Supplementary Online Content

Brito JP, Deng Y, Ross JS, et al. Association between generic-to-generic levothyroxine switching and thyrotropin levels among US adults. *JAMA Intern Med*. Published online February 28, 2022. doi:10.1001/jamainternmed.2022.0045

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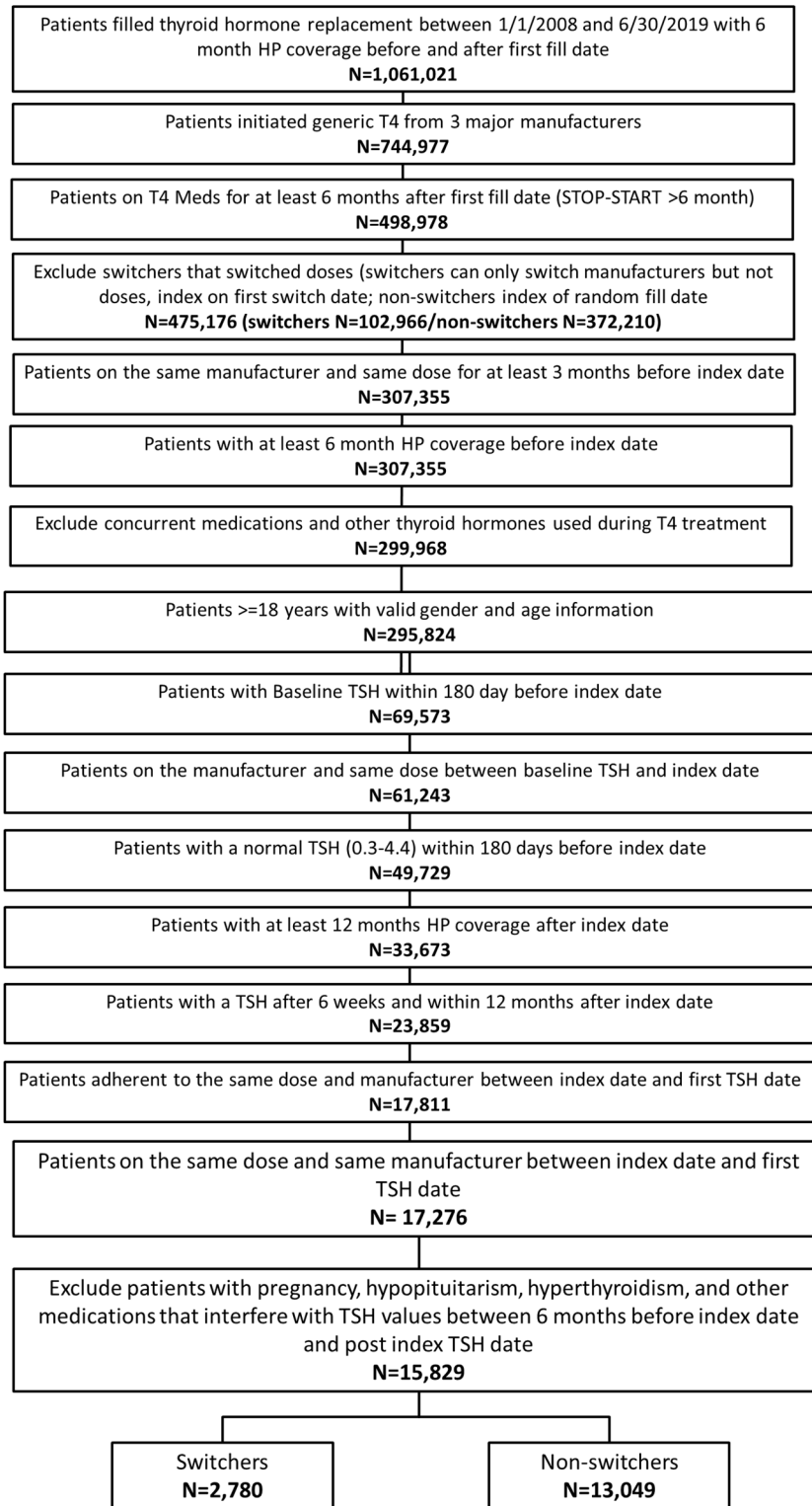**eTable 5.** TSH Levels Within 6 Weeks and 12 Months After Index Date Among Nonswitchers vs Switchers (Using Robust Estimator of the Variance)
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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Study Population Selection

Patients filled thyroid hormone replacement between 1/1/2008 and 6/30/2019 with 6 month HP coverage before and after first fill date
N=1,061,021

Patients initiated generic T4 from 3 major manufacturers
N=744,977

Patients on T4 Meds for at least 6 months after first fill date (STOP-START >6 month)
N=498,978

Exclude switchers that switched doses (switchers can only switch manufacturers but not doses, index on first switch date; non-switchers index of random fill date
N=475,176 (switchers N=102,966/non-switchers N=372,210)

Patients on the same manufacturer and same dose for at least 3 months before index date
N=307,355

Patients with at least 6 month HP coverage before index date
N=307,355

Exclude concurrent medications and other thyroid hormones used during T4 treatment
N=299,968

Patients >=18 years with valid gender and age information
N=295,824

Patients with Baseline TSH within 180 day before index date
N=69,573

Patients on the manufacturer and same dose between baseline TSH and index date
N=61,243

Patients with a normal TSH (0.3-4.4) within 180 days before index date
N=49,729

Patients with at least 12 months HP coverage after index date
N=33,673

Patients with a TSH after 6 weeks and within 12 months after index date
N=23,859

Patients adherent to the same dose and manufacturer between index date and first TSH date
N=17,811

Patients on the same dose and same manufacturer between index date and first TSH date
N= 17,276

Exclude patients with pregnancy, hypopituitarism, hyperthyroidism, and other medications that interfere with TSH values between 6 months before index date and post index TSH date
N=15,829

Switchers
N=2,780

Non-switchers
N=13,049

eTable 1. Clinically Relevant Medications That May Affect Thyroid Function

- Antithyroid Medications (PTU, Propylthiouracil, 6-N Propylthiouracil, Methimazole, Felimazole, Northyx, Tapazole, Thiamazole, Carbimazole, Benzylthiouracil, Methylthiouracil)

- Lithium carbonate

- Amiodarone hydrochloride

- Phenytoin

- Interferon alfa

- Interleukin 2

- Gefitinib

- Erlotinib

- Sorafenib

- Sunitinib

- Dasatinib

- Lenvatinib

- Imatinib

- Cabozantinib

- Vandetanib

eTable 2. TSH Levels Within 6 Weeks and 12 Months After Index Date Among Nonswitchers vs Switchers (Adjusted Regression Models)

	Patients, %		Risk or mean difference (95% CI)	P-value
	Nonswitchers (N=13,049)	Switchers (N=2780)		
TSH level				
Normal (0.3-4.4 mU/L)	84.4%	85.7%	Risk difference 0.013 (-0.001, 0.028)	0.08
Abnormal (<0.3 or >4.4 mU/L)	15.6%	14.3%	Risk difference -0.013 (-0.028, 0.001)	0.08
Markedly abnormal (<0.1 or >10 mU/L)	2.2%	1.8%	Risk difference -0.005 (-0.011, 0.001)	0.12
Adjusted mean TSH level (SD), mU/L	2.74	2.71	Mean difference -0.033 (-0.162, 0.096)	0.61
Adjusted mean TSH level change from baseline (SD)	0.54	0.51	Mean difference -0.033 (-0.162, 0.096)	0.61

eTable 3. Sensitivity Analysis Using TSH Levels Between 6 and 12 Weeks After Index Date Among Nonswitchers vs Switchers (Adjusted Regression Models)

	Patients, %		Risk or mean difference (95% CI)	P-value
	Non-switchers (N=2769)	Switchers (N=677)		
TSH level				
Normal (0.3-4.4 mU/L)	84.8%	85.0%	Risk difference: 0.002 (-0.028, 0.032)	0.91
Abnormal (<0.3 or >4.4 mU/L)	15.2%	15.0%	Risk difference: -0.002 (-0.032, 0.028)	0.91
Markedly abnormal (<0.1 or >10 mU/L)	2.4%	2.1%	Risk difference: -0.005 (-0.019, 0.009)	0.52
Adjusted mean TSH level (SD), mU/L	2.51	2.86	Mean difference: 0.251 (-0.133, 0.635)	0.20
Adjusted mean TSH change from baseline (SD)	0.39	0.64	Mean difference: 0.251 (-0.133, 0.635)	0.20

eTable 4. Subgroup Analyses: Patients on Varying Doses of Levothyroxine (Adjusted Regression Models)

Levothyroxine dose >100 mcg	Patients, %		Risk or mean difference (95% CI)	P-value
	Non-switchers (N=1845)	Switchers (N=367)		
TSH level				
Normal (0.3-4.4 mU/L)	75.0%	77.9%	Risk difference: 0.028 (-0.019, 0.075)	0.26
Abnormal (<0.3 or >4.4 mU/L)	25.0%	22.1%	Risk difference: -0.028 (-0.075, 0.019)	0.26
Markedly abnormal (<0.1 or >10 mU/L)	8.0%	6.4%	Risk difference: -0.016 (-0.044, 0.012)	0.28
Adjusted mean TSH level (SD), mU/L	2.49	2.64	Mean difference: 0.152 (-0.555, 0.858)	0.67
Adjusted mean TSH change from baseline (SD)	0.84	0.99	Mean difference: 0.152 (-0.555, 0.858)	0.67
Levothyroxine dose <=100 mcg	Non-switchers (N=11203)	Switchers (N=2413)	Risk or mean difference (95% CI)	P-value
TSH level				
Normal (0.3-4.4 mU/L)	85.8%	87.0%	Risk difference: 0.012 (-0.003, 0.027)	0.13
Abnormal (<0.3 or >4.4 mU/L)	14.2%	13.0%	Risk difference: -0.012 (-0.027, 0.003)	0.13
Markedly abnormal (<0.1 or >10 mU/L)	1.8%	1.5%	Risk difference: -0.003 (-0.009, 0.002)	0.28
Adjusted mean TSH level (SD), mU/L	2.78	2.73	Mean difference: -0.047 (-0.152, 0.057)	0.37
Adjusted mean TSH change from baseline (SD)	0.49	0.44	Mean difference: -0.048 (-0.152, 0.057)	0.37

eTable 5. TSH Levels Within 6 Weeks and 12 Months After Index Date Among Nonswitchers vs Switchers (Using Robust Estimator of the Variance)

	Patients, n (%)		Risk or mean difference (95% CI)	P-value
	Non-switchers (N=2780)	Switchers (N=2780)		
TSH level				
Normal (0.3-4.4 mU/L)	2298 (82.7%)	2348 (84.5%)	Risk difference: 0.018 (-0.001, 0.037)	0.07
Abnormal (<0.3 or >4.4 mU/L)	482 (17.3%)	432 (15.5%)	Risk difference: -0.018 (-0.037, 0.001)	0.07
Markedly abnormal (<0.1 or >10 mU/L)	87 (3.1%)	69 (2.5%)	Risk difference: -0.006 (-0.015, 0.002)	0.15
Mean TSH level (SD), mU/L	2.74 (2.34)	2.73 (3.29)	Mean difference: -0.006 (-0.156, 0.144)	0.94
Mean TSH change from baseline (SD)	0.51 (2.28)	0.53 (3.25)	Mean difference: 0.016 (-0.132, 0.163)	0.84

eTable 6. Sensitivity Analysis Using TSH Levels Between 6 and 12 Weeks After Index Date Among Nonswitchers vs Switchers (Using Robust Estimator of the Variance)

	Patients, n (%)		Risk or mean difference (95% CI)	P-value
	Non-switchers (N=675)	Switchers (N=675)		
TSH level				
Normal (0.3-4.4 mU/L)	559 (82.8%)	565 (83.7%)	Risk difference: 0.009 (-0.031, 0.049)	0.66
Abnormal (<0.3 or >4.4 mU/L)	116 (17.2%)	110 (16.3%)	Risk difference: -0.009 (0.049, 0.031)	0.66
Markedly abnormal (<0.1 or >10 mU/L)	28 (4.2%)	22 (3.3%)	Risk difference: -0.009 (-0.029, 0.011)	0.39
Mean TSH level (SD), mU/L	2.61 (2.73)	2.87 (4.89)	Mean difference: 0.260 (-0.162, 0.683)	0.23
Mean TSH change from baseline (SD)	0.44 (2.63)	0.67 (4.85)	Mean difference: 0.234 (-0.183 ,0.651)	0.27

eTable 7. Subgroup Analyses: Patients on Varying Doses of Levothyroxine (Using Robust Estimator of the Variance)

	Patients, n (%)		Risk or mean difference (95% CI)	P-value
Levothyroxine dose >100 mcg	Non-switchers (N=364)	Switchers (N=364)		
TSH level				
Normal (0.3-4.4 mU/L)	258 (70.9%)	279 (76.7%)	Risk difference: 0.058 (-0.006, 0.122)	0.08
Abnormal (<0.3 or >4.4 mU/L)	106 (29.1%)	85 (23.3%)	Risk difference: -0.058 (-0.122, 0.006)	0.08
Markedly abnormal (<0.1 or >10 mU/L)	32 (8.8%)	27 (7.4%)	Risk difference: -0.014 (-0.053, 0.026)	0.50
Mean TSH level (SD), mU/L	2.53 (3.09)	2.53 (6.40)	Mean difference: 0.000 (-0.731, 0.731)	1.00
Mean TSH change from baseline (SD)	0.84 (3.10)	0.93 (6.30)	Mean difference: 0.093 (-0.630, 0.815)	0.80
Levothyroxine dose <=100 mcg	Non-switchers (N=2409)	Switchers (N=2409)	Risk or mean difference (95% CI)	P-value
TSH level				
Normal (0.3-4.4 mU/L)	2034 (84.4%)	2062 (85.6%)	Risk difference: 0.012 (-0.009, 0.032)	0.26
Abnormal (<0.3 or >4.4 mU/L)	375 (15.6%)	347 (14.4%)	Risk difference: -0.012 (-0.032, 0.009)	0.26
Markedly abnormal (<0.1 or >10 mU/L)	50 (2.1%)	42 (1.7%)	Risk difference: -0.003 (-0.011, 0.004)	0.40
Mean TSH level (SD), mU/L	2.83 (2.61)	2.76 (2.51)	Mean difference: -0.066 (-0.211, 0.079)	0.37
Mean TSH change from baseline (SD)	0.55 (2.53)	0.47 (2.48)	Mean difference: -0.081 (-0.223, 0.060)	0.26