

A Natural Experiment in Mass Media Modulated Pharmacokinetics After a Change in Tablet Formulation

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Primary hypothyroidism is the most common endocrine disease.¹ The issue of bioequivalence studies for narrow therapeutic index drugs, such as levothyroxine, has been a subject of debate.²⁻⁵ Adverse outcomes have been associated with the approved generic substitution of levothyroxine products, frequently without the prescribing physician's knowledge.⁶

About 250,000 Israelis are treated for hypothyroidism with the drug levothyroxine, almost exclusively with the brand product Eltroxin, manufactured by GlaxoSmithKline. During the month of February 2011, a new formulation of Eltroxin was distributed in Israel in which changes had been made in the tablets' inert ingredients. Previously, an eruption in adverse effects reports was observed in New Zealand after a new formulation of Eltroxin had been introduced in 2007.⁷ However, this experience was not reported to the Pharmacy Division of the Israel Ministry of Health when the new product was registered in Israel in 2008 since the manufacturer dismissed the incident as being provoked by the media and less associated with the change in formulation. In September 2009, when GlaxoSmithKline sold the production of Eltroxin to Aspen Pharma, Perigo Israel acquired the registration rights for the product in Israel. Upon receiving Ministry of Health approval for the new formulation in February 2011, the new product was made available to pharmacies in Israel. Shortly after the new formulation was marketed, cases of side effects began to be reported to the Ministry of Health which included fatigue, weakness, depression, tremors, diarrhea, and arrhythmias. These reports generated extensive media coverage that reached peak intensity during the month of October 2011. Consequently, growing alarm and confusion emerged among treated patients and their families, resulting in a public outcry accusing all stakeholders involved of negligence and malfeasance.^{8,9}

In response, the director general of the Ministry of Health commissioned a board of inquiry. Although the commission was composed of both clinicians and regulators, the scope of the investigation was mostly limited to the registration process of the product and to the sporadic reports of side effects and complications.¹⁰ Of the approximately 800 reports received, only 105 (13.2%) mentioned thyroid-stimulating hormone (TSH) levels, 85 reported TSH elevation, 6 reported a drop, and 14 reported only a "change." Laboratory data corroborating the report

were received in only 35 of the reports, rendering large, population-based analyses unfeasible. To the best of our knowledge, the results of a longitudinal ob-

Background: After a new formulation of levothyroxine was distributed in Israel, side effects were reported to the Ministry of Health generating extensive media coverage. The purpose of this study was to determine whether the new formulation was associated with a change in thyroid-stimulating hormone (TSH) levels of treated patients and to evaluate the effect of the extensive media coverage on the incidence of laboratory test performance.

Study Design: Retrospective-cohort and cross-sectional analysis.

Methods: All patients from the Leumit Health Services of Israel treated with levothyroxine between October 2009 and February 2012 were included in the study. A retrospective cohort was constructed of patients treated and maintained within the desired target range (0.35-5 mIU/L) from January to July 2010. A longitudinal analysis was conducted to calculate the monthly distribution of TSH levels from laboratory tests during routine care over 26 months. Data were stratified by cohort and noncohort patients.

Results: Data were captured for 18,106 levothyroxine-treated patients; 1140 were included into the retrospective cohort. In both subpopulations a sharp rise in the number of tests performed monthly is observed at the peak of media coverage during October and November 2011. In the retrospective cohort the proportion of TSH results within target range fell to a low of 67.5% during December 2011, with 25.3% between 5.01 and 20 mIU/L. Results >20 mIU/L then peaked at 3.8% indicating an increase in patients who stopped taking levothyroxine.

Conclusions: These results demonstrate the power of mass media to influence patient behavior and to foment a public health scare.

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Take-Away Points

Stress induced by inaccurate or misunderstood messages from media coverage may have caused patients to stop taking an important drug necessary for their health and well-being.

- Medical decision makers should not underestimate the power of the mass media to both influence patient behavior and to foment a public health scare.
- Methods must be developed by providers to convey accurate information to both patients and healthcare providers when questions arise concerning the safety and efficacy of widely used products.
- Managed care information systems can provide the population-based data necessary to scientifically evaluate changes in patient response to new products.

servational study analyzing changes in TSH levels over the relevant period have not been reported.

We hypothesized that if the bioavailability of the new product was significantly inferior to that of its predecessor, measurable populationwide variance in TSH test results would be observed among levothyroxine-treated patients before and after the introduction of the new formula. Additionally, we postulated that the intense media coverage may have affected patient behavior both by inducing compliant patients to perform additional TSH tests and by motivating negligent patients to request blood tests at health maintenance organization (HMO) clinics. We also suspected that some patients, confused by the abundance of conflicting information, may have stopped taking Eltroxin, fearing that the new product was indeed unsafe. The purpose of this study was to determine whether the change in the formulation and later, the intense media coverage, were associated with a measurable change in TSH levels of treated patients, and to evaluate the effect of the extensive media coverage on the incidence of laboratory test performance.

METHODS

This study was conducted in the Leumit Health Services (LHS), a managed care organization that provides medical care and coverage to approximately 700,000 members throughout Israel. Since 1999, LHS has implemented an electronic patient record (EPR) system. During each patient visit, all physicians complete an EPR detailing the specific clinical services provided including diagnoses, drugs prescribed, and diagnostic tests ordered. Additionally, LHS operates a central laboratory which transmits all test results to a central data warehouse that interfaces with the EPR program. Similarly, all data on prescriptions dispensed in LHS-operated community pharmacies and in private pharmacies contracting with LHS are also transmitted to the data warehouse.

To test our research hypotheses and answer our primary research questions we implemented 3 individual study designs, as follows:

1. Population-based, cross-sectional analysis of TSH levels and frequency of testing in levothyroxine-treated patients.

To evaluate the number of TSH tests performed monthly by all patients in the HMO and the distribution of test results throughout the study period, we implemented a cross-sectional study. All patients treated with levothyroxine between October 1, 2009, and February 29, 2012, were included. Since Leumit patients can purchase a 3-month supply of levothyroxine, prescribing data from October to

December 2009 were included to identify all patients treated during January 2010. The number of tests performed, mean TSH results with 95% confidence intervals, and median TSH results were calculated for monthly results recorded over the study period (January 2010 until February 2012).

2. Retrospective cohort study of TSH levels and frequency of testing in levothyroxine-treated patients.

To eliminate incidence/prevalence bias, a retrospective cohort was constructed of patients with a record of at least 1 dispensed prescription for levothyroxine during the 4 months prior to February 1, 2010, and a recorded TSH laboratory test result within the target range (0.35-5 mIU/L) during January 2010. Furthermore, to avoid biases emanating from cases difficult to titrate or nonadherent patients, subjects were excluded from the cohort if additional test results not within target range were recorded between January 1, 2010, and June 30, 2010. A longitudinal analysis was conducted to calculate the monthly distribution of TSH levels as recorded from laboratory tests performed during routine care as previously described for the population-based cross-sectional analysis. Additionally, TSH levels were recoded into 4 subcategories (≤ 0.34 , 0.35-5.0, 5.1-20, and >20 mIU/mL). The monthly distributions of test results across the 4 categories in the retrospective cohort population were calculated and statistical significance was tested with the 2-sided χ^2 test. P value $<.05$ was considered statistically significant.

3. An evaluation of prevalence of TSH testing among untested levothyroxine-treated patients after the intense media coverage.

To determine whether intense media coverage motivated previously nonadherent patients (ie, nonadherence to laboratory testing) to perform TSH testing, we identified patients continuously treated with levothyroxine throughout the 12 months prior to the peak in media coverage (October 2011), but had no record of a TSH test recorded in their EPR during this 12-month period. Patients were included if dispensed prescriptions for levothyroxine were recorded continuously from June 2010 to November 2011, but a TSH test was not recorded in the EPR during the 12 months prior to October 2011 when the intense media coverage appeared. We calculated

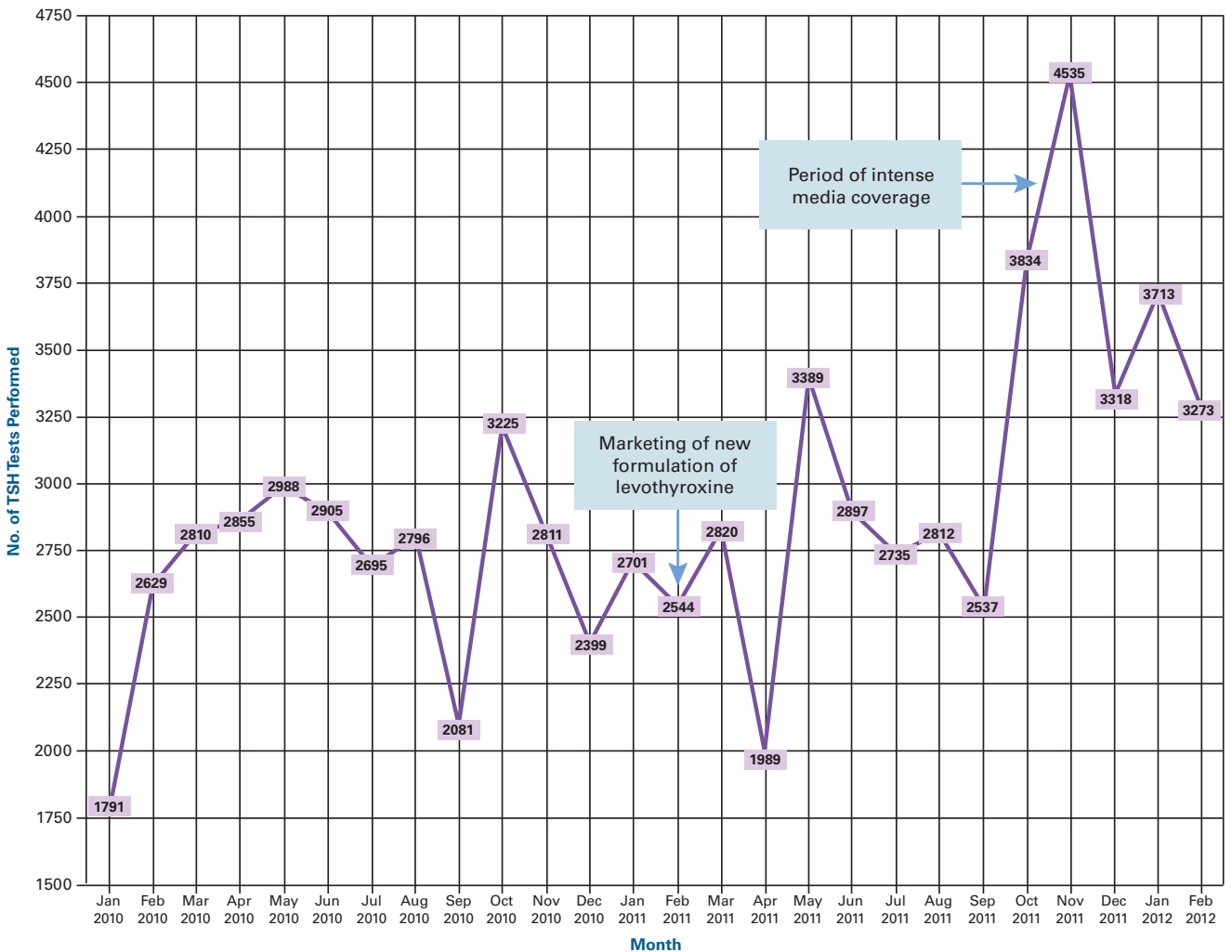
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■ **Table.** Patient Demographics

| Variable | Cohort | General Population Excluding Cohort | P ^a |
|---------------------------|-------------|-------------------------------------|----------------|
| Number of patients | 1140 | 16,966 | — |
| Age in years ± SD | 60.9 ± 17.9 | 57.1 ± 19.2 | P < .001 |
| % Female ± SD | 85.6 ± 1.0 | 81.6 ± 0.3 | P < .001 |
| Region % | | | P < .04 |
| North | 25.2 | 21.9 | |
| South | 29.1 | 30.3 | |
| Central | 30.4 | 33.1 | |
| Jerusalem | 15.3 | 14.7 | |

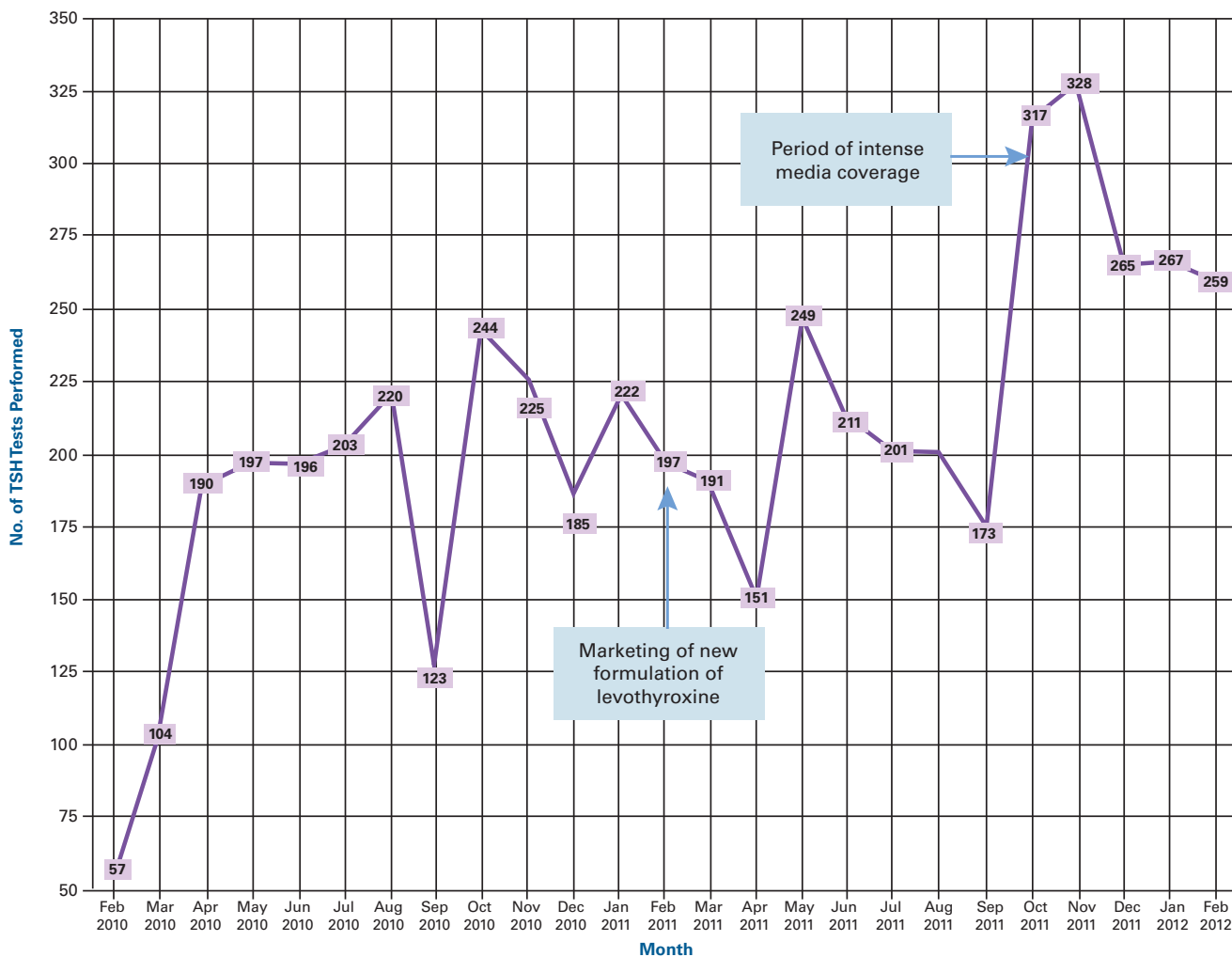
SD indicates standard deviation.
^aFor retrospective cohort vs general population excluding cohort.

■ **Figure 1.** Number of TSH Tests Performed Monthly in Noncohort Population



TSH indicates thyroid-stimulating hormone.

■ **Figure 2.** Number of TSH Tests Performed Monthly in Retrospective-Cohort Population



TSH indicates thyroid-stimulating hormone.

the number and proportion of these patients who performed at least 1 test during October and November 2011.

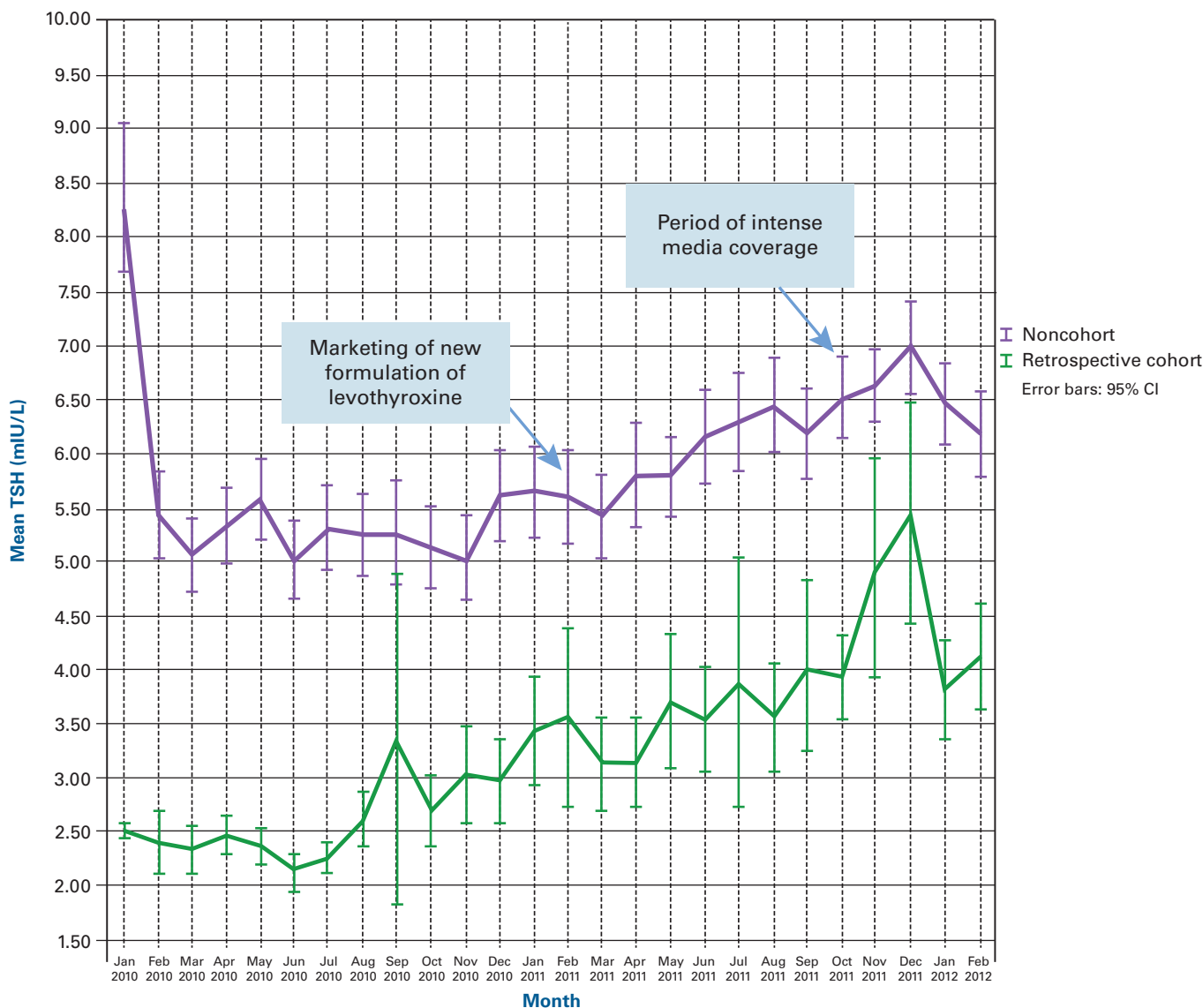
Drug dispensing and laboratory test data were captured from “LHS’s” data warehouse using IBM Cognos 8 BI Report Studio software. Results of queries were downloaded into Microsoft Excel spreadsheets and data analysis was performed using IBM SPSS Statistics version 20 software. A chart review was performed on a sample of electronic records of patients in the target population to glean relevant information recorded by physicians in free text. Ethics committee approval was obtained from LHS’s institutional review board.

RESULTS

Laboratory data were captured for 18,106 levothyroxine-treated patients during the study period, 1140 of whom met

the criteria for inclusion into the retrospective cohort (Table). Over the 26-month period 75,082 and 6328 tests were performed for the patients in the noncohort and cohort populations, respectively. The number of TSH tests performed monthly for each subpopulation is shown in Figures 1 and 2. In both subpopulations a sharp rise in the number of tests performed monthly is observed at the peak of the media coverage during the months of October and November 2011, dropping during the following month. The mean and median TSH results for both subpopulations per month appear in Figure 3 and Figure 4, respectively. A gradual nonstatistically significant increase in mean TSH values is observed in both populations after February 2011 with a steeper rise observed after October, peaking during December, and then decreasing during January 2012. This trend is particularly pronounced in the cohort population where mean TSH was 3.93 mIU/L during

■ **Figure 3.** Mean Value of TSH Results Stratified by Subpopulation per Month



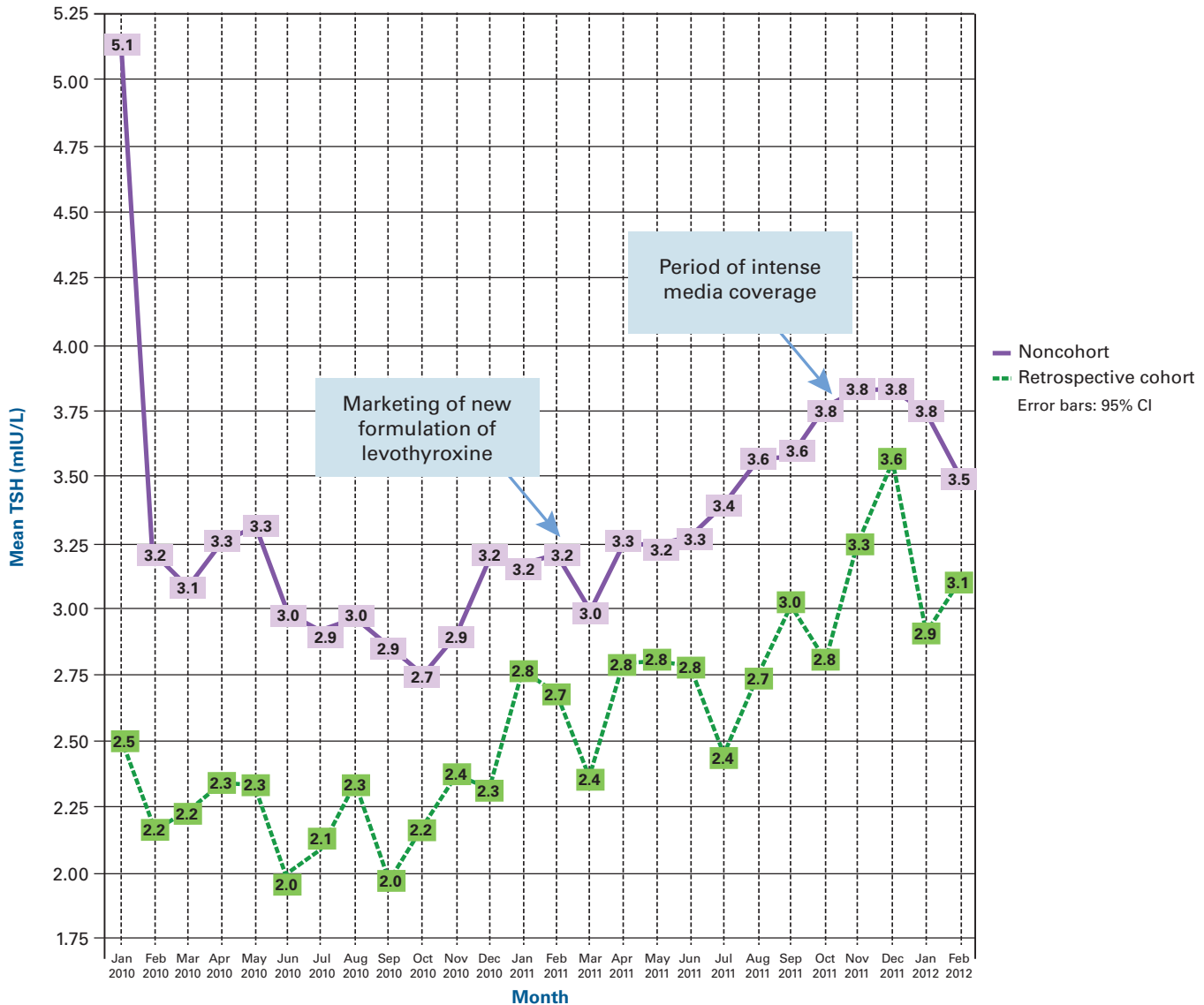
CI indicates confidence interval; TSH, thyroid-stimulating hormone.

October 2011, 5.44 mIU/L in December, then falling to 3.77 mIU/L in January 2012. Median TSH was calculated to be 2.81 mIU/L during October 2011, peaking at 3.57 mIU/L during December, and then falling to 2.91 in January 2012. This trend is further illustrated by the TSH value measured for the third quartile which only surpasses the 5 mIU/L mark (the upper boundary of the desired target range) during the 2 months following the intense media coverage, and then falling to 4.51 mIU/L during January 2012. The monthly distribution of TSH test stratified by range for the retrospective cohort is presented in **Figure 5**. During February 2011, the month the

new product was introduced, 84.8% of the tests were within the desired target range, 13.8% between 5.01 and 20 mIU/L, and 0.5% >20 mIU/L. The proportion of test results within target range fell to a low of 67.5% during December 2011, with 25.3% between 5.01 and 20 mIU/L and the proportion of test results >20 mIU/L peaking at 3.8%. The distribution observed 1 month later during January 2012 was similar to that observed the previous September before the story hit the press.

We identified 1078 patients treated with levothyroxine for at least 12 months prior to October 2011 for whom there is

■ **Figure 4.** Median TSH



TSH indicates thyroid-stimulating hormone.

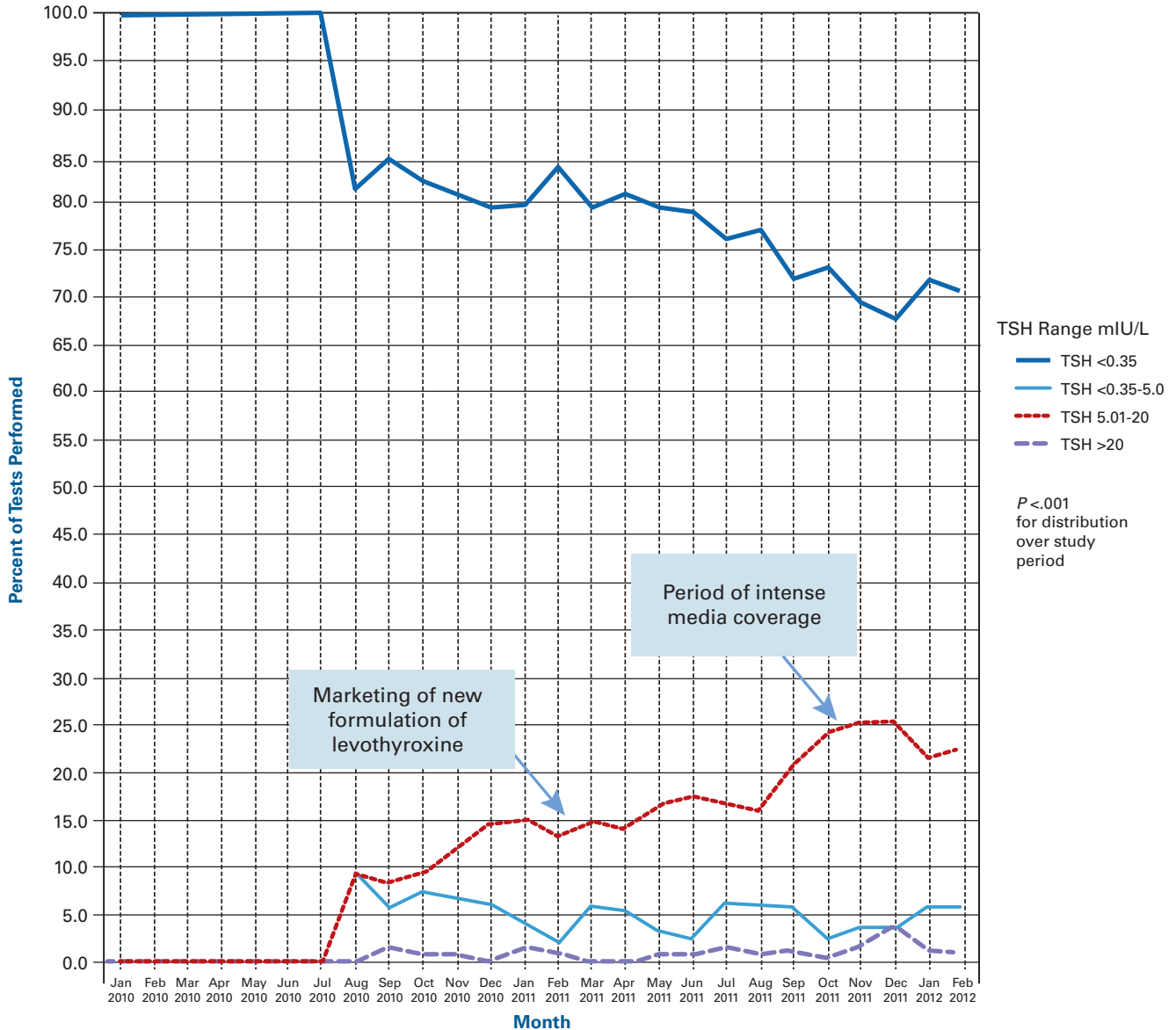
no record of a TSH test result in their EPR during this period. Of these patients, 462 (42.9%) performed at least 1 TSH test during the months of October and November 2011.

DISCUSSION

To the best of our knowledge this study is the first population-based quantitative analysis of patient response to a mass media-induced panic concerning a prescription drug for treatment of a chronic disease. Although a gradual rise in TSH levels is observed over time, clinically significant changes in mean, median, and third-quartile TSH levels are first observed the month after the story was extensively publicized. While not indicating that the new formulation brought about

prevalent, significant changes in patient health statuses, these findings do indicate that the behavior of portions of patients was significantly affected by the abundance of conflicting information to which they were exposed. It is noteworthy that the changes observed in mean TSH values observed from October to December resulted predominantly from outlier values >20 mIU/L, a result which generally indicates that the patient has stopped taking levothyroxine. (We performed a chart review of a small sample of these patients and in almost all cases the physician had recorded in free text that the patient had ceased taking medication at their own decision.) This finding is substantiated by the prevalence of test results >20 mIU/L which peaked to 3.5% in the cohort population during December 2011, the same month that the mean and median

■ **Figure 5.** Percent of Tests Within TSH Ranges



TSH indicates thyroid-stimulating hormone.

reached their peaks. Accordingly, the significant changes observed between October and December 2011 can be attributed predominantly to patients who, confused by the deluge of information, stopped taking their medication. We interpret these findings as such since, had these patients stopped taking levothyroxine without connection to the media reports, we would have seen similar behavior throughout the study period and not distinctively at this point in time.

This premise is supported by the trends observed in prevalence of laboratory test performance over the 26-month study period. Presumably, had the bioavailability of the new product been significantly inferior to its predecessor, we would have ex-

pected to observe an increase in the number of tests performed among patients seeking medical care and consultation upon the advent of signs and symptoms of hypothyroidisms approximately 6 weeks after the new product had been marketed. However, such behavior was not observed in this study population, either in the cohort or in the general population. Over the 26-month study period substantial increases in prevalence of TSH testing is first observed during October 2011, peaking during November and then subsiding during December. These results should however be evaluated with caution since they are confounded by the occurrence of the Jewish high holidays which in 2011 fell mostly in October. In Israel these are national holidays

when HMO clinics do not operate, all government offices and most businesses are closed, and Israelis are busy with preparations for the holidays or travel abroad. The crude data for this month therefore do not accurately reflect the magnitude of the phenomenon. When the number of tests performed by the cohort population in October 2011 (N = 317) is compared with those for September 2010, the month of the holidays that year (N = 123), a 258% increase in testing prevalence is calculated. This steep increase in utilization of laboratory resources during the holiday season vividly reflects the level of concern prevalent at that time. Accordingly, the results of this nationwide study do not support the allegation that the new product was seriously inferior to its predecessor. These results do, however, demonstrate the power of the mass media to both influence patient behavior and to foment a public health scare. The large proportion of patients untested for at least 1 year who sought care when the issue became a matter of major public concern provides lucid testimony of this phenomenon.

Our study has several strengths absent in the report from New Zealand.⁷ First, the study data were captured from a data warehouse of an HMO which has fully implemented an EPR system among all practicing physicians. Since this system interfaces with the HMO's laboratory and pharmacies we had all prescription and laboratory data necessary to evaluate changes in TSH levels over time in a defined patient population. Second, these data capabilities facilitated the implementation of a robust study design which included both a cross-sectional analysis and a retrospective cohort design. By including both designs in this study we were able to conduct a longitudinal analysis of testing prevalence among all treated patients while simultaneously presenting results for a subpopulation without biases caused by incident or difficult to titrate cases. Third, since LHF provides services to patients nationwide, this study included patients treated throughout Israel from all major ethnic and socioeconomic subpopulations. Limitations of this study include lack of laboratory data from hospitalized patients and deficiencies in surveillance due to patient nonadherence to TSH test ordering. Furthermore, since the new formulation had the same product code as the previous product we could not determine when patients started to take the new product. Similarly, the results obtained in the first weeks after the new product was introduced may have been biased by patients and pharmacies that had not yet finished supplies of the old formulation.

The major lesson learned from this analysis is that stress induced by inaccurate or misunderstood messages from media coverage may cause patients to stop taking an important drug necessary for their health and well-being. Since we have no expectations that media coverage in the future will be more responsible, methods must be developed by providers

to convey accurate information to both patients and health-care providers when questions arise concerning the safety and efficacy of widely used products. Additionally, this study demonstrates the potential contribution of healthcare information systems to provide the population-based data necessary to evaluate changes in patient response to new products. With generic switching and introduction of new formulations becoming more common internationally, the methodologies implemented in this study may be useful in future situations in other countries when changes in formulations or generic switching initiate a public scare.

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