2011 to 2013 combined ($p = 0.1$), but for every successive month in 2014 there was a sharp increase in dose escalations, followed by a persistent separation from most corresponding months in the previous years ($p < 0.001$ for between-year comparisons for all months except August). In absolute terms, the median number of new or

Table 1: Rate of new prescriptions of levothyroxine for the months of May to October, 2011–2014, in Calgary, Alberta

Year*	New prescriptions per 1000 population (95% CI)
2011	3.45 (3.36–3.55)
2012	3.20 (3.11–3.29)
2013	3.24 (3.15–3.33)
2014	4.06 (3.96–4.15)

Note: CI = confidence interval.
*New upper limit for reference range of thyroid-stimulating hormone was introduced on May 1, 2014.

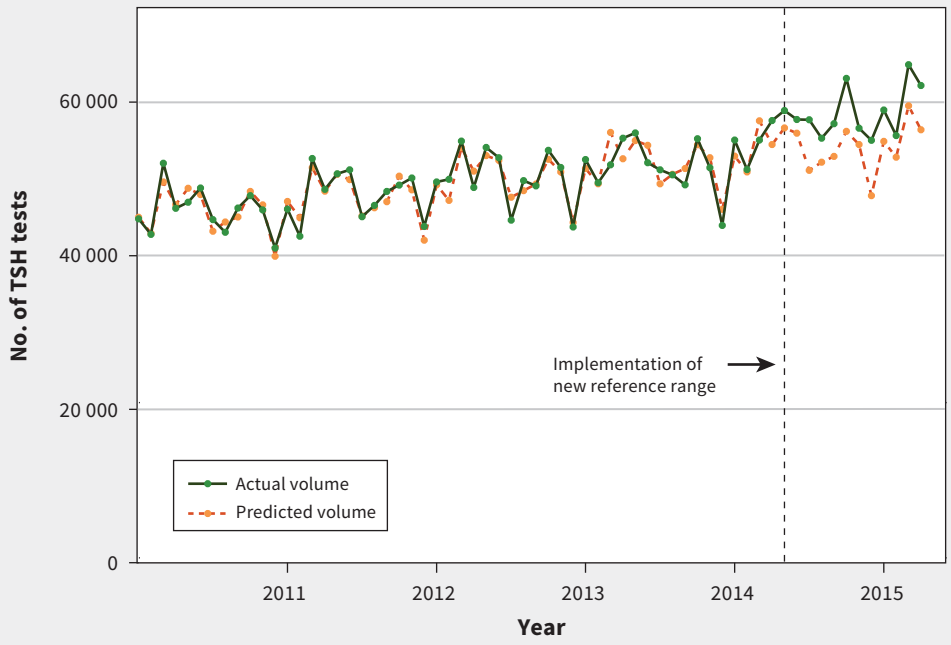

Figure 1: Predicted and actual number of requests for thyroid-stimulating hormone (TSH) tests at Calgary Laboratory Services, per month, during the years 2010 to 2015. Labels on the horizontal axis indicate the start of each calendar year.

increased-dose thyroxine prescriptions per month increased from 1297 (95% CI 1244–1339) in the years before the reference change to 1804 (95% CI 1614–1923) after the reference change (Figures 2 and 3).

Interpretation

We used administrative health data to study how a change in laboratory policy affected patient care and potentially health system costs. Following a minor change in the upper limit of the reference range for TSH, the resultant 7.3% increase in TSH testing added 3000 to 5000 tests per month at our laboratory and about 500 new thyroxine prescriptions per month. In a setting with a population of more than 1 million, our observed increase in new levothyroxine prescriptions and dose escalations for those already taking levothyroxine means that this reference change could have important clinical and economic implications.

We included a large number of TSH tests (about 3 million) to determine population trends. With access to data from the single provider of laboratory tests within our health care system, we were able to accurately capture all tests done within the population across several years before and after the change in reference range. The use of provincial pharmacy data also allowed accurate and comprehensive capture of population trends in the prescribing of levothyroxine.

Population-based studies defining the TSH upper limit support the decision in Calgary to reduce the upper limit of the reference range from 6 to 4 mIU/L.[18] However, this does not imply that treating a patient whose TSH falls between 4 and 6 mIU/L with levothyroxine has proven merit or avoids harm.[32] Several studies of the natural history of untreated biochemical subclinical hypothyroidism show low rates of conversion to overt hypothyroidism (i.e., raised TSH with frankly low free thyroxine). Indeed, one-third to one-half of patients in the cohorts studied reverted to normal TSH over 2 to 5 years of observation.[13–15,33]

More than a decade ago, investigators at the Mayo Clinic predicted that reducing the TSH upper limit from 5 to 3 mIU/L would lead to a fourfold rise in the "incidence" of hypothyroidism which, in their cohort, would constitute 20% of test reports.[24] A recent population study from Copenhagen suggested that primary care providers were increasingly likely (compared with past years) to offer thyroxine therapy for low degrees of abnormality in TSH, often after just a single measurement.[34] We have added to this observation by analyzing the actual population-level consequences of an evidence-based refinement in a laboratory test, which lowered the upper limit of the TSH reference range by 2 mIU/L. This change "instantly" tripled the cohort of patients who could be classified as having biochemical subclinical hypothyroidism. All of these "newly diagnosed" patients would have been considered biochemically euthyroid the day before the change in the reference range. Data from the United Kingdom have shown that thyroxine is the second most commonly prescribed medication in primary care.[35] Our study suggests that this may be driven by subtle and nonspecific abnormalities in exquisitely sensitive laboratory tests among patients with possibly nonspecific or no symptoms.[36] As such, one unintended consequence of setting a scientifically accurate, narrow reference range for a common laboratory test is a probable marked

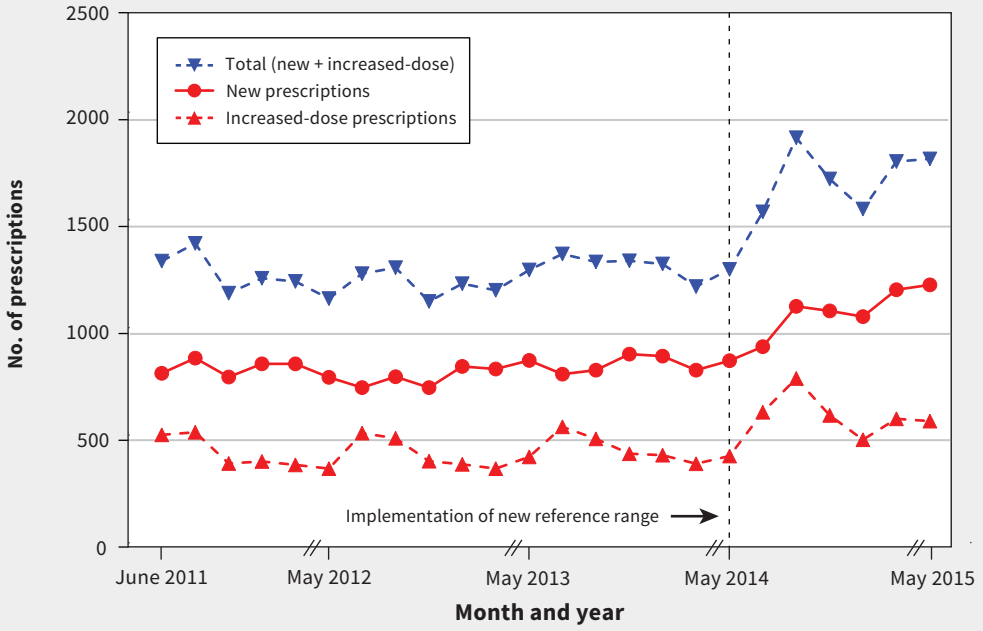

Figure 2: Absolute numbers of new prescriptions for levothyroxine and prescriptions with a dose increase, before and after implementation of a slightly lower upper limit of the reference range for thyroid-stimulating hormone. Data were analyzed for the months of May to October each year, as indicated.

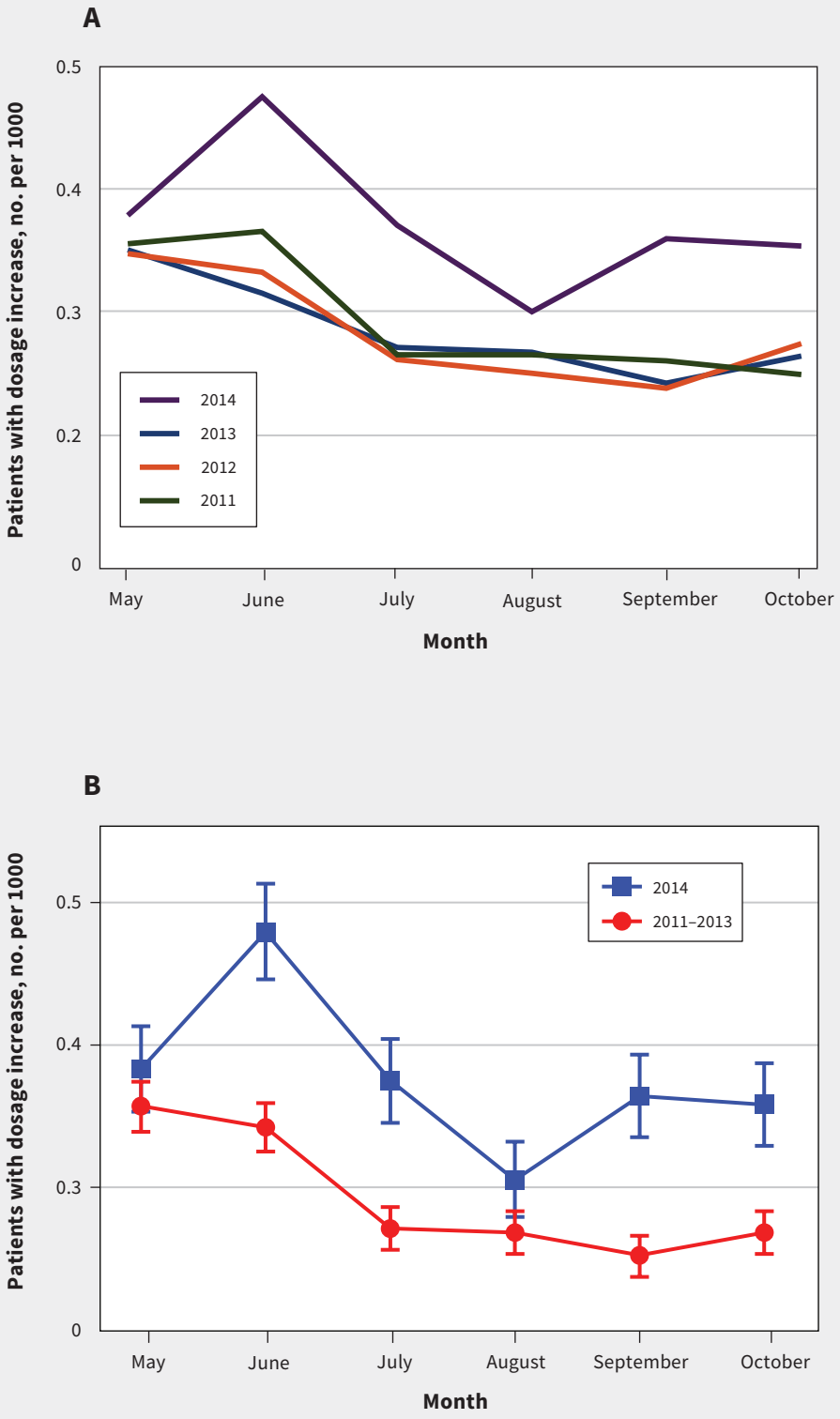

Figure 3: Monthly trends (May to October) in the number of patients with an increase in prescribed dose of levothyroxine per 1000 patients already using levothyroxine at a stable dose in the previous 24 months. Figure 3A shows that estimates for the years 2010 to 2013 did not differ, so the data for these years were collapsed and then compared with data for the year 2014 (Figure 3B). Figure 3B show estimates and 95% confidence intervals. The new upper limit for the reference range of thyroid-stimulating hormone was introduced on May 1, 2014.

increase in prescribing behaviour where subtle deviations from "normal" are taken to indicate the presence of disease.

Changing the TSH reference range may have several ramifications. Laboratories making such a change should consider using a specific knowledge translation intervention to help prescribers understand the potential pitfalls that may accompany even minor changes in reference ranges. For example, patients who may not need treatment and whose condition may spontaneously normalize without intervention may be classified as having a "disease." Patients may also be inconvenienced by requests for more laboratory tests, additions to their individual pill burden and the need to seek more frequent medical follow-up, all of which would be expected to increase the costs of medical care.

Limitations

The limitations of our study include the usual limitations of data derived from administrative databases. For example, our analysis of TSH testing did not directly link individual patients' results to dispensation of a new prescription for or increased dose of levothyroxine. It is possible that some patients filled prescriptions outside of the Calgary Zone, and these would not have been captured in the pharmacy database. We cannot account for possible patient migration into or out of the Calgary Zone for either blood tests or filling prescriptions. However, our use of 3 prior years of data for both laboratory testing and prescriptions helped to establish the lack of significant population variation in either measure before the date of the reference change, increasing the plausibility of the hypothesized relationship between the change in the reference range and the observed changes in laboratory utilization and prescribing behaviour.

Clustering of effects because of variation in physicians' prescribing and test-ordering behaviour could not be detected to determine whether the observed trends reflected widespread practice or were driven by a select few. However, with 3 million TSH measurements for a population of about 1.4 million, it is unlikely that a small subset of providers could explain the population trends that we observed.

We were unable to exclude pregnant women from our analysis. For them, trimester-specific TSH reference ranges may be more appropriate. Studying thyroid testing and thyroxine prescription in pregnancy were not objectives of this study.[37] However, we consider it unlikely that the relatively small numbers of women in a pregnancy testing cohort would substantially confound the results in this much larger one.

Finally, we were unable to ascertain whether the patients in our data set had any compelling clinical indications for levothyroxine therapy.

Conclusion

A minor lowering of the upper limit of the TSH reference range resulted in a substantial increase in laboratory test use, and possibly unnecessary levothyroxine prescribing and designation of patients as having subclinical hypothyroidism. Knowledge translation efforts are important for users of the medical biochemistry laboratory when a reference range is changed. Collaboration between clinical chemists and physicians is essential to ensure consideration of all potential outcomes. Efforts to improve both clinicians' and patients' knowledge about subclinical hypothyroidism are warranted.

References

1. Feller M, Snel M, Moutzouri E, et al. Association of thyroid hormone therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: a systematic review and meta-analysis. *JAMA* 2018;320:1349-59.
2. Jones DD, May KE, Geraci SA. Subclinical thyroid disease. *Am J Med* 2010;123:502-4.
3. Chu JW, Crapo LM. The treatment of subclinical hypothyroidism is seldom necessary. *J Clin Endocrinol Metab* 2001;86:4591-9.
4. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab* 2001;86:4585-90.
5. Portillo-Sanchez P, Rodriguez-Gutierrez R, Brito JP. Subclinical hypothyroidism in elderly individuals — overdiagnosis and overtreatment? A teachable moment. *JAMA Intern Med* 2016;176:1741-2.
6. Hak AE, Pols HAP, Visser TJ, et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med* 2000;132:270-8.
7. Chaker L, Baumgartner C, den Elzen WPJ, et al.; Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of stroke events and fatal stroke: an individual participant data analysis. *J Clin Endocrinol Metab* 2015;100:2181-91.
8. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA* 2006;295:1033-41.
9. Rodondi N, den Elzen WPJ, Bauer DC, et al.; Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010;304:1365-74.
10. Franklyn JA. The thyroid: too much and too little across the ages. The consequences of subclinical thyroid dysfunction. *Clin Endocrinol (Oxf)* 2013;78:1-8.
11. Parle J, Roberts L, Wilson S, et al. A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community-living elderly subjects with subclinical hypothyroidism: the Birmingham elderly thyroid study. *J Clin Endocrinol Metab* 2010;95:3623-32.
12. Stott DJ, Rodondi N, Kearney PM, et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med* 2017;376:2534-44.
13. Díez JJ, Iglesias P, Burman KD. Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab* 2005;90:4124-7.
14. Díez JJ, Iglesias P. Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. *J Clin Endocrinol Metab* 2004;89:4890-7.
15. Meyerovitch J, Rotman-Pikielny P, Sherf M, et al. Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians. *Arch Intern Med* 2007;167:1533-8.
16. Garber JR, Cobin RH, Gharib H, et al.; American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid* 2012;22:1200-35.
17. Villar HCCE, Saconato H, Valente O, et al. Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database Syst Rev* 2007;(3):CD003419.
18. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;87:489-99.
19. Somwaru LL, Arnold AM, Joshi N, et al. High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. *J Clin Endocrinol Metab* 2009;94:1342-5.
20. Collet TH, Gussekloo J, Bauer DC, et al.; Thyroid Studies Collaboration. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med* 2012;172:799-809.
21. Blum MR, Bauer DC, Collet TH, et al.; Thyroid Studies Collaboration. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA* 2015;313:2055-65.
22. Thienpont LM, Van Uytfanghe K, Beastall G, et al.; IFCC Working Group on Standardization of Thyroid Function Tests. Report of the IFCC Working Group for standardization of thyroid function tests; part 1: thyroid-stimulating hormone. *Clin Chem* 2010;56:902-11.

23. Strich D, Karavani G, Levin S, et al. Normal limits for serum thyrotropin vary greatly depending on method. *Clin Endocrinol (Oxf)* 2016;85:110-5.
24. Fatourechi V, Klee GG, Grebe SK, et al. Effects of reducing the upper limit of normal TSH values. *JAMA* 2003;290:3195-6.
25. Bromwich P, Cohen J, Steward I, et al. Decline in sperm counts: an artefact of changed reference range of "normal"? *BMJ* 1994;309:19-22.
26. Saintonge S, Bang H, Gerber LM. Implications of a new definition of vitamin D deficiency in a multiracial US adolescent population: the National Health and Nutrition Examination Survey III. *Pediatrics* 2009;123:797-803.
27. Mohammed EA, Naugler C, Far BH. Chapter 32: Emerging business intelligence framework for a clinical laboratory through big data analytics. In: *Emerging trends in computational biology, bioinformatics, and systems biology: algorithms and software tools*. 1st ed. Burlington (MA): Morgan Kaufmann Publishers; 2015.
28. Mohammed EA, Naugler C. Open-source software for demand forecasting of clinical laboratory test volumes using time-series analysis. *J Pathol Inform* 2017;8:7.
29. Naugler C, Hemmelgarn B, Quan H, et al. Implementation of an intervention to reduce population-based screening for vitamin D deficiency: a cross-sectional study. *CMAJ Open* 2017;5:E36-9.
30. Gill P, Guo M, Lau CK, et al. Implementation of an educational province-wide intervention to reduce redundant vitamin B_{12} testing: a cross-sectional study. *Clin Biochem* 2020;76:1-4.
31. Hughes CA, Guirguis LM, Wong T, et al. Influence of pharmacy practice on community pharmacists' integration of medication and lab value information from electronic health records. *J Am Pharm Assoc (2003)* 2011;51:591-8.
32. Taylor PN, Iqbal A, Minassian C, et al. Falling threshold for treatment of borderline elevated thyrotropin levels: balancing benefits and risks — evidence from a large community-based study. *JAMA Intern Med* 2014;174:32-9.
33. Somwaru LL, Rariy CM, Arnold AM, et al. The natural history of subclinical hypothyroidism in the elderly: the cardiovascular health study. *J Clin Endocrinol Metab* 2012;97:1962-9.
34. Medici BB, Nygaard B, la Cour JL, et al. Changes in prescription routines for treating hypothyroidism between 2001 and 2015: an observational study of 929,684 primary care patients in Copenhagen. *Thyroid* 2019;29:910-9.
35. *Leading chemical drugs dispensed in England in 2018, by items (in millions).* New York; Statistica, Inc.; 2019.
36. Walsh JP, Ward LC, Burke V, et al. Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial. *J Clin Endocrinol Metab* 2006;91:2624-30.
37. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011;21:1081-125.

Competing interests: None declared.

This article has been peer reviewed.

Affiliations: Department of Medicine/Endocrinology (Symonds, Kline), Physician Learning Program (Gjata), Department of Clinical Neurosciences (Cooke) and Department of Pathology and Laboratory Medicine (Naugler), Cumming School of Medicine, University of Calgary; Health Services Statistical & Analytic Methods (Rose) and Alberta Precision Laboratories (Guo), Alberta Health Services, Calgary, Alta.

Contributors: Christopher Symonds conceived of the project, contributed to the analysis and wrote the first draft of the manuscript. Gregory Kline co-wrote the first draft and generated the graphic displays. Inelda Gjata conducted the data gathering from the provincial Pharmaceutical Information Network. Marianne Rose performed the statistical analysis. Maggie Guo collected the data and constructed the laboratory database. Lara Cooke supervised the project construction and assisted in the ethics approval application and the primary analysis. Christopher Naugler performed statistical analysis of the laboratory data. All of the authors revised the manuscript for important intellectual content, approved the final version for publication and agreed to act as guarantors of the work.

Funding: This project was funded by the Physician Learning Program, a joint venture of the University of Alberta, the University of Calgary and the Alberta Medical Association.

Data sharing: The data used for this study are not publicly available because of privacy or ethics restrictions.

Accepted: Mar. 17, 2020

Correspondence to: Christopher Symonds, cjsymond@ucalgary.ca