The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

SUPPLEMENTARY ONLINE CONTENT

Contents

Methods S1. Micro simulation model

Troponin testing
After blood was drawn, samples for hsTnI testing were immediately centrifuged. Serum and EDTA plasma were separated and stored frozen at -80°C, within two hours. During March and April, 2012, previously unthawed samples were thawed, mixed, and centrifuged prior to analysis. The assay used was the final pre-commercial release version of the ARCHITECT High Sensitive STAT Troponin-I assay (Abbott Laboratories, Abbott Park, IL). The hsTnI assay has a 99th percentile concentration of 26.2ng/L with a corresponding co-efficient of variation of <5% and a limit of detection of 1.2ng/L. [1] Long-term stability of TnI has been demonstrated previously. [2]

Cost prediction model
In alignment with the study focus, activities that were available by patient were limited to the risk assessment and stratification period (ECG, stress test, troponin testing, MPS, CTCA, angiography, etc.). Information about inpatient treatment and management other than inpatient time were not available. Thus, the prediction of total costs based on the available data was expected to be biased with increasing inpatient time. In fact, the average costs per inpatient day decreased with increasing stay until a slight increase appeared for patients staying more than 15 days. This was regarded as an indicator for costs accrued from activities not captured in the collected data. By further analyzing the data, we excluded 2.5% of patients with an inpatient stay of more than 12 days, as this was the maximum length of stay threshold that did not affect quartiles, median, and the 95th percentile of the cost distribution of the original data, but also excluded effects of unknown inpatient activities from the prediction model.

Patient pathway
Patients were classified into risk groups according to the Queensland chest pain pathway (eFigure 1).[3] Low-risk patients were treated in the ED; intermediate-risk patients were managed in the ED with admission to the ED short-stay unit. High-risk patients were referred to inpatient cardiology. Patients requiring CABG were transferred to another institution.

Health economic model
The model distinguished five troponin statuses (eTable 2). On a positive troponin status, patients were referred to inpatient cardiology. Patients with a negative troponin status underwent further testing for coronary ischemia.

Further testing included the evaluation of the troponin status after the second test and additional objective testing (exercise stress test, myocardial perfusion scan, stress echocardiography, computed tomography coronary angiography or angiography). If objective testing was negative, patients were eligible for discharge from the chest pain pathway and exit the model. If objective testing or troponin results were positive, patients were referred for acute coronary syndrome (ACS) management in the inpatient ward.

In the accelerated diagnostic protocol (ADP) scenarios, patients meeting the Modified 2-hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial (ADAPT) criteria for low risk patients (thrombosis in myocardial infarction (TIMI) score ≤1 and hsTnI ≤ upper limit of normal (ULN)) were discharged and exited the model without further testing and workup.

Diagnosis was compared to the final adjudicated 30-days diagnosis for calculating the diagnostic accuracy.
A follow-up event within 30 days was assumed for individuals ruled-out by the respective strategy, and a reported 30-days clinical outcome of ACS (False-negative patients).

Occurrences and results of workup testing per individual were randomly sampled from binomial distributions on the basis of the troponin status using actual probabilities derived from the study cohort. Duration of workup was analyzed from the model cohort and transformed into statistical distributions. Times were randomly sampled from these distributions individually during simulation. To reflect the heterogeneity of hospital stay, LOS data of the model cohort were analyzed by final diagnosis (ACS, Non-ACS) and electrocardiogram status (normal, ischemic, abnormal).

Hospital LOS times were randomly sampled per individual from distributions with values limited between the observed minimum and maximum of the cohort. Inpatient stay was calculated by deducting all inpatient activities from the sampled LOS times. Inpatient time was only considered for individuals that were referred to ACS management. All next day discharges were counted as overnight stays.

Regression coefficients for predicting index costs were randomly sampled per individual case with a uniform distribution between the lower and upper bound of the 95% confidence interval. Follow up cost data were estimated by assuming that the patient was admitted to cardiology for angiography with an emergency department-LOS of one hour, 3 inpatient days, no exercise stress test, no myocardial perfusion scan, no computed tomography coronary angiography, and no echocardiography. Follow-up costs were assigned by randomly sampling from a uniform distribution between the upper and lower limit of the 95% CI of the predicated costs of this scenario ($5402-$8628).

The appropriate number of samples was estimated by conducting several pilot runs estimating the effect size. A reasonable distinction between confidence intervals for costs, an acceptable consistency between multiple run (n=5) and single run results, and a between-run variability of below 10% were used as criteria.[4] We regarded the latter as particularly important since it would allow for meaningful comparisons between different scenarios, settings and assumptions in subsequent evaluations. Based on results of the pilot runs (eFigure 6A-B) the sample size was set to 40,000 patients.

For the probabilistic sensitivity analysis Strategy-2 was compared against Strategy-1 by repeating the micro simulation 250 times with 40,000 patients each. Mean results and 95% confidence intervals for costs, referral accuracy, and diagnostic accuracy were compared to the micro simulation results (eFigure 5; eTable 11).

The impact of protocol time on costs was tested by running Strategy-2 and assuming constant troponin values and increasing but fixed protocol times. Variation in the discharge threshold between 6pm and 10pm were tested and compared to a scenario with no daytime restriction for discharge. Both analyses were done by sampling 40,000 individuals in 5 independent runs.

Model was developed in TreeAge Pro 2015, R1.0 (TreeAge Software, Williamstown, MA, USA). Statistical analyses were done in Minitab 16.1.0. A significance level of 0.05 was used in all analyses. Continuous data were analyzed conducting a 2-Sample t-test and Mann-Whitney test. For categorical data Fisher's exact test was used.

Additional information
By randomly sampling from the database, each of the 719 individual patients was sampled on average 55 to 56 times (Range 36 – 78). Each sample of a patient was consistent in age, sex, characteristics, ACS status and troponin values, but varied in terms of arrival time, protocol time, treatment times, additional cardiac testing if required, total inpatient LOS if referred for ACS management, and costs predictors. This generated a huge cohort of patients that reflected variation and heterogeneity in decision making, severity, and management. The result of the sampling approach is demonstrated in eFigure 9 which shows distribution of costs of the first 10 individuals as an example. Given the fact that cardiac testing such as exercise stress testing or myocardial perfusion scanning could potentially lead to positive results in patients with negative ACS condition (eTable 4A) some repetitions generated positive workup results that led to ACS management referrals (Italic numbers in eFigure 9). The inpatient stay after stratification and workup was by assumption only considered for patients referred to ACS management. Therefore, the observed variation in costs for patients referred to ACS management is mainly driven by variation in length of stay reflecting different treatments, underlying diseases, severity or management decisions. There was a potential risk that this variation would superimpose the focus of the study to evaluate different assessment strategies.

In line with a long-term perspective, previous research did not consider short term effects for hospitals or variation in troponin protocol time.[5-9] This model used a distribution around the recommended target derived from actual data reflecting a more realistic scenario (eFigure 3A).

eFigure 4 provides histograms of SSU times. The majority of patients were admitted to short stay unit (65% with short stay unit time > 0hrs, eFigure 4A); in the standard strategy utilizing cTnI some patients were managed around a mean of 7.5 hours, some required additional observation with a mean of 25.0 hours indicating

overnight stays. Replacing cTnI with hsTnI resulted in a substantial shift to lower short stay unit times as shown by mean values of 4.0 hours and 22.5 hours for those staying overnight (eFigure 4B). An additional direct rule-out strategy (limit of detection, LoD) decreased the number of short stay unit admissions significantly as indicated by an increased proportion of patients at 0h in eFigure 4B. As illustrated in eFigure 4C accelerated rule-out protocols for low risk patients (ADP) moved the SSU time distribution to distinctly lower values.

Testing the influence of different protocol times revealed that protocols with lower time targets would be less affected by variation and delays (eFigure 7). As a practical consequence, accelerated algorithms could be expected to result in more stable and more predictable emergency department processes, thus allowing for better management and resource allocation.

Patients may not be discharged immediately even if they are regarded as low risk. Prolonged protocol times could cause some clinically unnecessary overnight stays at the hospital's expense. We used the discharge threshold time to reflect such specific management rules. Since the threshold may not be fixed in real life we tested the impact of some flexibility. Data in eFigure 8 reveal no significant observable effect of a flexible threshold time on Strategy 2 (hsTnI) whereas Strategy 1 (cTnI, standard care) was strongly affected between 6 and 8pm. Although these findings depend on emergency department arrival pattern results suggested that hsTnI enabled algorithms would be less affected by variation. Given the fact that arrival pattern used in the model was derived from actual data accelerated protocols would likely lead to more stable and predictable emergency department processes.

Table S1. Patient selection criteria: Cost prediction model

Criteria	Excluded	N
All data		938
Exclude patients with CABG*	-14	924
Exclude long-stay outliers >12d (incl. non-cardiac complications)	-23	901
Exclude inconsistent or missing data	-6	895
Analyze extreme outliers	-4	891

*Patients receiving coronary bypass surgery (CABG) were excluded for the cost prediction model. Costs were unknown as patients were transferred to another hospital for surgery.
CABG=Coronary artery bypass graft

Table S2. Troponin statuses considered in the model

Status	Description	Evaluation for ACS
1	1^{st} troponin & 2^{nd} troponin ≤ ULN	Negative
2	1^{st} troponin ≤ ULN & 2^{nd} troponin > ULN	Positive
3	1^{st} troponin > ULN & 2^{nd} troponin ≤ ULN	Positive
4	1^{st} troponin & 2^{nd} troponin > ULN; difference < delta cut-off	Negative (Stable)
5	1^{st} troponin & 2^{nd} troponin > ULN; difference ≥ delta cut-off	Positive

ULN=Upper limit of normal, 99^{th} percentile of the reference population; ACS=Acute coronary syndrome

Table S3. Patient selection criteria: Micro simulation model

Minimum required dataset	Excluded	N
Basic characteristics	0	938
Time points stated	0	938
ECG information available	0	938
Baseline cTnI	0	928
Baseline hsTnI	-145	793
Second cTn (6hrs)	-57	736
Second hsTnI (2hrs)	-17	719
Final endpoint	0	719

Individuals with missing data in the minimum required dataset were excluded from the analysis.
ECG=echocardiogram, cTnI=sensitive cardiac troponin I, hsTnI=highly sensitive cardiac troponin I

Table S4A. Model parameter and assumptions: Objective testing probabilities.

Workup	Troponin status	N	Occurence	Result +-ve
Exercise Stress Test	1	582	60.1%	5.4%
	2	31	29.0%	11.1%
	3	15	33.3%	20.0%
	4	40	12.5%	40.0%
	5	51	2.0%	0.0%
Myocardial perfusion scan	1	582	14.3%	18.1%
	2	31	12.9%	75.0%
	3	15	20.0%	33.3%
	4	40	7.5%	0.0%
	5	51	2.0%	0.0%
Echocardiography	1	582	17.0%	data not available
	2	31	48.4%	
	3	15	20.0%	
	4	40	50.0%	
	5	51	70.6%	
Computed tomography coronary angiography	1	582	3.1%	data not available
	2	31	0.0%	
	3	15	6.7%	
	4	40	5.0%	
	5	51	0.0%	

Statistical evaluation of the model cohort (N=719)

Table S4B. Model parameter and assumptions: Probabilities for angiography.

Workup	Troponin status	N	Occurrence	Result +ve (ACS patients)	Result +ve (non-ACS patients)
Angiography	1	582	11.9%	50.0%	31.3%
	2	31	35.5%	100.0%	0.0%
	3	15	13.3%	0.0%	0.0%
	4	40	27.5%	83.3%	40.0%
	5	51	70.6%	96.8%	20.0%

Statistical evaluation of the model cohort (N=719)
ACS=Acute coronary syndrome

Table S4C. Model parameter and assumptions: Cardiac workup duration

Variable	Mean time, hours	Distribution
Arrival time (decimal time format)	0.45	Normal
Initial assessment time	0.45	Gamma
Protocol time cTnI	6.3	Gamma
Protocol time hsTnI	2.3	Gamma
Workup time (2nd Tn after 6.30pm)	17.1	Gamma
Probability of short workup time (2nd Tn before 6.30pm)	0.79	Binomial
Workup time (short; 2nd Tn before 6.30pm)	1.78	Gamma
Workup time (long; 2nd Tn before 6.30pm)	20.3	Gamma
Angiography	3.0	Gamma

cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I

Table S4D. Model parameter and assumptions: Hospital length of stay

Hospital LOS, hours	Mean	SD	Q1	Median	Q3	Min	Max	Distribution
ACS / ECG normal	154.4	99.6	66.5	100.6	273.4	48.7	280.4	Gamma
ACS / ECG ischemic	125.4	87.6	56.7	92.8	209.6	20.5	288.0	Gamma
ACS / ECG abnormal	110.3	81.5	59.3	85.5	166.0	15.8	283.9	Gamma
Non-ACS / ECG normal	33.1	49.7	6.0	19.6	27.6	0.0	284.0	Gamma
Non-ACS / ECG ischemic	91.9	90.5	25.0	64.7	121.3	0.0	284.0	Gamma
Non-ACS / ECG abnormal	58.9	71.7	8.0	25.3	80.5	0.0	282.4	Gamma

Statistical evaluation of the model cohort (N=719)
LOS=length of stay; ACS=acute coronary syndrome; ECG=electrocardiogram

Table S5. Patient characteristics of the selected and generated model cohort

Demographics	**Cohort (N = 719)**	**Generated cohort[a] (N = 40,000)**	**p-value**
Sex (% women)	39.4	39.5	0.94
Age, yrs. Mean (Range)	55 (19 - 97)	55 (19-97)	0.94
Risk factors			
Dyslipidaemia, %	42.1	Sampled and used for estimating the assessment status	
Diabetes, %	12.8		
Hypertension, %	43.3		
Tachycardia, %	1.7		
Obesity (BMI>30), %	35.5		
Smoking, %	26.8		
Medical History			
Angina, %	22.5	Sampled and used for estimating the assessment status	
Coronary artery disease, %	20.5		
Myocardial infarction, %	16.3		
Family coronary artery disease, %	46.6		
Arrhythmia, %	9.0		
Congestive heart failure, %	4.2		
CABG surgery, %	6.5		
Prior angioplasty, %	10.3		
Peripheral artery disease, %	1.8		
Aspirin use, %	25.3		
Stroke, %	9.0		
Initial assessment & final diagnosis			
ACS, %	11.0	11.0	1.00
ECG normal, %	49.5	49.1	0.85
ECG ischemic, %	7.8	7.7	0.94
ECG abnormal, %	42.7	43.2	0.82
TIMI 0, %	24.5	25.0	0.75
TIMI 1, %	33.0	33.9	0.61
TIMI 2, %	17.9	17.2	0.58
TIMI 3, %	12.2	12.1	0.86
TIMI 4, %	6.4	6.5	1.00
TIMI ≥5, %	6.0	5.4	0.51
High risk, %	33.7	33.5	0.94
Intermediate risk, %	65.1	65.3	0.94
Low risk, %	1.3	1.3	1.00
Baseline cTnI, ng/L (Mean, range)	118 (10 - 31000)	119 (10 - 31000)	0.97
Baseline hsTnI, ng/L (Mean, Range)	117.5 (0.3 - 38685)	119.2 (0.3 - 38685)	0.98
hsTnI < LoD at baseline[b], %	5.1	6.1	0.34

TIMI and risk assignment based on standard strategy

[a] Samples per individuals: Mean 55.6; Range 36-78; Mode: 52.

[b] Limit of detection for hsTnI 1.2ng/L

BMI=Body mass index; CABG=coronary artery bypass graft; ACS=acute coronary syndrome; ECG=electrocardiogram; TIMI=Thrombolysis in myocardial infarction; cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I, LoD=limit of detection

Table S6. Cost prediction model regression analysis

Term	Coef	SE Coeff	T	P-value	(95% CI)	VIF
Constant	3.57	0.04	101.5	<0.001	(3.51 – 3.64)	
ED time, hours	0.02	0.00	8.8	<0.001	(0.02 – 0.03)	1.15
Inpatient stay, days	0.19	0.01	37.7	<0.001	(0.18 – 0.20)	1.78
Exercise stress test	-0.09	0.02	-4.3	<0.001	(-0.13 – -0.05)	1.37
Myocardial perfusion scan	0.25	0.04	6.7	<0.001	(0.18 – 0.32)	1.22
Computed tomography coronary angiography	0.27	0.07	4.0	<0.001	(0.14 – 0.40)	1.02
Angiography	0.65	0.03	21.8	<0.001	(0.59 – 0.71)	1.34
Echocardiography	0.32	0.03	11.4	<0.001	(0.26 – 0.37)	1.49
Admission	0.39	0.03	11.6	<0.001	(0.33 – 0.46)	1.21

VIF: Variance inflation factor

Box-Cox transformation with Lambda= 0.189 (95%CI 0.135 – 0.245)

S	0.264
PRESS	63.4
R-Sq	88.3%
R-Sq(adj)	88.2%
R-Sq(pred)	88.0%

Admission considers admission to short-stay unit or inpatient ward

Table S7. Risk assignment of patients

Strategy			Initial risk assignement, %		
			Low-risk	Intermediate-risk	High- risk
Standard			**1.3**	**65.3**	**33.5**
hsTnI			**1.3**	**65.3**	**33.5**
Direct rule-out if baseline hsTnI < LoD (LoD)	No direct rule-out	**All**	**1.3**	**60.4**	**32.3**
	Direct rule-out[a]	**All**	**0.0**	**4.9**	**1.2**
		ACS	0.0	0.0	0.0
		No ACS	0.0	4.9	1.2
Accelerated rule-out if hsTnI values below the diagnostic cut-off and TIMI ≤1 (ADP)	No accelerated rule-out	**All**	**0.5**	**16.4**	**33.5**
	Accelerated rule-out[a]	**All**	**0.7**	**48.8**	**0.0**
		ACS	0.0	0.2	0.0
		No ACS	0.7	48.7	0.0
Direct rule-in if baseline hsTnI >52ng/L	No direct rule-in	**All**	**1.3**	**65.3**	**26.3**
	Direct rule-in[b]	**All**	**0.0**	**0.0**	**7.2**
		ACS	0.0	0.0	5.1
		No ACS	0.0	0.0	2.0

LoD=Limit of detection; ACS= Acute coronary syndrome;
TIMI=Thrombolysis in myocardial infarction;
ADP=Accelerated diagnostic protocol;
hsTnI=highly sensitive cardiac troponin I
[a] classified as low-risk
[b] classified as high-risk

Table S8. Troponin status by assay used

	hsTnI			Sum (cTnI), %
cTnI	**Negative, %**	**Stable, %**	**Positive, %**	
Negative, %	84.0	0.1	0.3	**84.4**
Stable, %	0.6	0.3	2.9	**3.4**
Positive, %	2.4	0.6	9.0	**11.9**
Sum (hsTnI), %	**86.9**	**1.0**	**12.1**	**100.0**

Troponin status interpretation according to eTable3
cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac TnI

Table S9. Total length of stay and costs per strategy and final diagnosis

Strategy	Category	Total costs, $				Total LOSs, hours			
		Median	(25th - 75th perc)	Mean	(95% CI)	Median	(25th - 75th perc)	Mean	(95% CI)
1	**All**	**2135**	**(1741 - 3109)**	**3267**	**(3236 - 3297)**	**22.6**	**(8.7 - 29.8)**	**34.0**	**(33.6 - 34.4)**
	No ACS	2022	(1708 - 2669)	2570	(2550 - 2590)	21.3	(8.6 - 27.7)	27.2	(26.9 - 27.5)
	ACS	8421	(5863 - 10248)	8895	(8756 - 9034)	74.8	(25.5 - 137)	89.2	(87 - 91.3)
2	**All**	**1983**	**(1597 - 2951)**	**3134**	**(3103 - 3165)**	**6.0**	**(4.4 - 25.3)**	**27.8**	**(27.4 - 28.2)**
	No ACS	1860	(1567 - 2478)	2417[a]	(2397 - 2436)	5.6	(4.3 - 23.1)	20.2[a]	(19.8 - 20.5)
	ACS	8269	(5827 - 10210)	8930	(8788 - 9073)	79.0	(23 - 139.2)	89.6	(87.4 - 91.8)
3	**All**	**1921**	**(1548 - 2878)**	**3057**	**(3026 - 3088)**	**3.6**	**(2.7 - 10.1)**	**20.4**	**(20 - 20.9)**
	No ACS	1805	(1517 - 2427)	2330[a]	(2310 - 2350)	3.3	(2.6 - 5.4)	11.9[a]	(11.6 - 12.2)
	ACS	8269	(5827 - 10210)	8930	(8788 - 9073)	78.7	(22.8 - 139.1)	89.3	(87.1 - 91.5)
4	**All**	**1695**	**(1560 - 2260)**	**2834**	**(2804 - 2864)**	**5.6**	**(4.2 - 24.8)**	**26.8**	**(26.4 - 27.3)**
	No ACS	1663	(1544 - 1862)	2079[a]	(2062 - 2096)	5.3	(4.1 - 22.6)	19.0[a]	(18.7 - 19.4)
	ACS	8268	(5851 - 10198)	8932	(8790 - 9074)	79.0	(23 - 139.2)	89.6	(87.4 - 91.8)
5	**All**	**1681**	**(1532 - 2231)**	**2781**	**(2751 - 2811)**	**3.5**	**(2.6 - 8.3)**	**20.1**	**(19.6 - 20.5)**
	No ACS	1648	(1514 - 1845)	2020[a]	(2002 - 2037)	3.2	(2.5 - 5.2)	11.5[a]	(11.2 - 11.8)
	ACS	8268	(5851 - 10198)	8932	(8790 - 9074)	78.7	(22.8 - 139.1)	89.3	(87.1 - 91.5)
6	**All**	**1681**	**(1532 - 2230)**	**2776**	**(2746 - 2807)**	**3.5**	**(2.6 - 8.8)**	**20.4**	**(19.9 - 20.8)**
	No ACS	1648	(1514 - 1845)	2020[a]	(2003 - 2037)	3.2	(2.5 - 5.2)	11.5[a]	(11.2 - 11.8)
	ACS	8151	(5702 - 10194)	8885	(8740 - 9029)	82.0	(24.8 - 140.5)	91.9	(89.7 - 94.1)

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+Rule in.
Total costs include index costs and 30 days follow-up costs.
All costs stated are in Australian dollars.
[a] p-value vs. Standard < 0.001
ACS=Acute coronary syndrome; hsTnI=highly sensitive troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol; LOS=Length of stay

Table S10A. Emergency department performance by strategy

Emergency department time, hours	Mean	(95% CI)	Median	(25th - 75th perc)	97.5th perc	≤4hrs
1) Standard	0.68	(0.66 - 0.7)	0.41	(0.26 - 0.63)	1.4	98.7%
2) hsTnI	0.58	(0.57 - 0.6)	0.41	(0.26 - 0.63)	1.4	99.0%
3) hsTnI+LoD	0.58	(0.57 - 0.6)	0.41	(0.26 - 0.63)	1.4	99.0%
4) hsTnI+ADP	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%
5) hsTnI+LoD+ADP	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%
6) hsTnI+LoD+ADP+Direct rule-in	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%

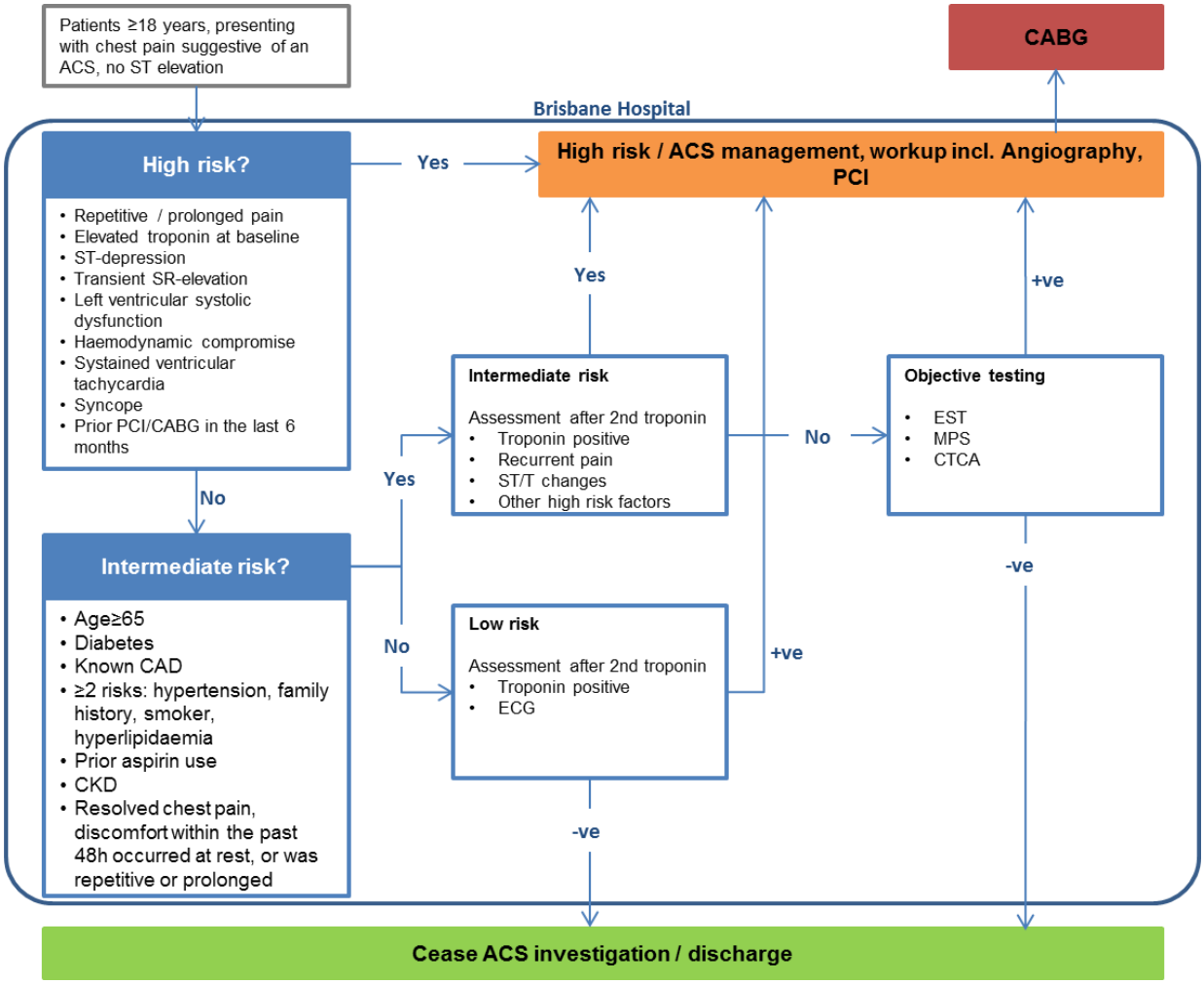
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

Table S10B. Short Stay Unit times per patient by strategy

SSU time, hours	Mean	(95% CI)	Median	(25th - 75th perc)	90th perc
1) Standard	9.9	(9.8 - 10)	7.54	(0.0 - 20.8)	25.7
2) hsTnI	5.1	(5.1 - 5.2)	3.49	(0.0 - 4.7)	21.2
3) hsTnI+LoD	4.7	(4.7 - 4.8)	3.31	(0.0 - 4.5)	20.7
4) hsTnI+ADP	2.4	(2.3 - 2.4)	2.06	(0.0 - 2.6)	3.8
5) hsTnI+LoD+ADP	2.2	(2.2 - 2.3)	1.99	(0.0 - 2.6)	3.8
6) hsTnI+LoD+ADP+Rule in	2.2	(2.2 - 2.3)	1.99	(0.0 - 2.6)	3.8

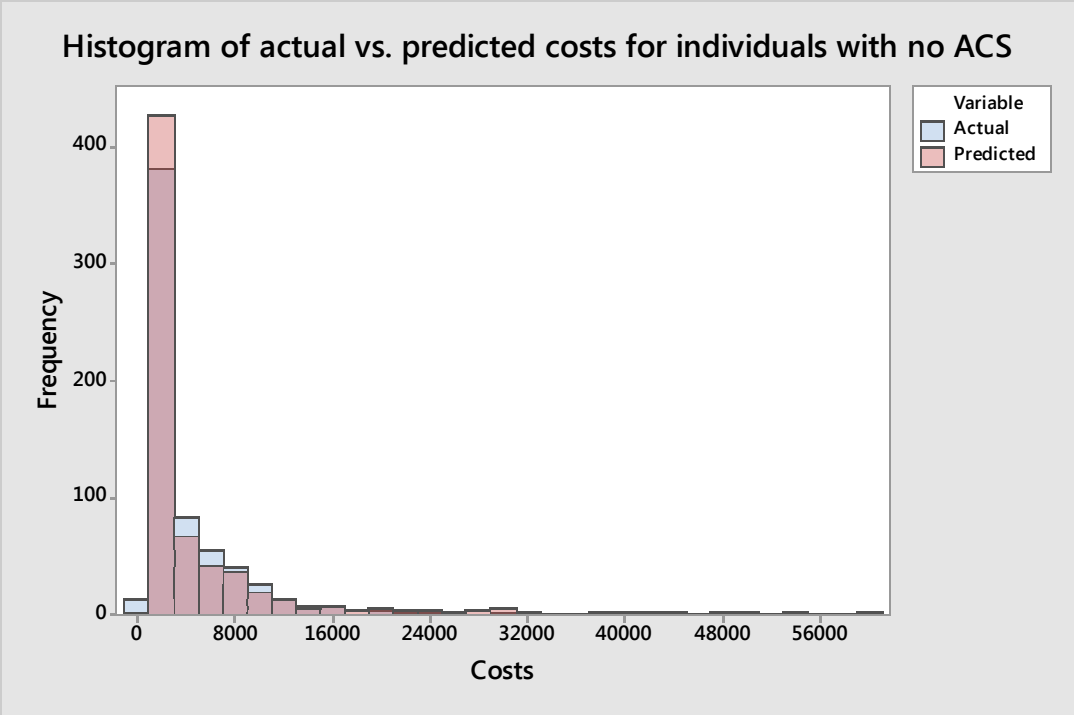
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

Figure S1. Risk stratification and process of care for possible acute coronary syndrome

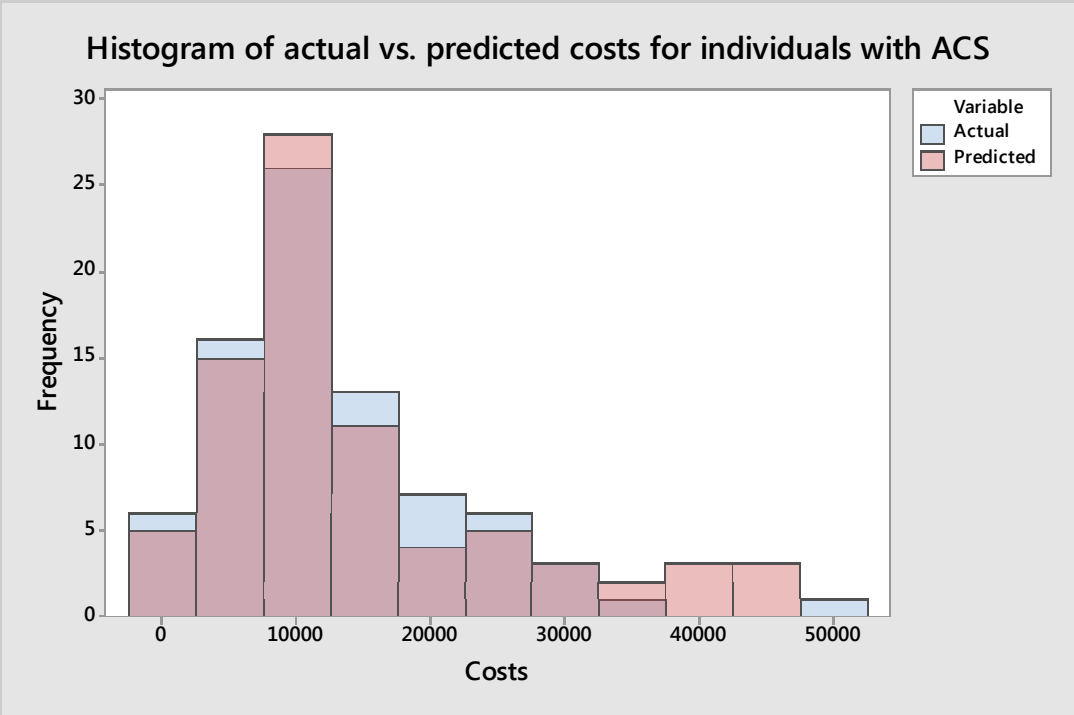


Risk stratification according to [3].

Figure S2A-B. Comparison of actual vs. predicted costs

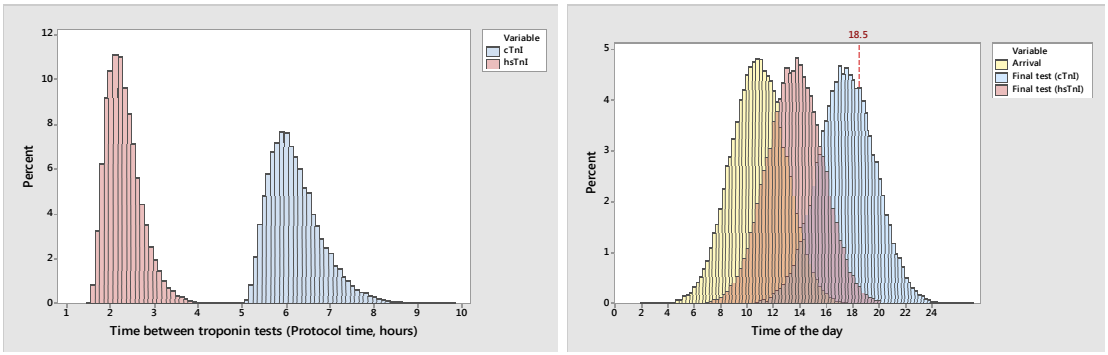


Data based on individuals with a final diagnosis of Non-ACS (640/719); p-value for Mean: 0.97



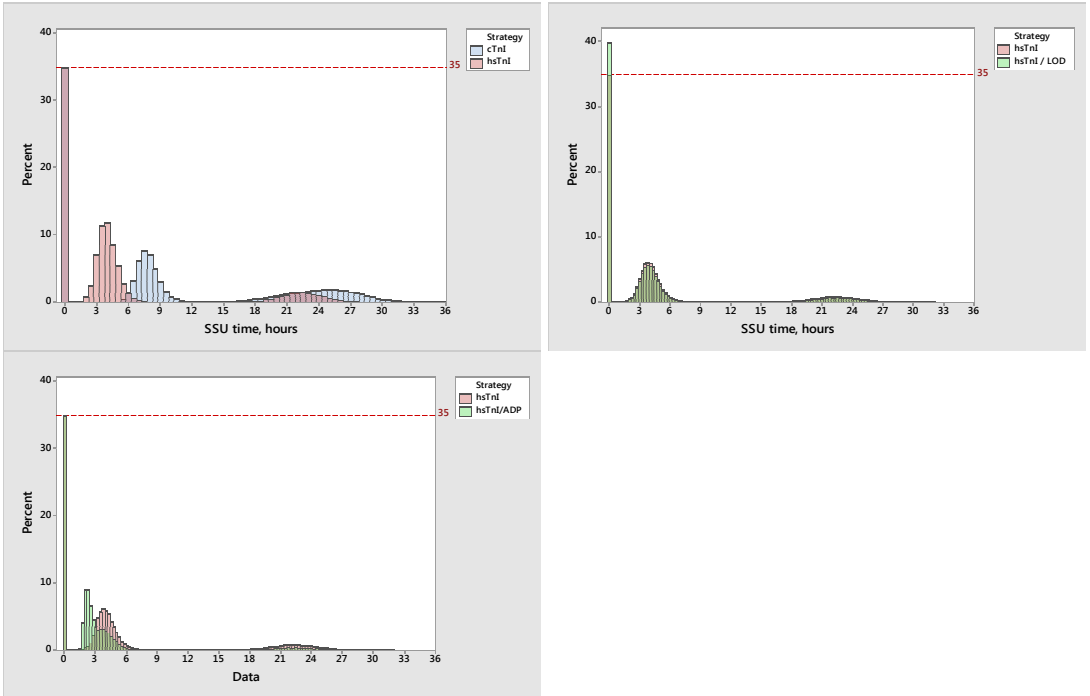
Data based on individuals with a final diagnosis of ACS (79/719); p-value for Mean: 0.39

Figure S3. Simulated troponin protocol times (A), patient arrival times, and times of final results for sensitive troponin I and highly sensitive troponin I (B).



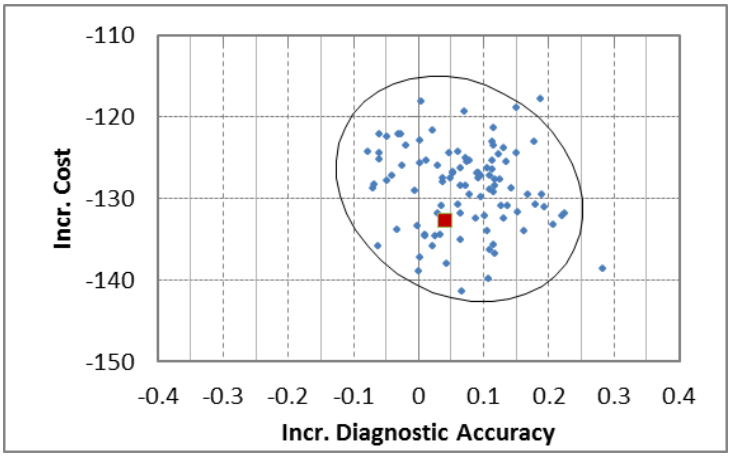
cTnI=sensitive cardiac troponin; hsTnI=highly sensitive cardiac troponin I

Figure S4A-C. Histograms of Short Stay Unit times for different strategies



A: Standard strategy (cTnI) vs. hsTnI;
B: hsTnI strategy vs. hsTnI / LoD strategy; C: hsTnI strategy vs. hsTnI / ADP strategy.
The reference line at 35% indicates the proportion of patients that were not admitted to Short Stay Unit in the standard strategy.
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

Figure S5. Incremental cost and effectiveness of Strategy 2 (hsTnI) vs. Strategy 1 (cTnI, usual care)



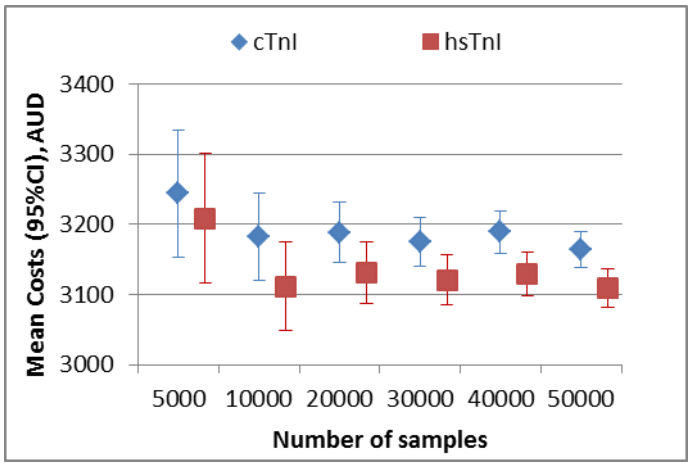
Results from multiple runs in a probabilistic sensitivity analysis (n=250). Each point represents results of a run with 40,000 sampled patients. The ellipse reflects the 95% confidence interval. Red box represents the result from the micro simulation.

Table S11. Comparison of results from single and multiple run micro simulations

Strategy	Analysis	Total costs		Referral Accuracy, %		Diagnostic Accuracy	
		A$	(95%CI)	Mean	(95%CI)	Mean	(95%CI)
Standard	MS	3267	(3236 - 3297)	71.8	(71.4 - 72.2)	90.00	(89.7 - 90.3)
	PSA	3253	(3251 - 3255)	72.0	(71.97 - 72.02)	90.21	(90.2 - 90.23)
hsTnI	MS	3134	(3103 - 3165)	72.8	(72.3 - 73.2)	90.04	(89.7 - 90.3)
	PSA	3124	(3122 - 3126)	73.0	(72.95 – 73.00)	90.3	(90.26 - 90.29)

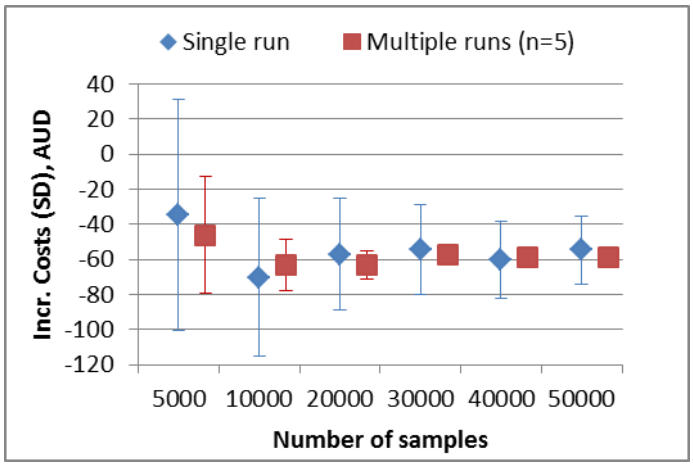
MS: Micro simulation (n=1 runs)
PSA: Probabilistic sensitivity analysis (n=250 runs)

Figure S6A. Mean costs based on number of samples in the micro simulation



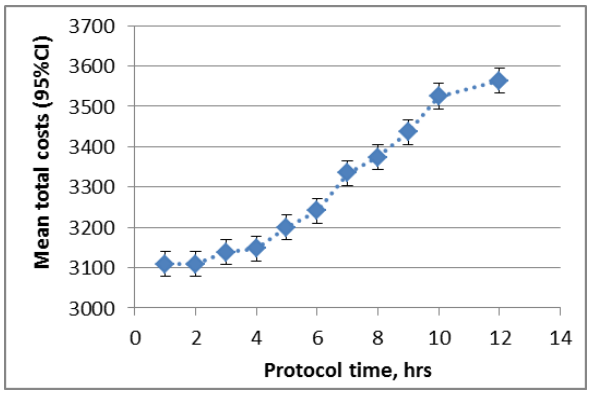
cTnI=sensitive cardiac troponin; hsTnI=highly sensitive cardiac troponin I

Figure S6B. Incremental costs based on different number of samples in the micro simulation



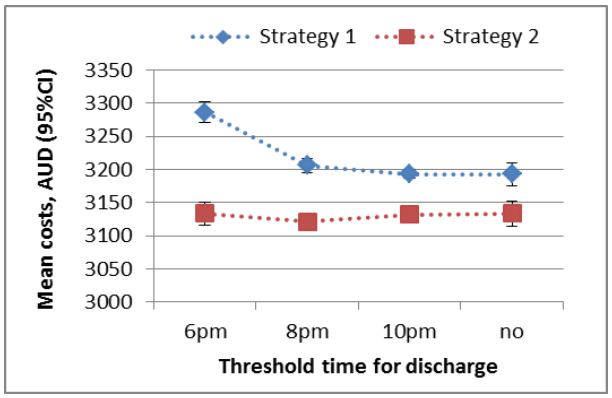
Incremental costs refer to Strategy-2 – Strategy 1

Figure S7. Impact of protocol time on costs



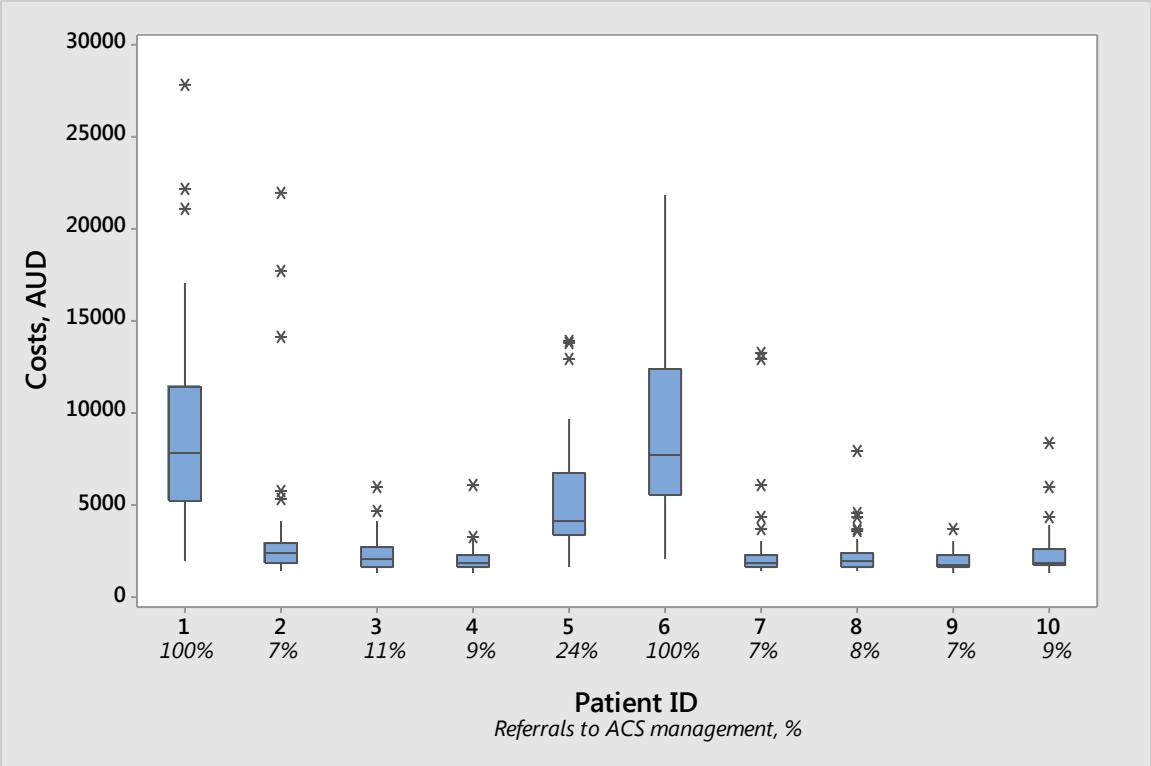
Analysis of strategy 2 (hsTnI) assuming constant troponin values and a fixed protocol time. Each data point represents the result of 5 independent runs with 40,000 patients per run.

Figure S8. Impact of threshold time for discharge on costs



Each data point represents the result of 5 independent runs with 40,000 patients per run.

Figure S9. Cost variation as a result of the sampling strategy illustrated for ten selected individuals



Box plots illustrate the variability in costs from multiple samples of the same individual as an example for the first 10 patients (Patient-ID 1 to 10).

By running 40,000 iterations, each of the 719 individuals was sampled on average 55 to 56 times (Range 36 – 78). This generated a huge cohort of patients that reflected variation and heterogeneity in decision making, severity, and management.

Each sample of an individual was consistent in age, sex, characteristics, ACS status and troponin values, but varied in terms of arrival time, protocol time, treatment times, additional cardiac testing if required, total inpatient LOS if referred for ACS management, and costs predictors. This resulted in a range of costs as demonstrated in the chart.
For individuals with non-ACS conditions, variation in subjective decision making or results from cardiac testing (exercise stress test or myocardial perfusion scan) led to admittance for ACS management in some cases (Patient ID 2-4, and 7-10). Italic numbers indicate the proportion of referrals to ACS management per patient. Patients with ACS were admitted for ACS management in 100% of iterations (Patient ID 1 and 6). Variation in costs between ACS patients was caused by sampling different LOS assumptions.

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