Supplementary Data

Survey Questions Regarding Combination Therapy

1. Do you prescribe and adjust levothyroxine therapy for patients with hypothyroidism?
a. If yes, please complete rest of survey
b. If no, thank you and you do not need to complete survey

Please answer some questions about yourself and your practice

2. How many years have you been in practice?
   a. Currently in training
   b. <5 years
   c. 5–10 years
   d. 10–20 years
   e. >20 years

3. Where do you practice?
   a. North America
      i. Please identify country
   b. South America
      i. Please identify country
   c. Europe
      i. Please identify country
   d. Asia
      i. Please identify country
   e. Other
      i. Please identify country

4. Which best describes your specialty?
   a. Endocrinologist
   b. Surgeon
   c. Nuclear medicine physician
   d. Internist or primary-care physician
   e. Other
      i. Please identify

Please answer the following questions about patients being treated for hypothyroidism. All patients have normal vital signs, are being treated for overt hypothyroidism, have been taking levothyroxine for at least 5 years, and are fully adherent to their therapy. None of the women are planning a pregnancy.

5. A 29-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. She feels well. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	120	80–180

Which would you do?
   a. Continue current levothyroxine
   b. Increase levothyroxine dose
   c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
   d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
   e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
   f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

6. A 29-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	120	80–180

Which would you do?
   a. Continue current levothyroxine
   b. Increase levothyroxine dose
   c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
   d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
   e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
   f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

7. A 29-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	3.9	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	120	80–180

Which would you do?
   a. Continue current levothyroxine
   b. Increase levothyroxine dose
   c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
   d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine

e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

8. A 29-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?
a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

9. A 29-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	3.9	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?
a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

10. A 29-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. She requests ''combination'' therapy. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?
a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

11. A 29-year-old woman with post-surgical hypothyroidism following a total thyroidectomy is taking 100 μg of levothyroxine regularly. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. She requests ''combination'' therapy. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?
a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

12. A 29-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine regularly. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. She tells you that a previous physician added T3 to her regimen and she felt better. She requests a return to

''combination'' therapy. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?

a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

13. A 29-year-old man with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. He is frustrated because he is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. He requests ''combination'' therapy. Physical examination suggests he is clinically euthyroid. His BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?

a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

14. A 29-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. She previously participated in a study that showed that she had a genetic problem with converting T4 to T3. She requests ''combination'' therapy. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?

a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

15. A 59-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. She requests ''combination'' therapy. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?

a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

16. A 29-year-old woman with Hashimoto's hypothyroidism is taking 100 μg of levothyroxine. She is frustrated because she is gaining excessive weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. She requests ''combination'' therapy. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m^2)	32	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?

a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

17. A 59-year-old woman with Hashimoto's hypothyroidism and steroid-induced osteoporosis is taking 100 μg of levothyroxine. She is frustrated because she is gaining weight despite regular exercise, is tired throughout the day, and has poor memory and work performance. She requests ''combination'' therapy. Physical examination suggests she is clinically euthyroid. Her BMI and laboratory values are below.

Parameter	*Patient value*	*Normal range*
BMI (kg/m2)	25	18.5–24.9
TSH (mIU/L)	2.2	0.4–4.0
fT4 (ng/dL)	1.3	0.8–1.8
TT3 (ng/dL)	75	80–180

Which would you do?

a. Continue current levothyroxine
b. Increase levothyroxine dose
c. Add 2.5 μg liothyronine (Cytomel) twice daily and reduce levothyroxine
d. Add 2.5 μg liothyronine (Cytomel) twice daily to current levothyroxine
e. Replace levothyroxine with thyroid extract (e.g., armour thyroid)
f. Replace levothyroxine with liothyronine (Cytomel) as single therapy

Supplementary Table S1. Patient Characteristics Affecting Physician Prescribing of LT4 Versus any T3-containing Therapy

(A) Univariate analyses			*(B) Multivariate analyses*		
Patient characteristic	*Unadjusted OR [CI]*	p-*Value*	*Patient characteristic*	*Adjusted OR [CI]*	p-*Value*
Symptom, Y vs. N	101.4 [33.2–309.2]	<0.0001	Symptom, Y vs. N	25.6 [9.0–73.0]	<0.0001
T3, 75 vs. 120 ng/dL	10.7 [8.6–13.2]	<0.0001	T3, 75 vs. 120 ng/dL	2.6 [2.1–3.3]	<0.0001
Requests LT3, Y vs. N	6.7 [5.7–7.9]	<0.0001	TSH, 2.2 vs 3.9 mIU/L	2.4 [1.9–2.9]	<0.0001
TSH, 2.2 vs. 3.9 mIU/L	5.4 [4.3–6.7]	<0.0001	Polymorphism, Y vs. N	2.4 [1.9–2.9]	<0.0001
Polymorphism, Y vs. N	4.9 [4.1–5.9]	<0.0001	Requests LT3, Y vs. N	2.3 [1.9–2.8]	<0.0001
LT3 preference, Y vs. N	3.2 [2.8–3.8]	<0.0001	LT3 preference, Y vs. N	1.6 [1.4–1.9]	<0.0001
Athyreotic, Y vs. N	2.0 [1.8–2.3]	<0.0001	Athyreotic, Y vs. N	1.03 [0.9–1.2]	0.5634
BMI, 32 vs. 25 kg/m^2	2.0 [1.7–2.2]	<0.0001	BMI, 32 vs. 25 kg/m^2	1.0 [0.9–1.1]	0.8745
Male, M vs. F	1.8 [1.6–2.0]	<0.0001	Male, M vs. F	0.9 [0.8–1.1]	0.2827
Age. 59 vs. 29 years	1.2 [1.0–1.3]	0.0169	Comorbidity, Y vs. N	0.8 [0.7–0.9]	0.0002
Comorbidity, Y vs. N	1.002 [0.86–1.17]	0.9828	Age, 59 vs. 29 years	0.7 [0.6–0.8]	<0.0001

Supplementary Table S2. Patient Characteristics Affecting Physician Prescribing Continued LT4 Versus Increasing LT4 Versus Adding LT3 to LT4 Versus Replacing LT4 with T3-Containing Therapy

		(A) Univariate analyses			*(B) Multivariate analyses*			
Patient scenario	*Therapeutic options*	*Unadjusted OR*	*CI*		*Adjusted OR*	*CI*		p-*Value for model*
Symptoms, Y vs. N	1 vs. 2	77.8	31.6	191.7	48.8	18.4	129.3	<0.0001
	1 vs. 3	582.0	80.9	>999.9	99.6	13.3	748.5	
	1 vs. 4	331.3	77.2	>999.9	46.2	9.2	232.3	
Serum TSH, 2.2 vs. 3.9 mIU/L	1 vs. 2	0.03	0.02	0.03	0.03	0.02	0.05	<0.0001
	1 vs. 3	10.5	5.8	18.8	3.5	1.8	6.8	
	1 vs. 4	0.65	0.46	0.92	0.22	0.13	0.35	
Serum T3, 75 vs. 120 ng/dL	1 vs. 2	1.15	0.95	1.4	1.6	1.2	2.2	<0.0001
	1 vs. 3	34.0	24.0	48.1	3.9	2.4	6.5	
	1 vs. 4	24.6	17.4	34.9	8.0	5.0	12.8	
Requests LT3, Y vs. N	1 vs. 2	0.37	0.30	0.45	0.64	0.36	1.1	<0.0001
	1 vs. 3	26.1	19.9	34.2	6.6	3.9	11.1	
	1 vs. 4	8.7	6.8	11.1	3.8	2.2	6.7	
Athyreotic, Y vs. N	1 vs. 2	0.88	0.60	1.3	1.9	1.0	3.7	0.1527
	1 vs. 3	2.5	1.8	3.4	1.1	0.65	1.9	
	1 vs. 4	3.0	2.1	4.3	1.6	0.9	3.0	
LT3 preference, Y vs. N	1 vs. 2	0.35	0.20	0.59	0.51	0.24	1.1	<0.0001
	1 vs. 3	5.0	3.6	7.0	2.8	1.7	4.9	
	1 vs. 4	3.8	2.6	5.5	2.5	1.4	4.5	
Male, M vs. F	1 vs. 2	0.70	0.47	1.0	1.4	0.71	2.7	0.7077
	1 vs. 3	2.3	1.7	3.2	0.97	0.57	1.7	
	1 vs. 4	1.9	1.3	2.7	0.90	0.50	1.7	
Polymorphism, Y vs. N	1 vs. 2	0.78	0.47	1.3	1.4	0.66	3.1	<0.0001
	1 vs. 3	9.5	6.5	13.9	6.2	3.5	10.8	
	1 vs. 4	12.3	8.2	18.4	9.2	5.0	16.8	
Age, 59 vs. 29 years	1 vs. 2	0.36	0.27	0.48	0.77	0.40	1.5	0.0002
	1 vs. 3	1.4	1.1	1.7	0.57	0.34	0.96	
	1 vs. 4	0.52	0.39	0.70	0.26	0.14	0.48	
BMI, 32 vs. 25 kg/m^2	1 vs. 2	0.76	0.51	1.1	1.6	0.80	3.1	0.3589
	1 vs. 3	2.3	1.6	3.2	0.99	0.58	1.7	
	1 vs. 4	2.7	1.9	3.9	1.4	0.79	2.6	
Comorbidity, Y vs. N	1 vs. 2	0.33	0.22	0.49	0.67	0.36	1.26	0.0423
	1 vs. 3	1.0	0.78	1.4	0.55	0.34	0.90	
	1 vs. 4	0.42	0.29	0.63	0.50	0.27	0.91	

Continuing LT4 = therapeutic option 1 (reference), increasing LT4 = therapeutic option 2, adding LT3 to same or reduced LT4 = option 3, replacing LT4 with DTE or LT3 = option 4.

Supplementary Table S3. Univariate Analyses of Detailed Country Comparisons

(A) Comparison of binary response options
LT4 vs. any T3-containing therapy

Country of practice	*OR*	*CI*	p-*Value*
North America vs. others	1.8	1.4–2.4	<0.0001
South America vs. others	0.4	0.2–0.7	0.002
Europe vs. others	0.6	0.4–0.9	0.009
Asia vs. others	0.8	0.5–1.3	0.36
North American vs. South America	2.8	1.6–5.0	0.0003
North America vs. Europe	1.8	1.3–2.7	0.0014
North America vs. Asia	1.5	0.9–2.7	0.11

(B) Comparison of grouped response options[a]

Country of practice	*Treatment options*	*OR*	*CI*	p-*Value*
North America vs. others	1 vs. 2	0.89	0.66–1.2	0.45
North America vs. others	1 vs. 3	1.8	1.2–2.7	0.0054
North America vs. others	1 vs. 4	1.6	0.95–2.6	0.076
South America vs. others	1 vs. 2	0.49	0.27–0.88	0.017
South America vs. others	1 vs. 3	0.25	0.1–0.59	0.0016
South America vs. others	1 vs. 4	0.41	0.15–1.1	0.07
Europe vs. others	1 vs. 2	1.3	0.93–1.9	0.12
Europe vs. others	1 vs. 3	0.77	0.45–1.3	0.34
Europe vs. others	1 vs. 4	0.51	0.27–0.98	0.04
Asia vs. others	1 vs. 2	0.85	0.49–1.5	0.55
Asia vs. others	1 vs. 3	0.65	0.3–1.4	0.28
Asia vs. others	1 vs. 4	0.96	0.4–2.3	0.92
North American vs. South America	1 vs. 2	1.8	1.0–3.3	0.047
North American vs. South America	1 vs. 3	4.6	1.9–11.0	0.0007
North American vs. South America	1 vs. 4	2.7	1.0–7.4	0.026
North America vs. Europe	1 vs. 2	0.76	0.52–1.1	0.14
North America vs. Europe	1 vs. 3	1.5	0.9–2.6	0.12
North America vs. Europe	1 vs. 4	2.1	1.1–4.0	0.033
North America vs. Asia	1 vs. 2	1.1	0.64–1.9	0.71
North America vs. Asia	1 vs. 3	1.8	0.85–4.0	0.12
North America vs. Asia	1 vs. 4	1.2	0.5–3.0	0.65

[a]Continuing LT4 = therapeutic option 1 (reference), increasing LT4 = therapeutic option 2, adding LT3 to same or reduced LT4 = option 3, replacing LT4 with DTE or LT3 = option 4.