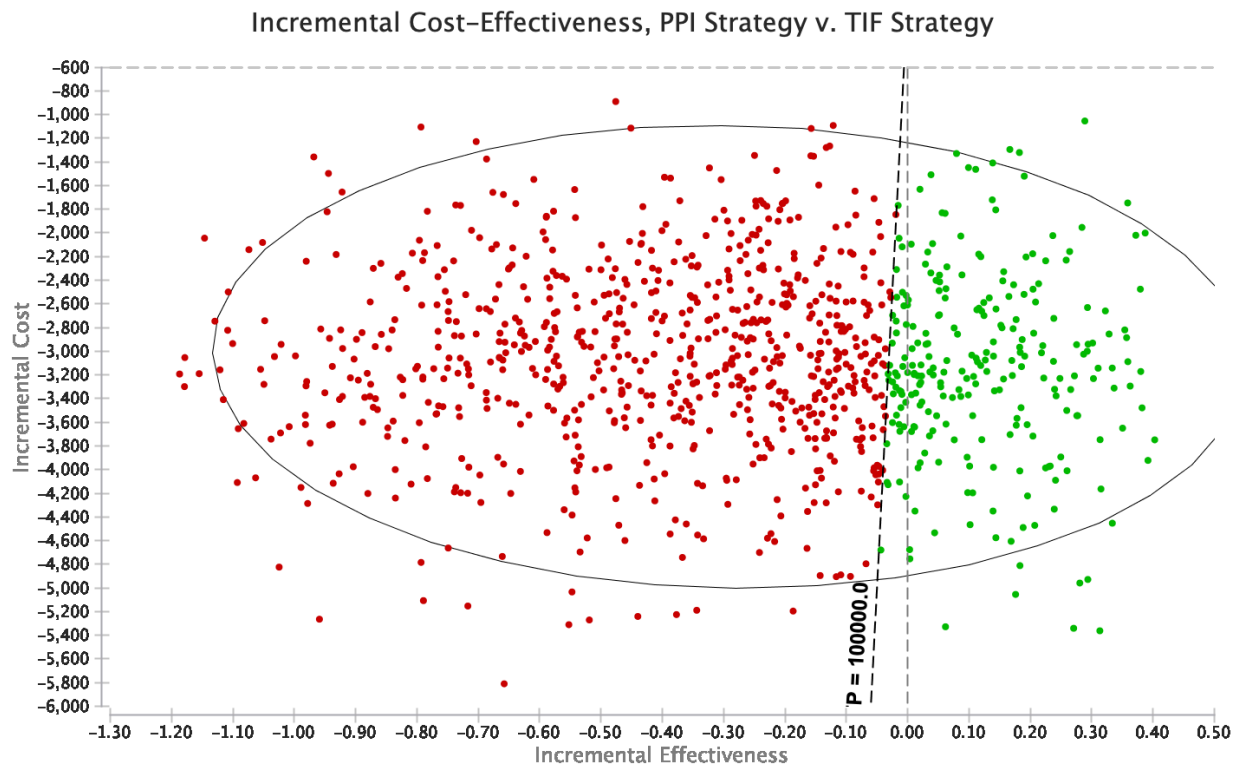


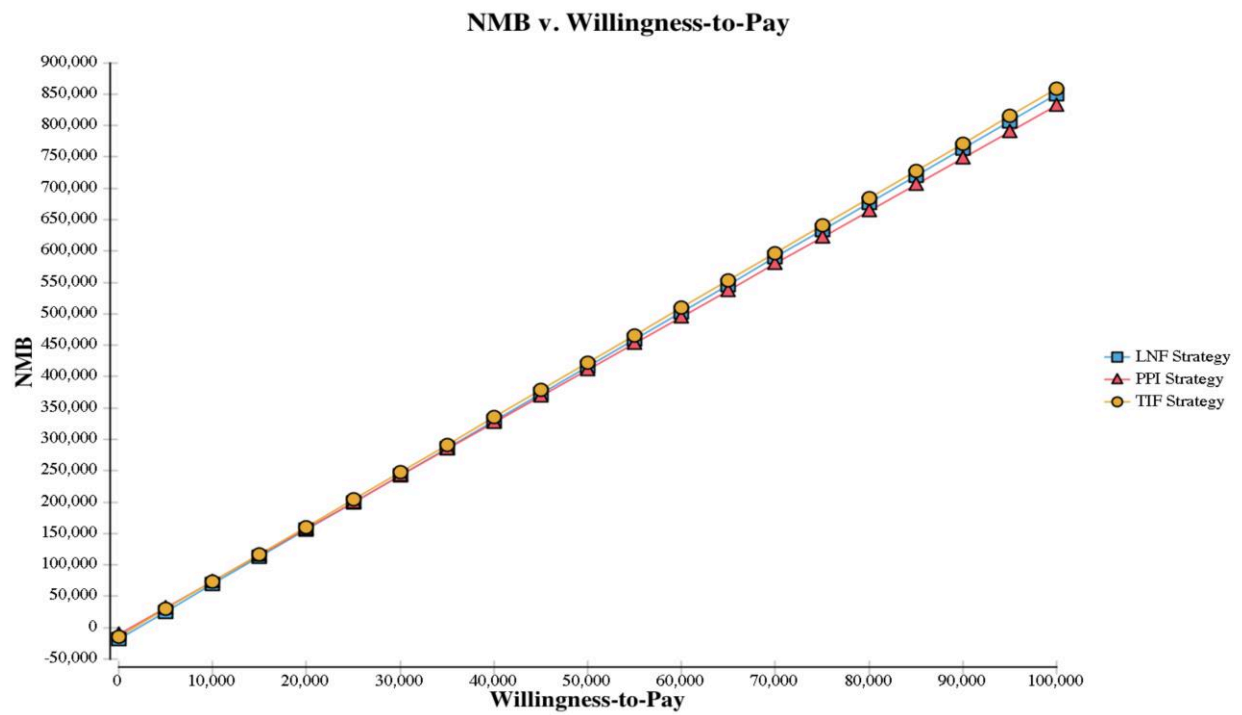
Supplementary material

Supplemental Material

Supplemental Figure 1. Incremental Cost-Effectiveness Scatterplot of Probabilistic Sensitivity Analysis Comparing PPI Only Strategy to TIF 2.0 Demonstrating the Distribution of Costs versus QALYs Based on Model Parameter Uncertainties.

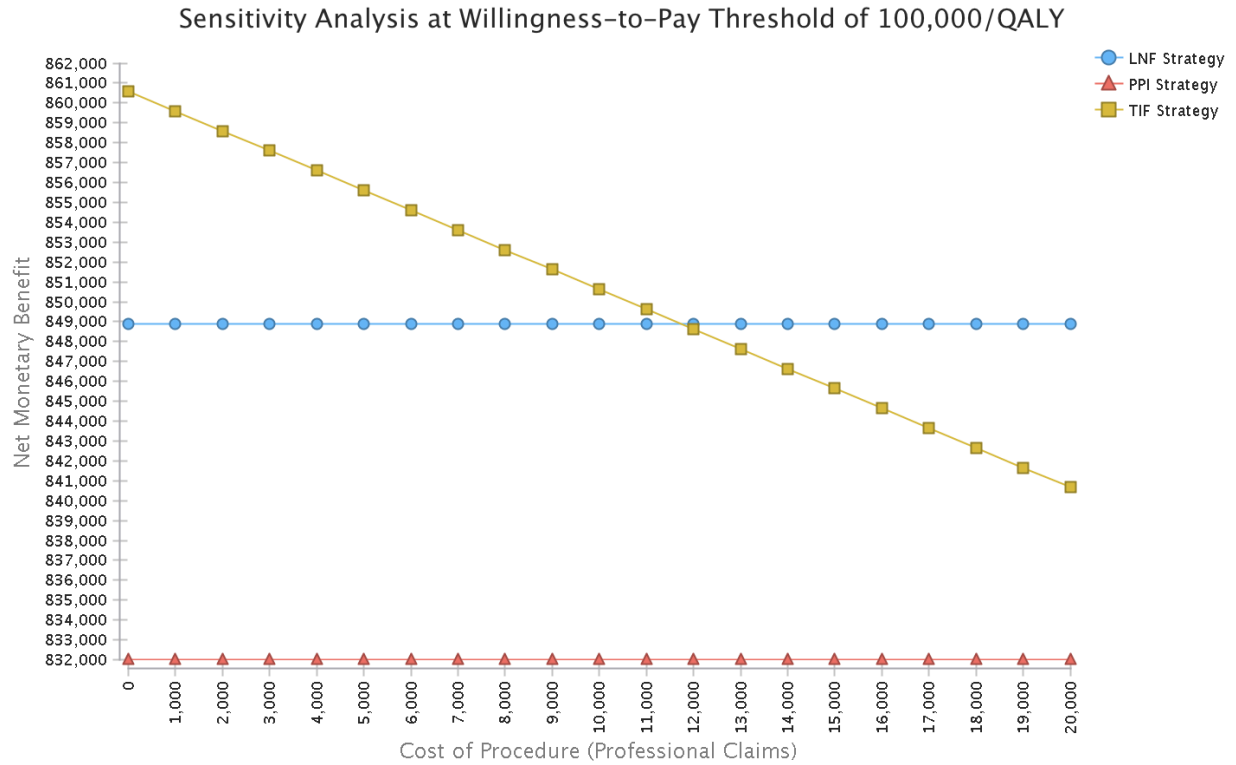


Supplementary material

Supplemental Figure 2. Net Monetary Benefit Compared up to a Willingness-to-Pay of \$100,000 for Pharmacologic vs Endoscopic vs Surgical Strategies.

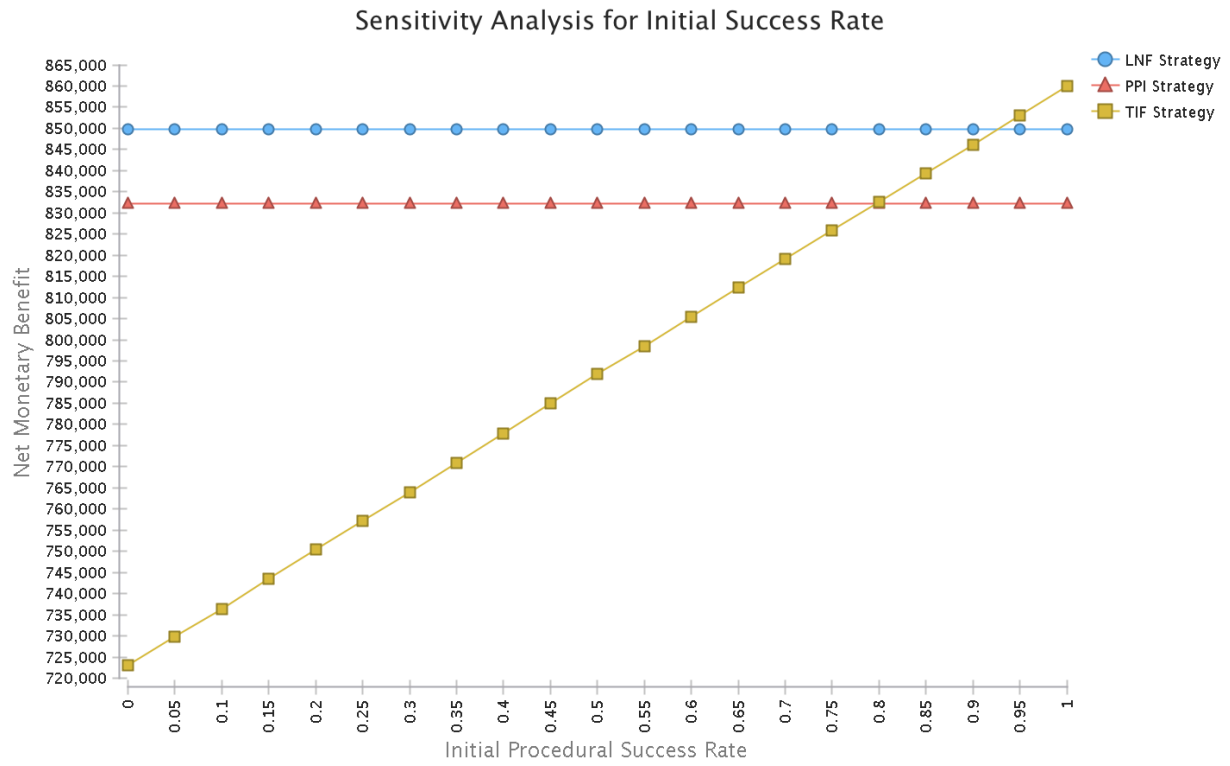
Supplementary material

Supplemental Figure 3. One-Way Sensitivity Analysis to Determine Cost-Threshold for TIF 2.0 to No Longer be Cost-Effectiveness at a Willingness-to-Pay Threshold of \$100,000.



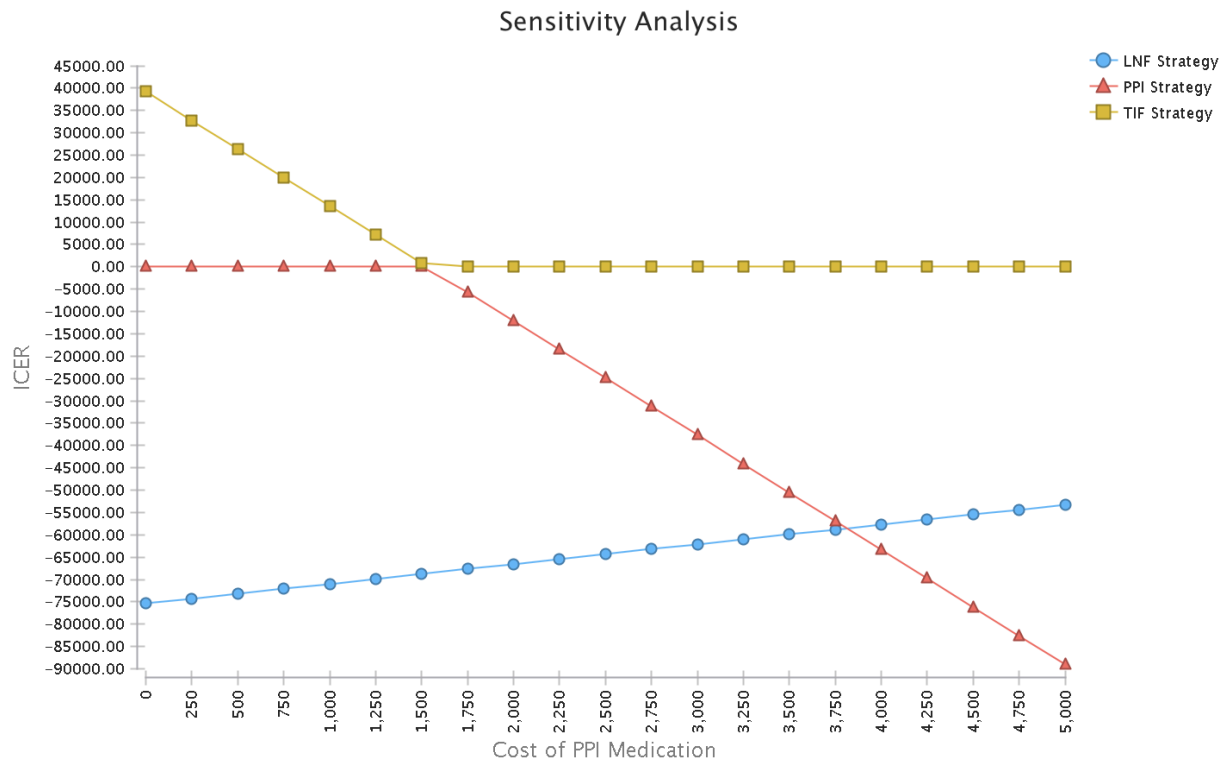
Supplementary material

Supplemental Figure 4. One-Way Sensitivity Analysis to Determine Initial Success-Threshold for TIF 2.0 to No Longer be Cost-Effectiveness at a Willingness-to-Pay Threshold of \$100,000.



Supplementary material

Supplemental Figure 5. One-Way Sensitivity Analysis to Determine Threshold Cost of PPI for TIF 2.0 to No Longer be Cost-Effectiveness at a Willingness-to-Pay Threshold of \$100,000. Annual Cost of PPI Pharmacotherapy versus Incremental Cost-Effectiveness Ratio (ICER).



Supplementary material

Supplemental Table 1. Sensitivity Analyses for PPI vs TIF 2.0 vs LNF Across Multiple Age Groups – 18 to 79 Years of Age

Initial Age	Strategy	Cost (U.S. \$)	Effectiveness (QALY)	ICER (\$/QALY)	Net Monetary Benefit (\$)
18	PPI Strategy	11,164.64	8.61	-	850,243.02
18	TIF Strategy	13,855.38	8.93	8,478.07	879,289.95
18	LNF Strategy	18,846.11	8.84	(55,865.98)	865,365.83
19	PPI Strategy	11,162.05	8.61	-	850,045.79
19	TIF Strategy	13,853.88	8.93	8,499.71	879,023.69
19	LNF Strategy	18,844.49	8.84	(56,015.08)	865,123.67
20	PPI Strategy	11,157.27	8.61	-	849,681.65
20	TIF Strategy	13,851.89	8.93	8,502.02	878,680.89
20	LNF Strategy	18,841.63	8.84	(55,989.31)	864,779.19
21	PPI Strategy	11,153.04	8.61	-	849,359.77
21	TIF Strategy	13,849.46	8.92	8,492.20	878,415.03
21	LNF Strategy	18,838.61	8.83	(55,944.32)	864,507.81
22	PPI Strategy	11,149.47	8.60	-	849,087.84
22	TIF Strategy	13,846.13	8.92	8,510.66	878,076.90
22	LNF Strategy	18,834.79	8.83	(55,999.27)	864,179.80
23	PPI Strategy	11,145.50	8.60	-	848,785.60
23	TIF Strategy	13,843.37	8.92	8,521.81	877,746.13
23	LNF Strategy	18,831.01	8.83	(55,967.91)	863,846.88
24	PPI Strategy	11,142.69	8.60	-	848,571.72
24	TIF Strategy	13,841.55	8.91	8,544.01	877,460.56
24	LNF Strategy	18,828.53	8.82	(56,154.52)	863,592.76
25	PPI Strategy	11,140.03	8.60	-	848,368.52
25	TIF Strategy	13,840.13	8.91	8,537.63	877,294.34
25	LNF Strategy	18,826.75	8.82	(56,068.35)	863,413.90
26	PPI Strategy	11,137.79	8.59	-	848,198.62
26	TIF Strategy	13,839.08	8.91	8,557.55	877,063.44
26	LNF Strategy	18,825.51	8.82	(56,263.14)	863,214.31
27	PPI Strategy	11,134.58	8.59	-	847,953.58
27	TIF Strategy	13,837.77	8.91	8,555.24	876,847.32
27	LNF Strategy	18,823.52	8.82	(56,300.57)	863,005.97
28	PPI Strategy	11,132.32	8.59	-	847,781.54
28	TIF Strategy	13,836.72	8.90	8,576.09	876,611.35
28	LNF Strategy	18,822.00	8.82	(56,296.38)	862,770.65
29	PPI Strategy	11,129.24	8.59	-	847,547.18
29	TIF Strategy	13,834.35	8.90	8,595.35	876,313.83
29	LNF Strategy	18,819.11	8.81	(56,324.83)	862,479.04
30	PPI Strategy	11,126.56	8.58	-	847,342.69

Supplementary material

30	TIF Strategy	13,832.53	8.90	8,613.09	876,053.71
30	LNF Strategy	18,816.98	8.81	(56,401.57)	862,231.83
31	PPI Strategy	11,122.80	8.58	-	847,056.68
31	TIF Strategy	13,831.07	8.90	8,621.19	875,762.51
31	LNF Strategy	18,814.52	8.81	(56,372.86)	861,938.89
32	PPI Strategy	11,119.26	8.58	-	846,787.30
32	TIF Strategy	13,829.25	8.89	8,629.76	875,480.10
32	LNF Strategy	18,811.97	8.80	(56,358.17)	861,656.20
33	PPI Strategy	11,116.08	8.58	-	846,545.26
33	TIF Strategy	13,827.04	8.89	8,647.03	875,185.58
33	LNF Strategy	18,809.22	8.80	(56,327.94)	861,358.44
34	PPI Strategy	11,111.30	8.57	-	846,181.11
34	TIF Strategy	13,824.96	8.89	8,650.69	874,836.68
34	LNF Strategy	18,806.41	8.80	(56,427.08)	861,027.11
35	PPI Strategy	11,106.62	8.57	-	845,824.23
35	TIF Strategy	13,822.47	8.88	8,700.27	874,324.14
35	LNF Strategy	18,802.61	8.79	(56,644.86)	860,552.15
36	PPI Strategy	11,102.13	8.57	-	845,482.72
36	TIF Strategy	13,819.92	8.88	8,707.86	873,975.72
36	LNF Strategy	18,799.10	8.79	(56,650.10)	860,207.18
37	PPI Strategy	11,096.12	8.56	-	845,024.66
37	TIF Strategy	13,817.32	8.87	8,706.84	873,557.07
37	LNF Strategy	18,795.34	8.79	(56,661.37)	859,793.49
38	PPI Strategy	11,090.62	8.56	-	844,606.30
38	TIF Strategy	13,815.00	8.87	8,712.21	873,152.74
38	LNF Strategy	18,792.21	8.78	(56,634.76)	859,387.27
39	PPI Strategy	11,083.84	8.55	-	844,089.33
39	TIF Strategy	13,812.46	8.86	8,724.04	872,637.81
39	LNF Strategy	18,788.65	8.78	(56,596.71)	858,869.27
40	PPI Strategy	11,076.27	8.55	-	843,513.02
40	TIF Strategy	13,808.68	8.86	8,782.46	871,892.79
40	LNF Strategy	18,783.69	8.77	(57,004.70)	858,190.41
41	PPI Strategy	11,066.26	8.54	-	842,750.59
41	TIF Strategy	13,804.11	8.85	8,788.11	871,166.82
41	LNF Strategy	18,777.54	8.76	(56,862.81)	857,447.01
42	PPI Strategy	11,054.78	8.53	-	841,876.74
42	TIF Strategy	13,798.18	8.84	8,850.77	870,129.54
42	LNF Strategy	18,769.00	8.75	(56,948.60)	856,430.12
43	PPI Strategy	11,042.68	8.52	-	840,955.50
43	TIF Strategy	13,792.96	8.83	8,895.83	869,121.64
43	LNF Strategy	18,747.21	8.74	(56,989.55)	855,474.12

Supplementary material

44	PPI Strategy	11,030.82	8.51	-	840,052.19
44	TIF Strategy	13,786.90	8.82	8,987.75	867,960.92
44	LNF Strategy	18,689.74	8.73	(57,167.87)	854,481.85
45	PPI Strategy	11,016.09	8.50	-	838,929.89
45	TIF Strategy	13,778.96	8.80	9,071.67	866,623.12
45	LNF Strategy	18,596.28	8.72	(57,193.44)	853,382.96
46	PPI Strategy	10,999.44	8.49	-	837,662.01
46	TIF Strategy	13,770.49	8.79	9,145.73	865,189.77
46	LNF Strategy	18,467.06	8.71	(57,684.82)	852,351.41
47	PPI Strategy	10,980.99	8.47	-	836,257.53
47	TIF Strategy	13,785.52	8.77	9,326.73	863,522.73
47	LNF Strategy	18,294.14	8.70	(58,616.47)	851,322.37
48	PPI Strategy	10,962.01	8.46	-	834,811.64
48	TIF Strategy	13,843.87	8.75	9,711.42	861,604.73
48	LNF Strategy	18,080.89	8.68	(60,825.78)	850,401.87
49	PPI Strategy	10,939.04	8.44	-	833,062.65
49	TIF Strategy	13,933.63	8.73	10,213.41	859,388.22
49	LNF Strategy	17,806.61	8.67	(64,966.01)	849,553.69
50	PPI Strategy	10,913.92	8.42	-	831,149.74
50	TIF Strategy	14,055.67	8.71	10,928.03	856,757.42
50	LNF Strategy	17,470.83	8.66	(75,257.54)	848,804.29
51	PPI Strategy	10,888.77	8.40	-	829,233.83
51	TIF Strategy	14,161.73	8.68	11,741.01	853,837.18
51	LNF Strategy	17,255.30	8.64	(86,186.44)	847,154.21
52	PPI Strategy	10,858.36	8.38	-	826,917.93
52	TIF Strategy	14,233.98	8.65	12,354.90	850,864.48
52	LNF Strategy	17,165.40	8.62	(96,257.60)	844,887.66
53	PPI Strategy	10,831.03	8.36	-	824,836.82
53	TIF Strategy	14,275.39	8.62	12,884.53	848,125.01
53	LNF Strategy	17,033.91	8.60	(112,355.84)	842,911.33
54	PPI Strategy	10,801.18	8.33	-	822,564.04
54	TIF Strategy	14,290.04	8.59	13,409.64	845,092.71
54	LNF Strategy	16,856.33	8.58	(146,879.50)	840,779.22
55	PPI Strategy	10,770.57	8.31	-	820,232.34
55	TIF Strategy	14,064.46	8.57	12,557.68	843,168.57
55	LNF Strategy	16,632.74	8.56	(150,215.30)	838,890.56
56	PPI Strategy	10,737.07	8.28	-	817,681.64
56	TIF Strategy	13,601.27	8.56	10,498.60	842,099.18
56	LNF Strategy	16,357.45	8.53	(121,392.47)	837,072.54
57	PPI Strategy	10,702.19	8.26	-	815,025.08
57	TIF Strategy	13,006.27	8.55	7,926.06	841,790.66

Supplementary material

57	LNF Strategy	16,013.01	8.52	(95,869.38)	835,647.63
58	PPI Strategy	10,670.39	8.23	-	812,603.31
58	TIF Strategy	12,250.61	8.54	5,107.42	841,962.91
58	LNF Strategy	15,615.62	8.50	(77,422.96)	834,251.63
59	PPI Strategy	10,634.11	8.20	-	809,840.45
59	TIF Strategy	11,967.19	8.52	4,266.11	839,755.54
59	LNF Strategy	15,463.60	8.47	(74,527.20)	831,567.68
60	PPI Strategy	10,593.70	8.17	-	806,763.39
60	TIF Strategy	11,956.34	8.48	4,407.14	836,319.54
60	LNF Strategy	15,451.94	8.44	(74,380.47)	828,124.32
61	PPI Strategy	10,552.74	8.14	-	803,644.08
61	TIF Strategy	11,945.21	8.45	4,552.36	832,839.48
61	LNF Strategy	15,440.94	8.40	(76,024.60)	824,745.59
62	PPI Strategy	10,506.28	8.11	-	800,105.55
62	TIF Strategy	11,933.53	8.41	4,740.44	828,786.26
62	LNF Strategy	15,428.46	8.36	(76,228.55)	820,706.53
63	PPI Strategy	10,452.66	8.06	-	796,021.88
63	TIF Strategy	11,918.94	8.36	4,935.61	824,263.87
63	LNF Strategy	15,413.78	8.32	(76,445.89)	816,197.39
64	PPI Strategy	10,396.75	8.02	-	791,764.03
64	TIF Strategy	11,903.89	8.31	5,186.18	819,317.75
64	LNF Strategy	15,397.90	8.27	(76,725.43)	811,269.84
65	PPI Strategy	10,338.26	7.98	-	787,310.24
65	TIF Strategy	11,889.70	8.26	5,539.05	813,767.84
65	LNF Strategy	15,383.91	8.21	(76,700.30)	805,717.95
66	PPI Strategy	10,265.09	7.92	-	781,737.56
66	TIF Strategy	11,871.15	8.19	5,874.06	807,473.04
66	LNF Strategy	15,363.76	8.15	(78,095.03)	799,508.17
67	PPI Strategy	10,185.31	7.86	-	775,662.43
67	TIF Strategy	11,851.65	8.13	6,211.60	800,822.34
67	LNF Strategy	15,344.16	8.08	(79,349.94)	792,928.44
68	PPI Strategy	10,099.70	7.79	-	769,142.90
68	TIF Strategy	11,829.68	8.05	6,706.47	793,208.51
68	LNF Strategy	15,321.43	8.01	(80,816.03)	785,396.15
69	PPI Strategy	9,999.86	7.72	-	761,539.48
69	TIF Strategy	11,802.47	7.96	7,251.46	784,595.34
69	LNF Strategy	15,293.53	7.92	(81,565.63)	776,824.21
70	PPI Strategy	9,893.73	7.63	-	753,456.66
70	TIF Strategy	11,774.47	7.87	7,936.40	775,273.61
70	LNF Strategy	15,264.20	7.83	(81,698.91)	767,512.42
71	PPI Strategy	9,771.11	7.54	-	744,118.77

Supplementary material

71	TIF Strategy	11,742.20	7.77	8,656.35	764,918.17
71	LNF Strategy	15,231.38	7.72	(81,940.48)	757,170.81
72	PPI Strategy	9,639.76	7.44	-	734,115.79
72	TIF Strategy	11,705.08	7.65	9,837.55	753,044.67
72	LNF Strategy	15,192.64	7.60	(81,920.42)	745,299.85
73	PPI Strategy	9,493.99	7.33	-	723,014.82
73	TIF Strategy	11,664.90	7.52	11,117.29	740,371.22
73	LNF Strategy	15,149.17	7.48	(81,474.42)	732,610.42
74	PPI Strategy	9,331.35	7.20	-	710,628.48
74	TIF Strategy	11,619.89	7.38	12,850.13	726,149.42
74	LNF Strategy	15,102.53	7.34	(83,409.46)	718,491.42
75	PPI Strategy	9,151.07	7.06	-	696,899.99
75	TIF Strategy	11,567.66	7.22	15,534.43	710,039.74
75	LNF Strategy	15,047.10	7.17	(84,553.79)	702,445.25
76	PPI Strategy	8,958.88	6.91	-	682,263.48
76	TIF Strategy	11,510.09	7.04	19,238.84	692,972.98
76	LNF Strategy	14,986.03	7.00	(86,345.63)	685,471.42
77	PPI Strategy	8,743.60	6.75	-	665,868.60
77	TIF Strategy	11,445.91	6.86	22,839.67	674,997.97
77	LNF Strategy	14,917.16	6.83	(90,081.29)	667,673.27
78	PPI Strategy	8,513.75	6.57	-	648,364.65
78	TIF Strategy	11,378.37	6.66	30,013.39	655,044.51
78	LNF Strategy	14,844.15	6.63	(91,803.48)	647,803.51
79	PPI Strategy	8,264.29	6.38	-	629,366.57
79	TIF Strategy	11,303.96	6.45	41,710.00	633,614.54
79	LNF Strategy	14,763.20	6.41	(94,758.75)	626,504.72

Supplementary material

Supplemental References¹⁻³⁰

1. Quine MA, Bell GD, McCloy RF, Matthews HR. Prospective audit of perforation rates following upper gastrointestinal endoscopy in two regions of England. *Br J Surg* 1995;82:530-3.
2. Carlson MA, Frantzides CT. Complications and results of primary minimally invasive antireflux procedures: a review of 10,735 reported cases. *J Am Coll Surg* 2001;193:428-39.
3. Funk LM, Zhang JY, Drosdeck JM, Melvin WS, Walker JP, Perry KA. Long-term cost-effectiveness of medical, endoscopic and surgical management of gastroesophageal reflux disease. *Surgery* 2015;157:126-36.
4. Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 2011;305:1969-77.
5. Rantanen TK, Salo JA, Sipponen JT. Fatal and life-threatening complications in antireflux surgery: analysis of 5,502 operations. *Br J Surg* 1999;86:1573-7.
6. McCarty TR, Itidiare M, Njei B, Rustagi T. Efficacy of transoral incisionless fundoplication for refractory gastroesophageal reflux disease: a systematic review and meta-analysis. *Endoscopy* 2018;50:708-25.
7. Allen CJ, Anvari M. Preoperative symptom evaluation and esophageal acid infusion predict response to laparoscopic Nissen fundoplication in gastroesophageal reflux patients who present with cough. *Surg Endosc* 2002;16:1037-41.
8. Richards WO, Houston HL, Torquati A, Khaitan L, Holzman MD, Sharp KW. Paradigm shift in the management of gastroesophageal reflux disease. *Ann Surg* 2003;237:638-47; discussion 48-9.
9. Du X, Wu JM, Hu ZW, et al. Laparoscopic Nissen (total) versus anterior 180 degrees fundoplication for gastro-esophageal reflux disease: A meta-analysis and systematic review. *Medicine (Baltimore)* 2017;96:e8085.
10. Tian ZC, Wang B, Shan CX, Zhang W, Jiang DZ, Qiu M. A Meta-Analysis of Randomized Controlled Trials to Compare Long-Term Outcomes of Nissen and Toupet Fundoplication for Gastroesophageal Reflux Disease. *PLoS One* 2015;10:e0127627.
11. Aiolfi A, Asti E, Bernardi D, et al. Early results of magnetic sphincter augmentation versus fundoplication for gastroesophageal reflux disease: Systematic review and meta-analysis. *Int J Surg* 2018;52:82-8.
12. Trad KS, Fox MA, Simoni G, et al. Transoral fundoplication offers durable symptom control for chronic GERD: 3-year report from the TEMPO randomized trial with a crossover arm. *Surg Endosc* 2017;31:2498-508.
13. Bloomston M, Nields W, Rosemurgy AS. Symptoms and antireflux medication use following laparoscopic Nissen fundoplication: outcome at 1 and 4 years. *JLS* 2003;7:211-8.
14. Antoniou SA, Delivorias P, Antoniou GA, et al. Symptom-focused results after laparoscopic fundoplication for refractory gastroesophageal reflux disease--a prospective study. *Langenbecks Arch Surg* 2008;393:979-84.
15. Cadiere GB, Van Sante N, Graves JE, Gawlicka AK, Rajan A. Two-year results of a feasibility study on antireflux transoral incisionless fundoplication using EsophyX. *Surg Endosc* 2009;23:957-64.

Supplementary material

16. Muls V, Eckardt AJ, Marchese M, et al. Three-year results of a multicenter prospective study of transoral incisionless fundoplication. *Surg Innov* 2013;20:321-30.
17. Bell RC, Fox MA, Barnes WE, et al. Univariate and multivariate analyses of preoperative factors influencing symptomatic outcomes of transoral fundoplication. *Surg Endosc* 2014;28:2949-58.
18. Lee TG, Lee IS, Kim BS, Jung HY, Choi YB. Surgical outcomes and over one-year follow-up results of laparoscopic Nissen fundoplication for gastroesophageal reflux disease: Single-center experiences. *Asian J Surg* 2019;42:557-62.
19. Trad KS, Barnes WE, Prevou ER, et al. The TEMPO Trial at 5 Years: Transoral Fundoplication (TIF 2.0) Is Safe, Durable, and Cost-effective. *Surg Innov* 2018;25:149-57.
20. Testoni PA, Testoni S, Distefano G, Mazzoleni G, Fanti L, Passaretti S. Transoral incisionless fundoplication with EsophyX for gastroesophageal reflux disease: clinical efficacy is maintained up to 10 years. *Endosc Int Open* 2019;7:E647-E54.
21. Lodrup A, Pottegard A, Hallas J, Bytzer P. Use of proton pump inhibitors after antireflux surgery: a nationwide register-based follow-up study. *Gut* 2014;63:1544-9.
22. Chimukangara M, Jalilvand AD, Melvin WS, Perry KA. Long-term reported outcomes of transoral incisionless fundoplication: an 8-year cohort study. *Surg Endosc* 2019;33:1304-9.
23. CMS, Center for Medicare and Medicaid Services. 2019.
24. Red Book - Healthcare Drug Pricing Resource. Micromedex 2.0. Truven Health Analytics, Inc. 2016. Available at: <https://www.micromedexsolutions.com/> Accessed 15 June 2020.
25. Blue Health Intelligence (BHI) Claims Data. Corporate Medical Policy. April 2020. .
26. Spiegel BM, Dulai GS, Lim BS, Mann N, Kanwal F, Gralnek IM. The cost-effectiveness and budget impact of intravenous versus oral proton pump inhibitors in peptic ulcer hemorrhage. *Clin Gastroenterol Hepatol* 2006;4:988-97.
27. Ofman JJ, Dorn GH, Fennerty MB, Fass R. The clinical and economic impact of competing management strategies for gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2002;16:261-73.
28. Moayyedi P, Armstrong D, Hunt RH, Lei Y, Bukoski M, White RJ. The gain in quality-adjusted life months by switching to esomeprazole in those with continued reflux symptoms in primary care: EncompASS--a cluster-randomized trial. *Am J Gastroenterol* 2010;105:2341-6.
29. Gerson LB, Robbins AS, Garber A, Hornberger J, Triadafilopoulos G. A cost-effectiveness analysis of prescribing strategies in the management of gastroesophageal reflux disease. *Am J Gastroenterol* 2000;95:395-407.
30. Comay D, Adam V, da Silveira EB, Kennedy W, Mayrand S, Barkun AN. The Stretta procedure versus proton pump inhibitors and laparoscopic Nissen fundoplication in the management of gastroesophageal reflux disease: a cost-effectiveness analysis. *Can J Gastroenterol* 2008;22:552-8.