

SUPPLEMENTAL MATERIAL

Cost Analyses

Cost estimates were derived from three primary sources: 1) the Premier Research Database for index diagnostic testing, 2) hospital billing data for hospital costs, and 3) Current Procedural Terminology or Healthcare Common Procedure Coding System codes in the 2014 Medicare national reimbursement schedule for physician costs. Total costs (fixed plus variable) were discounted at a 3% annual rate and adjusted to 2014 U.S. dollars using the Producer Price Index for hospital care. A repeated measures, mixed model was used to assess the association between inconclusive test results and costs over the first 24 months after randomization. A random intercept was included for each subject to account for clustering in the data. Time points for repeated measures were every 3 months. A multivariable repeated measures regression model was fitted to assess the association between inconclusive test results and costs over the first 24 months from randomization after adjusting for key characteristics. The linearity assumption was used for all continuous adjustment variables, and an appropriate nonlinear form was used in cases where the assumption did not hold. The mean cost (95% CI) for inconclusive and negative conclusive tests was presented by quarter. The mean difference between inconclusive and negative conclusive test results (95% CI) and p-value were presented for the unadjusted and adjusted regression models.

Table I: Association between NIT Modality and NIT Inconclusiveness in Intention-to-Treat Population

Comparison	Frequency of Inconclusiveness (# Events/Sample Size)		Unadjusted*		Adjusted†	
	Stress Test	CTA	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Stress vs. CTA	458/4718 (9.71%)	316/4821 (6.55%)	1.53 (1.32-1.78)	<0.001	1.53 (1.32-1.79)	<0.001

NIT = noninvasive test, CTA = computed tomographic angiogram

* Unadjusted model contains NIT modality (stress test vs. CTA).

† Adjusted model contains NIT modality (stress test vs. CTA), age, sex, BMI, diabetes, smoker (ever/never), CAD equivalent, site characterization of chest pain, provider estimation of likelihood of obstructive epicardial disease (high or very high), hypertension, dyslipidemia, family history of premature CAD, participate in physical activity, Framingham Risk Score (2008), Diamond-Forrester (2011) score.

Table II: Association between NIT Type and NIT Inconclusiveness in Intention-to-Treat Population

Comparison	Frequency of Inconclusiveness (# Events/Sample Size)		Unadjusted*		Adjusted†	
	Stress Test	CTA	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Stress Nuclear vs. CTA	229/3197 (7.16%)	316/4821 (6.55%)	1.10 (0.92-1.31)	0.289	1.07 (0.90-1.29)	0.429
Stress Echo vs. CTA	121/1049 (11.53%)	316/4821 (6.55%)	1.86 (1.49-2.32)	<0.001	1.98 (1.58-2.48)	<0.001
Exercise ECG vs. CTA	108/472 (22.88%)	316/4821 (6.55%)	4.23 (3.32-5.39)	<0.001	4.42 (3.43-5.68)	<0.001

NIT = noninvasive test, CTA = computed tomographic angiogram, ECG = electrocardiogram

* Unadjusted model contains NIT test type (stress nuclear, stress echo, exercise ECG vs. CTA).

† Adjusted model contains NIT test type (stress nuclear, stress echo, exercise ECG vs. CTA), age, sex, BMI, diabetes, smoker (ever/never), CAD equivalent, site characterization of chest pain, provider estimation of likelihood of obstructive epicardial disease (high or very high), hypertension, dyslipidemia, family history of premature CAD, participate in physical activity, Framingham Risk Score (2008), Diamond-Forrester (2011) score.

Table III: Association between Stress Test Type and NIT Inconclusiveness

Comparison	Frequency of Inconclusiveness (# Events/Sample Size)		Unadjusted*		Adjusted†	
	Imaging Stress Test	Exercise ECG	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Stress Nuclear vs. Exercise ECG	215/3096 (6.94%)	104/438 (23.74%)	0.24 (0.18-0.31)	<0.001	0.23 (0.17-0.30)	<0.001
Stress Echo vs. Exercise ECG	119/999 (11.91%)	104/438 (23.74%)	0.43 (0.32-0.58)	<0.001	0.44 (0.32-0.59)	<0.001

NIT = noninvasive test, ECG = electrocardiogram

* Unadjusted model contains stress test type (stress nuclear, stress echo vs. exercise ECG).

† Adjusted model contains stress test type (stress nuclear, stress echo, vs. exercise ECG), age, sex, body mass index (BMI), diabetes, smoker (ever/never), coronary artery disease (CAD) equivalent, site characterization of chest pain, provider estimation of likelihood of obstructive epicardial disease (high or very high), hypertension, dyslipidemia, family history of premature CAD, participate in physical activity, Framingham Risk Score (2008), Diamond-Forrester (2011) score.

Table IV: Association between Inconclusive Test Results and Process of Care by Stress Test Type

Process of Care/Outcome	Frequency of Event (# Events/Sample Size)		Unadjusted		Adjusted*	
	Inconclusive or Conclusive Positive	Conclusive Negative	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Exercise ECG						
Referral to 2nd NIT within 90 Days of 1st NIT						
Conclusive Positive vs. Conclusive Negative	23/54 (42.6%)	28/280 (10.0%)	6.68 (3.42-13.02)	<0.001	5.99 (2.96-12.14)	<0.001
Inconclusive vs. Conclusive Negative	23/104 (22.1%)	28/280 (10.0%)	2.56 (1.39-4.69)	0.003	2.46 (1.30-4.64)	0.006
Referral to ICA within 90 Days of Randomization						
Conclusive Positive vs. Conclusive Negative	16/54 (29.6%)	2/280 (0.7%)	58.53 (12.89-265.67)	<0.001	99.49 (16.35-605.50)	<0.001
Inconclusive vs. Conclusive Negative	3/104 (2.9%)	2/280 (0.7%)	4.13 (0.68-25.19)	0.124	3.62 (0.50-26.43)	0.203
Stress Echo						
Referral to 2nd NIT within 90 Days of 1st NIT						
Conclusive Positive vs. Conclusive Negative	19/75 (25.3%)	53/805 (6.6%)	4.81 (2.67-8.69)	<0.001	4.79 (2.56-8.97)	<0.001
Inconclusive vs. Conclusive Negative	15/119 (12.6%)	53/805 (6.6%)	2.05 (1.11-3.76)	0.021	1.98 (1.04-3.79)	0.039
Referral to ICA within 90 Days of Randomization						
Conclusive Positive vs. Conclusive Negative	44/75 (58.7%)	10/805 (1.2%)	112.84 (51.95-245.09)	<0.001	121.17 (51.53-284.91)	<0.001
Inconclusive vs. Conclusive Negative	6/119 (5.0%)	10/805 (1.2%)	4.22 (1.50-11.85)	0.006	4.02 (1.33-12.13)	0.014
Stress Nuclear						
Referral to 2nd NIT within 90 Days of 1st NIT						
Conclusive Positive vs. Conclusive Negative	103/435 (23.7%)	218/2446 (8.9%)	3.17 (2.44-4.12)	<0.001	3.06 (2.33-4.02)	<0.001
Inconclusive vs. Conclusive Negative	26/215 (12.1%)	218/2446 (8.9%)	1.41 (0.91-2.17)	0.123	1.48 (0.96-2.29)	0.079
Referral to ICA within 90 Days of Randomization						
Conclusive Positive vs. Conclusive Negative	203/435 (46.7%)	73/2446 (3.0%)	28.44 (21.08-38.38)	<0.001	27.83 (20.30-38.14)	<0.001

Table IV: Association between Inconclusive Test Results and Process of Care by Stress Test Type

Process of Care/Outcome	Frequency of Event (# Events/Sample Size)		Unadjusted		Adjusted*	
	Inconclusive or Conclusive Positive	Conclusive Negative	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Inconclusive vs. Conclusive Negative	15/215 (7.0%)	73/2446 (3.0%)	2.44 (1.37-4.33)	0.002	2.47 (1.38-4.43)	0.002

NIT = noninvasive test, ICA = invasive coronary angiogram

* Adjustment variables include age, sex, race, ethnicity, body mass index, hypertension, diabetes, dyslipidemia, smoking (ever), depression, participate in physical activity, family history of CAD, peripheral arterial disease or cerebrovascular disease, and site characterization of chest pain

Table V: Association between Inconclusive Test Results and Outcomes by Stress Test Type

Process of Care/Outcome	Frequency of Event (# Events/Sample Size)		Unadjusted		Adjusted*	
	Inconclusive	Conclusive	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Exercise ECG[†]						
All-Cause Death/MI/UAH						
Conclusive Positive vs. Conclusive Negative	1/54 (1.9%)	2/280 (0.7%)				
Inconclusive vs. Conclusive Negative	2/104 (1.9%)	2/280 (0.7%)				
CV Death/MI						
Conclusive Positive vs. Conclusive Negative	0/54 (0.0%)	1/280 (0.4%)				
Inconclusive vs. Conclusive Negative	1/104 (1.0%)	1/280 (0.4%)				
Stress Echo						
All-Cause Death/MI/UAH						
Conclusive Positive vs. Conclusive Negative	4/75 (5.3%)	13/805 (1.6%)	3.21 (1.05-9.86)	0.041	2.08 (0.63-6.89)	0.228
Inconclusive vs. Conclusive Negative	5/119 (4.2%)	13/805 (1.6%)	2.66 (0.95-7.46)	0.063	1.93 (0.63-5.93)	0.248
CV Death/MI						
Conclusive Positive vs. Conclusive Negative	2/75 (2.7%)	5/805 (0.6%)	3.93 (0.76-20.29)	0.102	3.59 (0.57-22.42)	0.172
Inconclusive vs. Conclusive Negative	2/119 (1.7%)	5/805 (0.6%)	2.79 (0.54-14.40)	0.220	1.71 (0.23-12.55)	0.600
Stress Nuclear						
All-Cause Death/MI/UAH						
Conclusive Positive vs. Conclusive Negative	42/435 (9.7%)	54/2446 (2.2%)	4.62 (3.09-6.92)	<0.001	3.84 (2.52-5.83)	<0.001
Inconclusive vs. Conclusive Negative	9/215 (4.2%)	54/2446 (2.2%)	1.89 (0.93-3.83)	0.077	1.77 (0.87-3.60)	0.113
CV Death/MI						
Conclusive Positive vs. Conclusive Negative	17/435 (3.9%)	37/2446 (1.5%)	2.58 (1.45-4.58)	0.001	1.98 (1.09-3.62)	0.026

Table V: Association between Inconclusive Test Results and Outcomes by Stress Test Type

Process of Care/Outcome	Frequency of Event (# Events/Sample Size)		Unadjusted		Adjusted*	
	Inconclusive	Conclusive	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Inconclusive vs. Conclusive Negative	8/215 (3.7%)	37/2446 (1.5%)	2.43 (1.13-5.21)	0.023	2.36 (1.09-5.09)	0.029

ECG = electrocardiogram, MI = myocardial infarction, UAH = unstable angina hospitalization

* Adjustment variables include age, sex, race, ethnicity, body mass index, hypertension, diabetes, dyslipidemia, smoking (ever), depression, participate in physical activity, family history of CAD, peripheral arterial disease or cerebrovascular disease, and site characterization of chest pain

† The number of events in the exercise ECG group are too low to get an accurate hazards ratio.

Table VI: Pretest/Provider Assessment and Characteristics Among Inconclusive Test Results that Did or Did Not Lead to Additional Testing			
	Second NIT or ICA		
Characteristic	Yes	No	P-value
N	240	496	
ASCVD (2013)	20.3 (13.47)	15.5 (12.24)	<0.001
Framingham Risk Score (2008)	29.0 (16.98)	23.5 (16.71)	<0.001
Provider characteristic of chest pain cardiac			0.570
Non-cardiac	26 (10.8%)	61 (12.3%)	
Typical/Atypical	214 (89.2%)	436 (87.7%)	
Provider assessment of significant epicardial coronary stenosis or left main stenosis			<0.001
Very Low/Low (<30%)	79 (32.9%)	191 (38.4%)	
Intermediate (31-70%)	130 (54.2%)	284 (57.1%)	
High/Very High (≥70%)	31 (12.9%)	22 (4.4%)	
ASCVD = atherosclerotic cardiovascular disease			

Table VII: Association between Inconclusive Test Results from Initial NIT and Total Medical Costs for Overall Stress and CTA						
	Total Medical Costs (\$, Cumulative) LS Means (95% CI)		Unadjusted Difference in Costs (\$)		Adjusted Difference in Costs (\$) *	
Time from Randomization	Comparison Group	Conclusive Negative	Difference (95% CI)	P-value	Difference (95% CI)	P-value
Conclusive Positive vs. Conclusive Negative						
<i>CTA</i>						
3 Months	10932 (10350-11513)	1175 (957-1393)	9757 (9136-10378)	<0.001	9052 (8240-9864)	<0.001
6 Months	12797 (12102-13492)	1652 (1392-1912)	11145 (10403-11887)	<0.001	10604 (9574-11634)	<0.001
9 Months	13511 (12770-14253)	1970 (1692-2248)	11541 (10749-12333)	<0.001	10839 (9755-11922)	<0.001
12 Months	13975 (13150-14799)	2406 (2096-2715)	11569 (10689-12450)	<0.001	10988 (9761-12214)	<0.001
15 Months	14805 (13915-15695)	2768 (2429-3106)	12037 (11085-12989)	<0.001	11588 (10245-12931)	<0.001
18 Months	15580 (14578-16581)	3188 (2807-3570)	12392 (11320-13463)	<0.001	11735 (10224-13247)	<0.001
21 Months	15995 (14891-17100)	3503 (3084-3922)	12492 (11311-13673)	<0.001	11962 (10254-13669)	<0.001
24 Months	16862 (15600-18123)	3893 (3413-4373)	12969 (11619-14318)	<0.001	11258 (9373-13143)	<0.001
<i>Stress</i>						
3 Months	7316 (6817-7815)	1541 (1343-1739)	5775 (5238-6311)	<0.001	6235 (5516-6953)	<0.001
6 Months	8833 (8220-9447)	2081 (1837-2325)	6752 (6091-7412)	<0.001	7034 (6211-7857)	<0.001
9 Months	9495 (8825-10164)	2379 (2114-2644)	7116 (6396-7836)	<0.001	7199 (6314-8084)	<0.001
12 Months	10210 (9471-10949)	2684 (2393-2976)	7526 (6731-8320)	<0.001	7604 (6587-8620)	<0.001
15 Months	10469 (9666-11272)	2972 (2655-3289)	7497 (6634-8360)	<0.001	7641 (6571-8711)	<0.001
18 Months	11568 (10588-12547)	3420 (3027-3812)	8148 (7093-9203)	<0.001	8395 (7195-9595)	<0.001
21 Months	11712 (10620-12803)	3838 (3400-4276)	7874 (6697-9050)	<0.001	8810 (7417-10202)	<0.001
24 Months	12597 (11340-13854)	4199 (3693-4704)	8399 (7044-9753)	<0.001	9150 (7571-10729)	<0.001
Inconclusive vs. Conclusive Negative						
<i>CTA</i>						
3 Months	4372 (3569-5175)	1175 (957-1393)	3197 (2365-4029)	<0.001	2902 (1888-3916)	<0.001

Table VII: Association between Inconclusive Test Results from Initial NIT and Total Medical Costs for Overall Stress and CTA						
Time from Randomization	Total Medical Costs (\$, Cumulative) LS Means (95% CI)		Unadjusted Difference in Costs (\$)		Adjusted Difference in Costs (\$)*	
	Comparison Group	Conclusive Negative	Difference (95% CI)	P-value	Difference (95% CI)	P-value
6 Months	5885 (4923-6846)	1652 (1392-1912)	4233 (3237-5229)	<0.001	4198 (2912-5484)	<0.001
9 Months	6827 (5802-7853)	1970 (1692-2248)	4857 (3794-5920)	<0.001	4375 (3025-5724)	<0.001
12 Months	7368 (6233-8503)	2406 (2096-2715)	4962 (3786-6139)	<0.001	4234 (2714-5754)	<0.001
15 Months	7438 (6189-8687)	2768 (2429-3106)	4671 (3376-5965)	<0.001	4147 (2453-5841)	<0.001
18 Months	7987 (6559-9415)	3188 (2807-3570)	4799 (3321-6277)	<0.001	4155 (2190-6119)	<0.001
21 Months	8738 (7148-10327)	3503 (3084-3922)	5235 (3591-6878)	<0.001	4356 (2164-6548)	<0.001
24 Months	9335 (7562-11108)	3893 (3413-4373)	5442 (3605-7279)	<0.001	4030 (1656-6404)	<0.001
<i>Stress</i>						
3 Months	2004 (1438-2569)	1541 (1343-1739)	462 (-137-1061)	0.130	447 (-332-1226)	0.260
6 Months	2679 (1982-3375)	2081 (1837-2325)	597 (-140-1335)	0.113	497 (-400-1393)	0.278
9 Months	2944 (2176-3712)	2379 (2114-2644)	566 (-247-1378)	0.172	484 (-499-1467)	0.334
12 Months	3538 (2693-4382)	2684 (2393-2976)	853 (-40-1746)	0.061	676 (-447-1799)	0.238
15 Months	4242 (3330-5155)	2972 (2655-3289)	1271 (305-2236)	0.010	1447 (275-2619)	0.016
18 Months	4627 (3515-5739)	3420 (3027-3812)	1207 (28-2386)	0.045	1860 (543-3177)	0.006
21 Months	5406 (4160-6652)	3838 (3400-4276)	1568 (248-2889)	0.020	2592 (1079-4105)	<0.001
24 Months	5789 (4334-7244)	4199 (3693-4704)	1591 (50-3131)	0.043	2905 (1197-4614)	<0.001
NIT = noninvasive test, CTA = computed tomographic angiogram						
* Adjustment based on single repeated measures multivariate model. Adjustment variables include age, sex, race, ethnicity, body mass index, hypertension, diabetes, dyslipidemia, smoking (ever), depression, participate in physical activity, family history of CAD, peripheral arterial disease or cerebrovascular disease, and site characterization of chest pain.						

Table VIII: Secondary Process of Care by Test Type Among Inconclusive Test Results	
Secondary Process of Care	Frequency
Exercise ECG	
Nothing	82 (76.6%)
2nd NIT	24 (22.4%)
Functional	22 (91.7%)
CTA	2 (8.3%)
ICA	1 (0.9%)
Stress Echocardiography	
Nothing	101 (84.9%)
2nd NIT	15 (12.6%)
Functional	9 (60.0%)
CTA	6 (40.0%)
ICA	3 (2.5%)
Stress Nuclear	
Nothing	177 (82.3%)
2nd NIT	26 (12.1%)
Functional	13 (50.0%)
CTA	13 (50.0%)
ICA	12 (5.6%)
CTA	
Nothing	139 (46.5%)
2nd NIT	109 (36.5%)
Functional	94 (86.2%)
CTA	15 (13.8%)
ICA	51 (17.1%)
ECG = electrocardiogram, NIT = noninvasive test, CTA = computed tomographic angiogram, ICA = invasive coronary angiogram	

SUPPLEMENTAL FIGURE LEGENDS

Figure I – CONSORT Diagram

Figure II – Definition of Test Conclusiveness for Exercise ECG Test. ETT = exercise treadmill test; ECG = electrocardiogram.

Figure III – Definition of Test Conclusiveness for Exercise Echocardiography Test

Figure IV – Definition of Test Conclusiveness for Exercise Nuclear Test. GI = gastrointestinal.

Figure V – Definition of Test Conclusiveness for Pharmacologic Echocardiography Test

Figure VI – Definition of Test Conclusiveness for Pharmacologic Nuclear Test

Figure VII – Definition of Test Conclusiveness for Computed Tomographic Angiography (CTA) Test

Figure VIII – Frequency of inconclusiveness by stress test type versus CTA with adjusted odds ratio and 95% CI. CTA = computed tomographic angiogram, ECG = electrocardiogram, Echo = echocardiogram.

Figure IX – Frequency of Inconclusiveness Within Stress Test Type of Exercise Electrocardiogram (ECG) Against Stress Echocardiogram (Echo) and Stress Nuclear With Adjusted Odds Ratio and 95% CI

Figure I

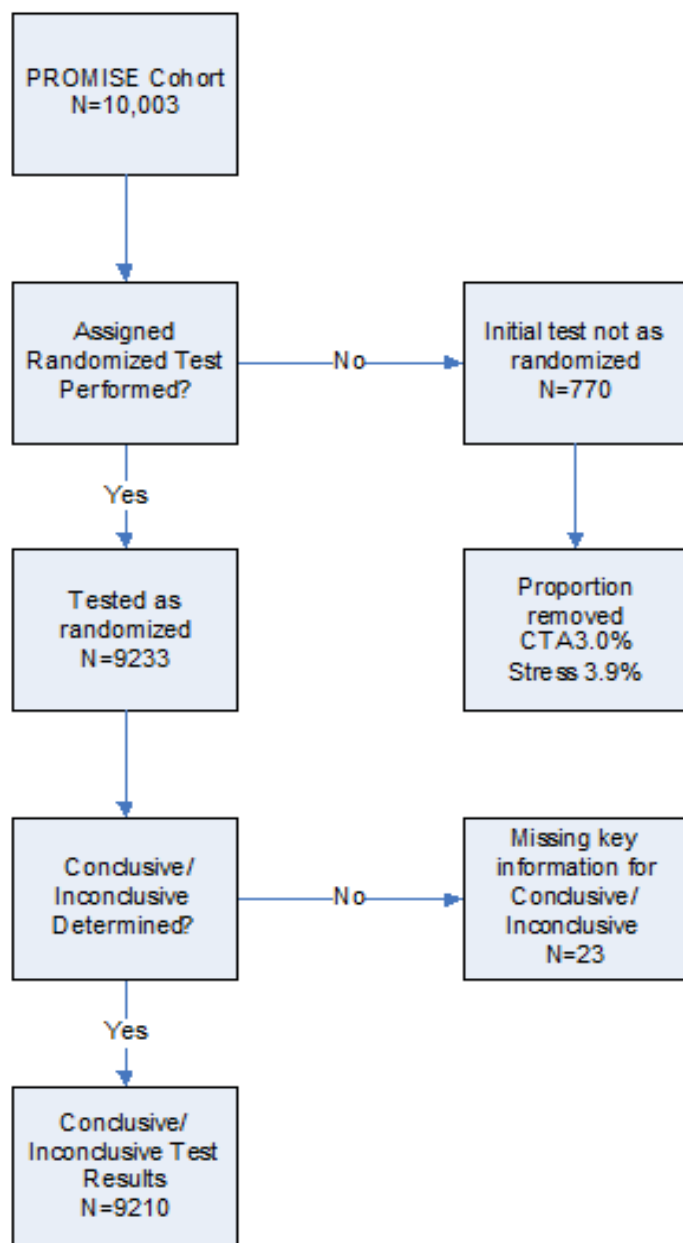


Figure II

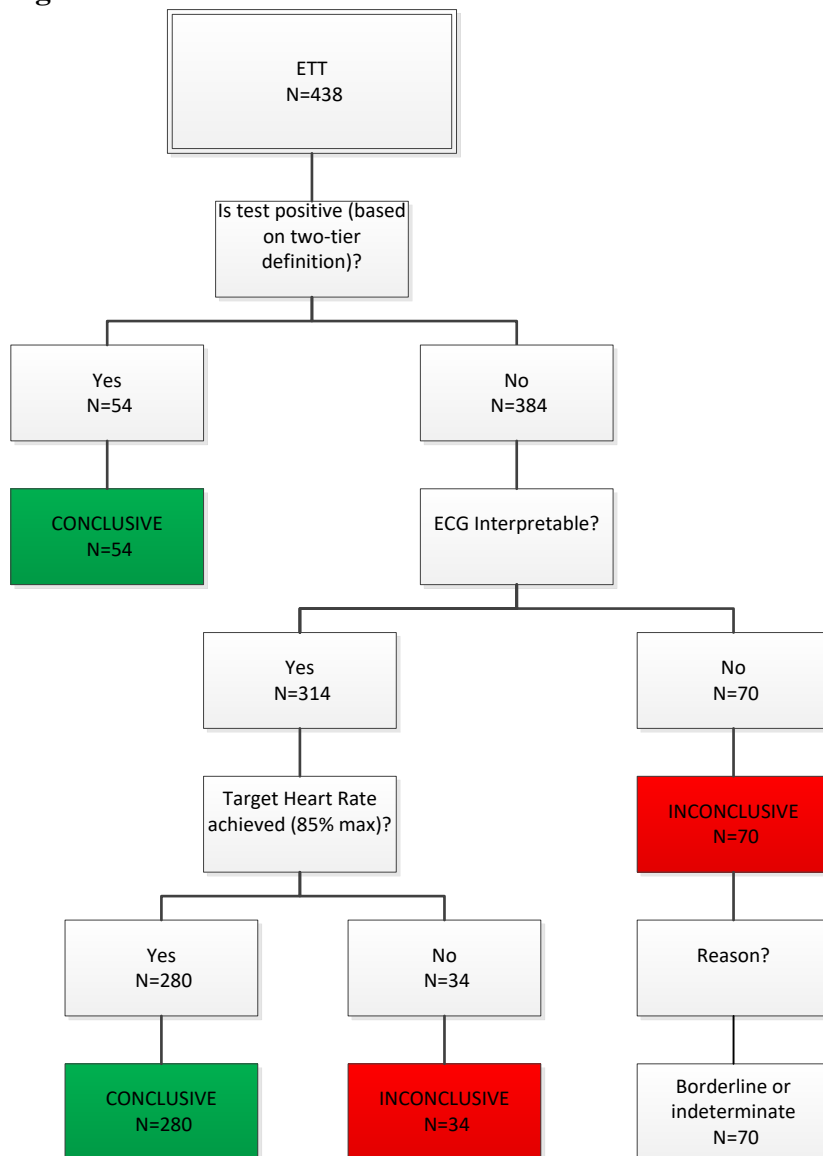


Figure III

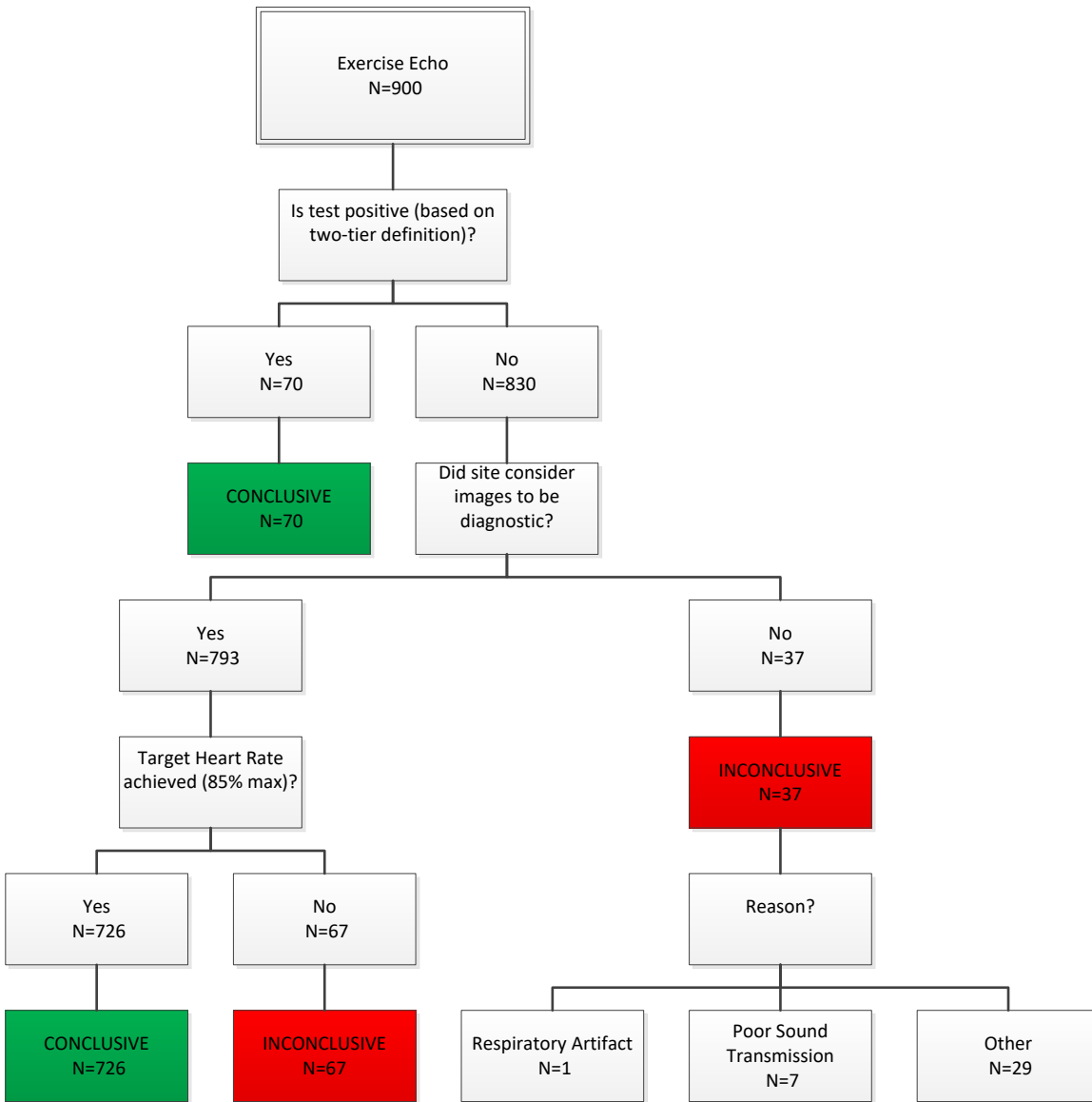


Figure IV

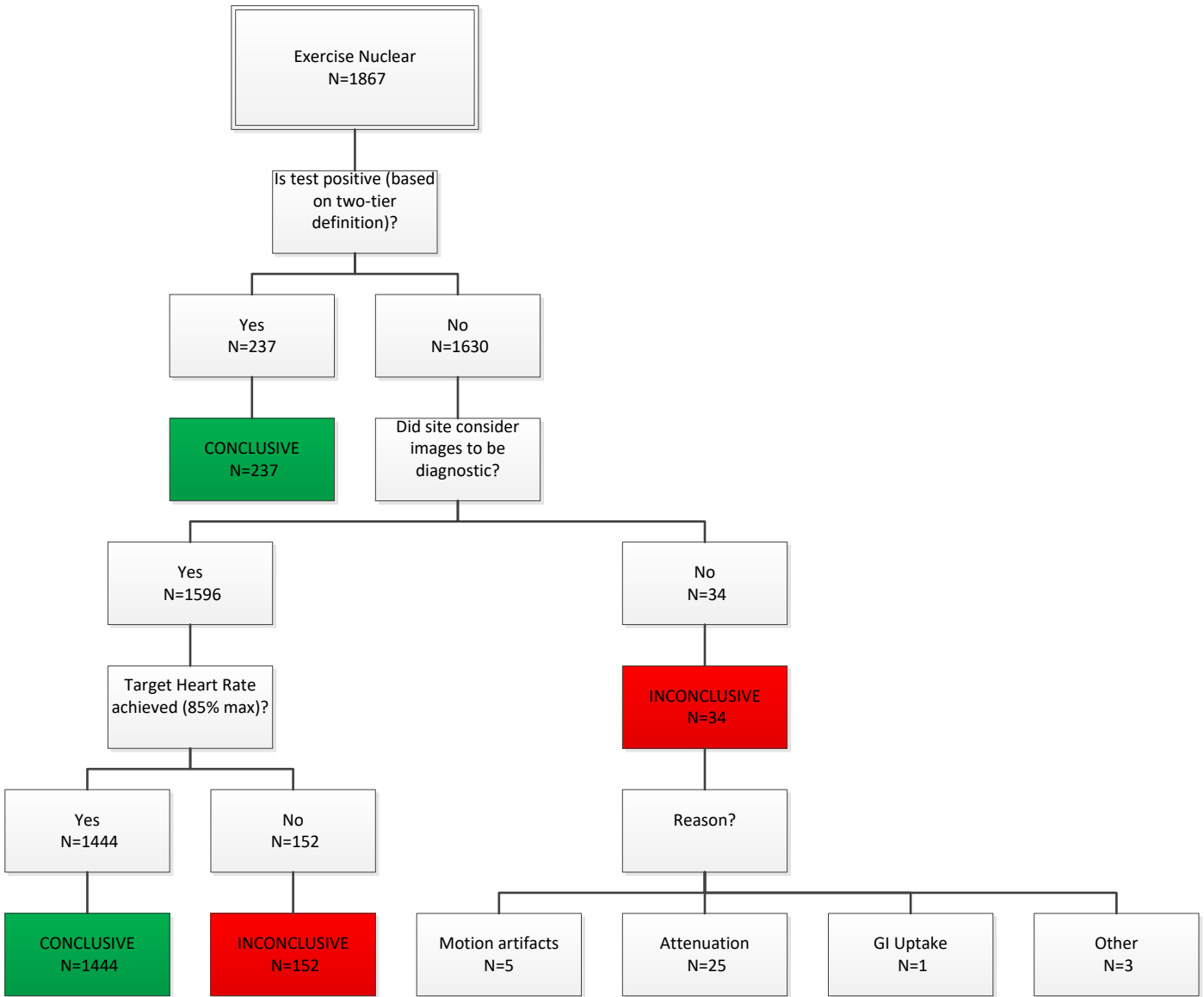


Figure V

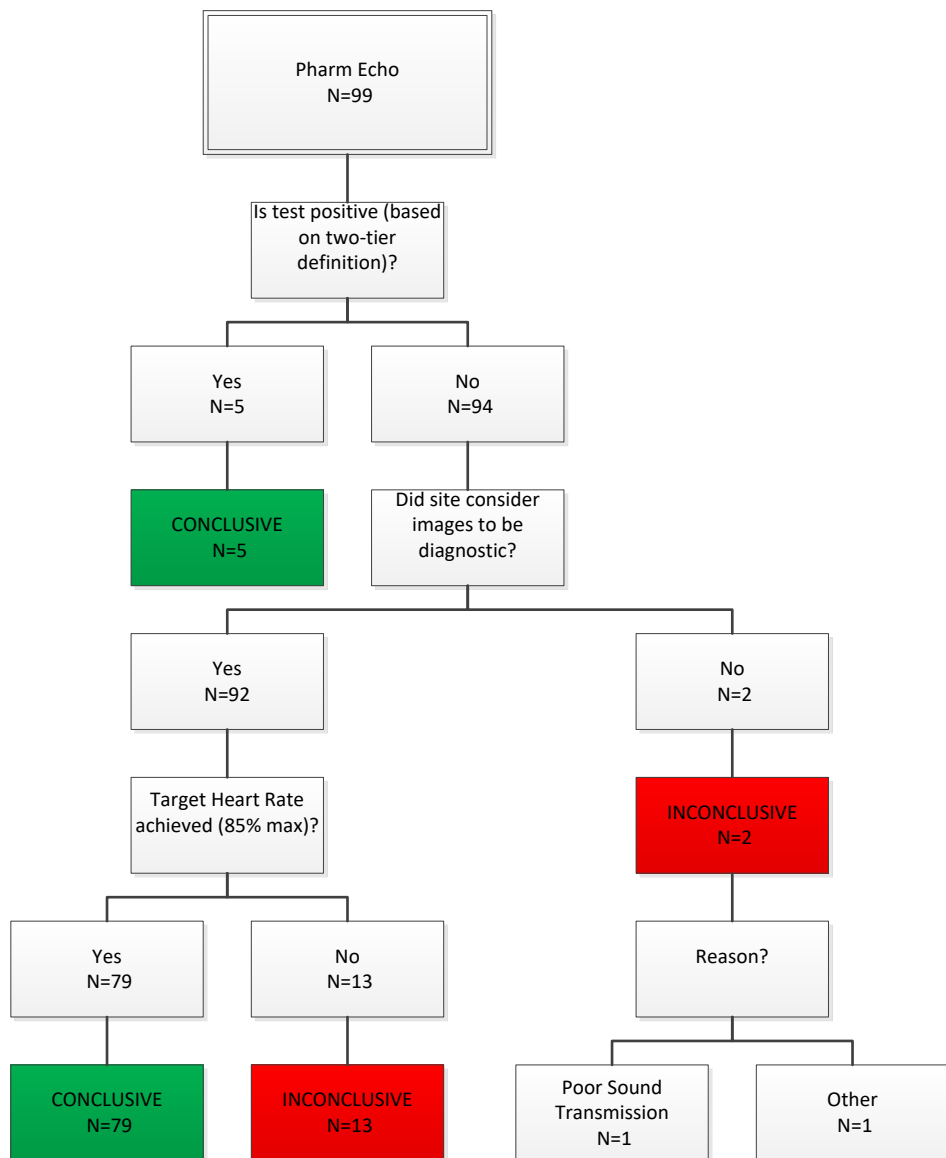


Figure VI

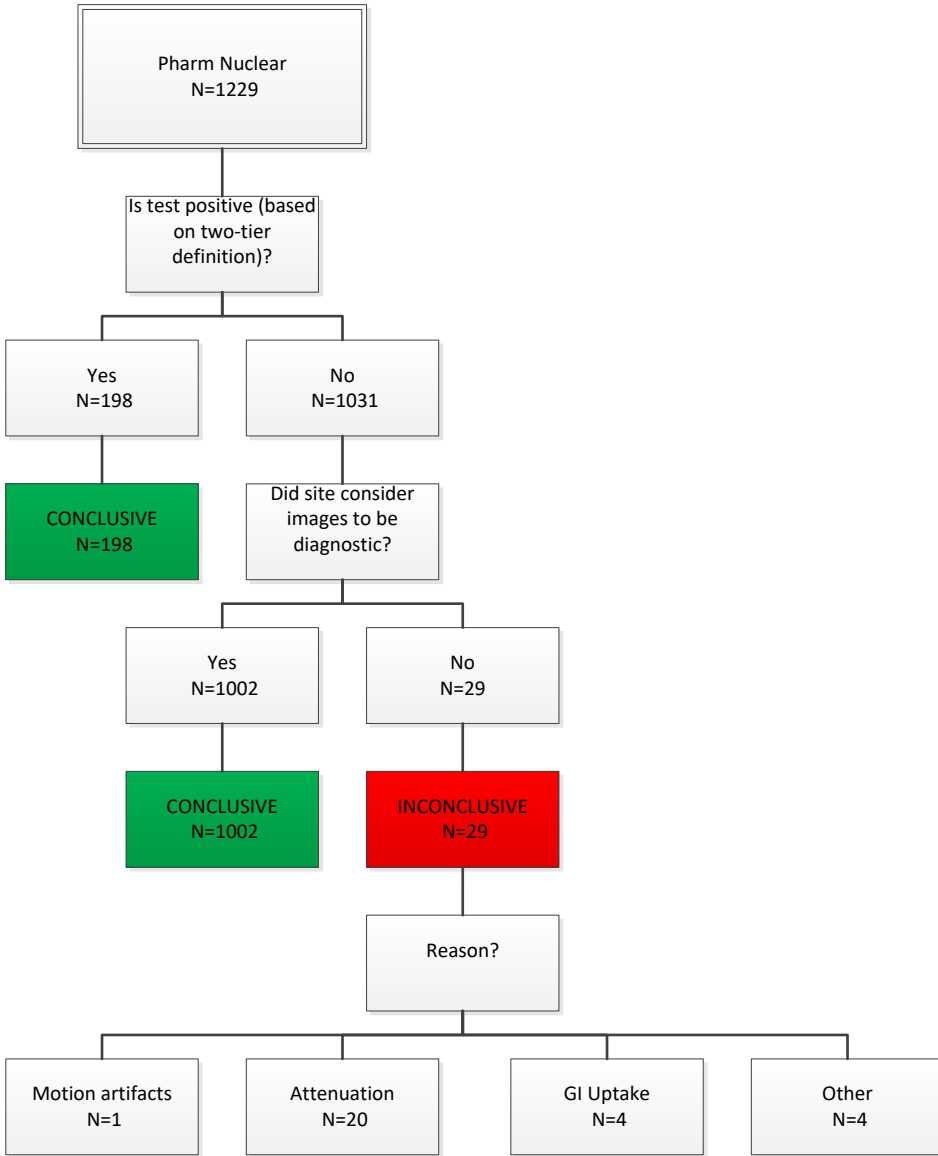


Figure VII

