SUPPLEMENTAL MATERIAL

Table S1. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Appendix 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1, Figure 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11, Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-14, Appendix 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 2-4, Figure 3

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Table S2. Search strategies in Medline, Embase, Econlit, Web of Science Core, NHSEED database and HTA database.

Medline via Ovid ®

No	Search
1	(Cost Benefit Analys$ or CBA).mp. or exp Cost-Benefit Analysis/
2	Cost$ analys$.mp. or exp "Costs and Cost Analysis"/
3	(Cost effectiveness or cost-effectiveness or CEA or cost-utility analys$ or cost utility analys$ or CUA).mp.
4	Pharmacoeconomic$.mp. or exp Economics, Pharmaceutical/
5	Econ$ Evaluat$.mp.
6	1 or 2 or 3 or 4 or 5
7	Pharmacogenetic$.mp. or exp PHARMACOGENETICS/
8	Pharmacogenomic$.mp.
9	Precision Medicin$.mp. or exp Precision Medicine/
10	Individuali?ed Medicin$.mp.
11	Individuali?ed treatment$.mp.
12	Personali?ed Medicin$.mp.
13	Personali?ed treatment$.mp.
14	Personali?ed therap*.mp.
15	(Genetic$ screen$ or Genetic Test$).mp. or exp Genetic Testing/
16	Genotype$.mp. or exp GENOTYPE/
17	genetic marker$.mp. or exp Genetic Markers/
18	genomic marker$.mp.
19	exp Genes/ or exp Mutation/ or genetic analys$.mp. or exp Phenotype/
20	exp Genetic Variation/ or exp Genomics/
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	cardiovascular disease$.mp. or exp Cardiovascular Diseases/
23	coronary arter$ disease$.mp. or exp Coronary Artery Disease/
24	Coronary Arteriosclero$.mp.
25	Angina Pectoris.mp. or exp Angina Pectoris/
26	Myocardial Infarct$.mp. or exp Myocardial Infarction/
27	Myocardial Reperfusion.mp. or exp Myocardial Reperfusion/
28	exp MYOCARDIUM/ or Myocardium.mp.
29	Heart Attack$.mp.
30	exp STROKE/
31	Heart Failure$.mp. or exp Heart Failure/
32	exp HYPERTENSION, PULMONARY/ or exp HYPERTENSION/ or exp HYPERTENSION, RENAL/ or exp WHITE COAT HYPERTENSION/ or Hypertensi$.mp. or exp HYPERTENSION, RENOVASCULAR/ or exp HYPERTENSION, PORTAL/ or exp ESSENTIAL HYPERTENSION/ or exp HYPERTENSION, MALIGNANT/ or exp MASKED HYPERTENSION/ or exp HYPERTENSION, PREGNANCY-INDUCED/
33	high blood pressure.mp.
34	Rheumatic Heart Disease$.mp. or exp Rheumatic Heart Disease/

35	exp DIABETIC CARDIOMYOPATHIES/ or exp CARDIOMYOPATHIES/ or Cardiomyopath$.mp.
36	Heart Valve Disease$.mp. or exp Heart Valve Diseases/
37	Myocarditis.mp. or exp MYOCARDITIS/
38	Aortic Aneurysm$.mp. or exp Aortic Aneurysm/
39	Peripheral Arterial Disease$.mp. or exp Peripheral Vascular Diseases/ or exp Peripheral Arterial Disease/ or exp Coronary Disease/ or exp Arteriosclerosis/ or exp Cardiovascular Diseases/
40	Venous Thrombo$.mp. or exp Venous Thrombosis/
41	Acute rheumatic fever.mp. or exp Rheumatic Fever/
42	pericarditis.mp. or exp PERICARDITIS/
43	endocarditis.mp. or exp ENDOCARDITIS/
44	exp Heart Diseases/ or chronic rheumatic heart disease$.mp.
45	isch?emic heart disease$.mp. or exp Myocardial Ischemia/
46	cerebrovascular disease$.mp. or exp Cerebrovascular Disorders/
47	phlebitis.mp. or exp PHLEBITIS/
48	thrombophlebitis.mp. or exp THROMBOPHLEBITIS/
49	hypotension.mp. or exp HYPOTENSION, ORTHOSTATIC/ or exp HYPOTENSION/
50	Rheumatic chorea.mp. or exp Chorea/
51	Coronary thrombo$.mp. or exp Coronary Thrombosis/
52	exp EMBOLISM/ or embolism$.mp. or exp PULMONARY EMBOLISM/
53	Atheroscleros?s.mp. or exp ATHEROSCLEROSIS/
54	Mitral steno$.mp. or exp Mitral Valve Stenosis/
55	Atrial Fibrillation/
56	((atria* or atrium or auricular) adj6 fibril*).tw, kf, ot.
57	AF.tw,kf. and (flutter or fibril?at* or arr?yth?m* or atrial or atrium or atria).mp.
58	((recurr* or persistent* or long-dur* or long-stand* or longstand* or long-last* or longlast* or prolonged or continuing or chronic* or refractory or non-valv* or nonvalv* or nonparoxysm* or non-paroxysm*) adj3 AF).tw.
59	(LPAF or LSPAF or LSP-AF or PsAF or Ps-AF or R-AF or PerAF or Per-Af or CPAF).tw.
60	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
61	6 and 21 and 60
62	limit 61 to humans

Embase via Ovid ®

No	Search
1	(cost effectiveness or cost-effectiveness).mp.
2	exp "cost effectiveness analysis"/
3	"cost benefit analys$".mp.
4	exp "cost benefit analysis"/
5	"cost utility analys$".mp.
6	exp "cost utility analysis"/
7	econ$ evaluat$.mp. or exp economic evaluation/
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	Pharmacogenetic$.mp. or exp pharmacogenetics/
10	Pharmacogenomic$.mp. or exp pharmacogenomics/
11	Precision Medicin$.mp. or exp personalized medicine/
12	Individuali?ed Medicin$.mp.
13	Individuali?ed treatment$.mp.
14	Personali?ed Medicin$.mp.
15	Personali?ed treatment$.mp.
16	Personali?ed therap$.mp.
17	exp genetic screening/ or Genetic$ screen$.mp.
18	exp genetic analysis/ or Genetic Test$.mp.
19	exp genotype/ or Genotype$.mp.
20	genetic marker$.mp. or exp genetic marker/
21	exp marker/ or genomic marker$.mp.
22	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	cardiovascular disease$.mp. or exp cardiovascular disease/
24	coronary arter$ disease$.mp. or exp coronary artery disease/
25	Coronary Arteriosclero$.mp. or exp coronary artery atherosclerosis/
26	Angina Pectoris.mp. or exp angina pectoris/
27	Myocardial Infarct$.mp. or exp heart infarction/
28	Myocardial Reperfusion.mp. or exp heart muscle reperfusion/
29	Myocardium.mp. or exp cardiac muscle/
30	Heart Attack$.mp. or exp heart infarction/
31	stroke$.mp. or exp cerebrovascular accident/
32	Heart Failure$.mp. or exp heart failure/
33	exp hypoxia-induced pulmonary hypertension/ or exp persistent pulmonary hypertension/ or exp hereditary hypertension/ or exp resistant hypertension/ or exp deoxycorticosterone-salt induced hypertension/ or exp masked hypertension/ or exp portal hypertension/ or exp chronic thromboembolic pulmonary hypertension/ or exp maternal hypertension/ or exp borderline hypertension/ or exp intraabdominal hypertension/ or exp malignant hypertension/ or exp portopulmonary hypertension/ or hypertension.mp. or exp systolic hypertension/ or exp renovascular hypertension/ or exp experimental pulmonary hypertension/ or exp white coat hypertension/ or exp diabetic hypertension/ or exp idiopathic intracranial hypertension/ or exp intracranial hypertension/ or exp intraocular hypertension/ or exp orthostatic hypertension/ or exp hypertension/ or exp essential hypertension/ or exp pulmonary hypertension/ or exp monocrotaline-induced pulmonary hypertension/ or exp experimental hypertension/

34	high blood pressure.mp.
35	exp hypertrophic cardiomyopathy/ or exp restrictive cardiomyopathy/ or exp congestive cardiomyopathy/ or exp hypertrophic obstructive cardiomyopathy/ or exp nonischemic cardiomyopathy/ or exp tachycardia induced cardiomyopathy/ or cardiomyopathy.mp. or exp ischemic cardiomyopathy/ or exp cardiomyopathy/ or exp diabetic cardiomyopathy/ or exp peripartum cardiomyopathy/ or exp takotsubo cardiomyopathy/ or exp familial hypertrophic cardiomyopathy/
36	Heart Valve Disease$.mp. or exp valvular heart disease/
37	Aortic Aneurysm$.mp. or exp abdominal aorta aneurysm/ or exp aneurysm rupture/ or exp aortic aneurysm/ or exp aorta rupture/ or exp aorta aneurysm/
38	Peripheral Arterial Disease$.mp. or exp peripheral occlusive artery disease/
39	Peripheral Vascular Disease$.mp. or exp peripheral vascular disease/
40	Coronary Disease.mp. or exp coronary artery disease/
41	Arteriosclero$.mp. or exp experimental arteriosclerosis/ or exp arteriosclerosis/ or exp atherosclerosis/ or exp ischemic heart disease/ or exp peripheral occlusive artery disease/ or exp coronary artery atherosclerosis/
42	heart disease$.mp.
43	exp heart ventricle extrasystole/ or exp heart disease/ or exp congestive heart failure/ or chronic heart disease.mp. or exp coronary artery disease/
44	isch?emic heart disease$.mp. or exp ischemic heart disease/
45	cerebrovascular disease$.mp. or exp cerebrovascular disease/
46	Coronary Thrombo$.mp. or exp coronary artery thrombosis/
47	exp embolism prevention/ or exp paradoxical embolism/ or exp fat embolism/ or exp kidney artery embolism/ or exp artery embolism/ or embolism.mp. or exp gas embolism/ or exp cholesterol embolism/ or exp air embolism/ or exp lung embolism/ or exp vein embolism/ or exp embolism/
48	Atherosclero$.mp. or exp atherosclerosis/ or exp coronary artery atherosclerosis/ or exp aortic atherosclerosis/ or exp carotid atherosclerosis/ or exp brain atherosclerosis/ or exp experimental atherosclerosis/
49	mitral steno$.mp. or exp mitral valve stenosis/
50	Atrial Fibrillation/
51	((atria* or atrium or auricular) adj6 fibril*).tw,kw,ot.
52	AF.tw,kw. and (flutter or fibril?at* or arr?yth?m* or atrial or atrium or atria).mp.
53	((recurr* or persistent* or long-dur* or long-stand* or longstand* or long-last* or longlast* or prolonged or continuing or chronic* or refractory or non-valv* or nonvalv* or nonparoxysm* or non-paroxysm*) adj3 AF).tw.
54	(LPAF or LSPAF or LSP-AF or PsAF or Ps-AF or R-AF or PerAF or Per-Af or CPAF).tw.
55	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56	8 and 22 and 55
57	limit 56 to human

Econlit,via ProQuest ®

No.	Search
1	(pharmacogenetic* OR pharmacogenomic* OR Precision Medicin* OR Individuali?ed Medicin* OR Personali?ed Medicin* OR Individuali?ed treatment* OR Personali?ed treatment* OR Personali?ed therap* OR Individuali?ed therap* OR genetic* screen* OR genetic test* OR genotype* OR genetic marker* OR genomic marker* OR gene* OR mutation* OR genetic analys* OR phenotype* OR genetic variation OR genomics)
2	(cardiovascular disease* OR coronary arter* disease OR Coronary Arteriosclero* OR Angina Pectoris OR Myocardial Infarct* OR Myocardial repercussion OR Myocardium OR Heart Attack* OR Stroke OR Heart Failure* OR hypertensi* OR high blood pressure OR Rheumatic Heart Disease* OR Cardiomyopath* OR Heart Valve Disease* OR Myocarditis OR Aortic Aneurysm* OR Peripheral Arterial Disease* OR Peripheral Vascular Disease* OR Coronary Disease* OR Arteriosclero* OR Venous Thrombo* OR Acute rheumatic fever OR pericarditis OR endocarditis OR rheumatic heart disease* OR heart disease* OR isch?emic heart disease* OR Myocardial Ischemia OR cerebrovascular disease* OR Cerebrovascular Disorder* OR phlebitis OR thrombophlebitis OR hypotension OR Rheumatic chorea OR chorea OR Coronary thrombo* OR embolism* OR Atheroscleros* OR Mitral steno* OR Mitral Valve Steno* OR atrial fib* OR Atrial fibrillation OR atrial flutter OR atrial tachycardia OR paroxysmal atrial OR supraventricular tachycardia* OR Arrhythmia)
3	1 AND 2

Web of Science Core Collection

No.	Search
# 1	TS=("cost benefit analys*" or CBA or "cost-benefit analysis")
# 2	TS=(cost* NEAR/2 analys* or "costs and cost analysis")
# 3	TS=(cost NEAR/2 effectiveness or "cost-effectiveness" or CEA)
# 4	TS = ("cost-utility analys*" or "cost utility analys*" or CUA
# 5	TS=(pharmacoeconomic* or "pharmaceutical economics")
# 6	TS = ("econ* evaluat*")
# 7	#6 OR #5 OR #4 OR #3 OR #2 OR #1
# 8	TS = (pharmacogenetic*)
# 9	TS = (pharmacogenomic*)
# 10	TS = ("precision medicin*")
# 11	TS = ("individuali?ed medicin*")
# 12	TS = ("individuali?ed treatment*")
# 13	TS = ("personali?ed medicin*")
# 14	TS = ("personali?ed treatment*")
# 15	TS = ("personali?ed therap*")
# 16	TS = ("genetic* screen*" "genetic* test*" or "genetic testing")
# 17	TS = genotype*
# 18	TS=(genomic*)
# 19	TS=(genetic*)
# 20	#19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8
# 21	TS = ("cardiovascular disease*")
# 22	TS = ("coronary arter* disease*")
# 23	TS = ("coronary arteriosclero*")
# 24	TS = ("angina pectoris")
# 25	TS = ("myocardial infarct*")
# 26	TS = ("myocardial reperfusion")
# 27	TS = (myocardium)
# 28	TS = ("heart attack*")
# 29	TS = (stroke)
# 30	TS = ("heart failure*")
# 31	TS = (hypertensi* or hypertension)
# 32	TS = ("high blood pressure")
# 33	TS = ("rheumatic heart disease")
# 34	TS = (cardiomyopath* or "diabetic cardiomyopathy")
# 35	TS = ("heart valve disease*")
# 36	TS = (myocarditis)
# 37	TS = ("aortic aneurysm*")
# 38	TS=("peripheral arterial disease*" or "peripheral vascular disease*" or "peripheral arterial disease" or "coronary disease*" or arteriosclerosis)
# 39	TS = ("venous thrombosis" or "venous thrombo*")
# 40	TS = ("acute rheumatic fever" or "rheumatic fever")
# 41	TS = (pericarditis)
# 42	TS = (endocarditis)

# 43	TS = ("heart disease*" or "chronic rheumatic heart disease*")
# 44	TS = ("isch?emic heart disease*" or "myocardial ischemia")
# 45	TS = ("cerebrovascular disease*" or "cerebrovascular disorder*")
# 46	TS = (phlebitis)
# 47	TS = (thrombophlebitis)
# 48	TS = (hypotension)
# 49	TS = ("rheumatic chorea" or chorea)
# 50	TS = ("coronary thrombo*" or "coronary thrombosis")
# 51	TS = (embolism* or "pulmonary embolism*")
# 52	TS = (atheroscleros?s)
# 53	TS = ("mitral steno*" or "mitral valve stenosis")
# 54	TS=(Atrial Fibrillation)
# 55	TS= (("atria*" or "atrium" or "auricular") NEAR/6 fibril*)
# 56	TS = (AF and (flutter or "fibril?at*" or "arr?yth?m*" or atrial or atrium or atria))
# 57	TS= (("recurr*" or "persistent*" or "long-dur*" or "long-stand" or "longstand*" or "long-last*" or "longlast*" or prolonged or continuing or "chronic*" or refractory or "non-valv*" or "nonvalv*" or "nonparoxysm*" or "non-paroxysm*") NEAR/3 AF)
# 58	TS=(LPAF or LSPAF or LSP-AF or PsAF or Ps-AF or R-AF or PerAF or Per-Af or CPAF)
# 59	#58 OR #57 OR #56 OR #55 OR #54 OR #53 OR #52 OR #51 OR #50 OR #49 OR #48 OR #47 OR #46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21
# 60	#59 AND #20 AND #7

NHSEED database and HTA database via University of York Centre for Reviews & Dissemination https://www.crd.york.ac.uk/CRDWeb/

No.	Search
1	MeSH DESCRIPTOR Pharmacogenetics EXPLODE ALL TREES IN NHSEED,HTA
2	MeSH DESCRIPTOR Pharmacogenomic Testing EXPLODE ALL TREES IN NHSEED,HTA
3	((((Precision Medicin*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
4	MeSH DESCRIPTOR Precision Medicine EXPLODE ALL TREES IN NHSEED,HTA
5	((((Individuali?ed Medicin*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
6	((((Individuali?ed treatment*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
7	((((Individuali?ed therap*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
8	((((Personali?ed Medicin*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
9	((((Personali?ed treatment*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
10	((((Personali?ed therap*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
11	((((Genetic* screen*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
12	MeSH DESCRIPTOR Genetic Testing EXPLODE ALL TREES IN NHSEED,HTA

13	((((Genetic* test*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
14	((((Genotype*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
15	MeSH DESCRIPTOR Genotype EXPLODE ALL TREES IN NHSEED,HTA
16	MeSH DESCRIPTOR Genetic Markers EXPLODE ALL TREES IN NHSEED,HTA
17	MeSH DESCRIPTOR Genes EXPLODE ALL TREES IN NHSEED,HTA
18	((((Mutation*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
19	MeSH DESCRIPTOR Mutation EXPLODE ALL TREES IN NHSEED,HTA
20	MeSH DESCRIPTOR Cytogenetic Analysis EXPLODE ALL TREES IN NHSEED,HTA
21	((((Phenotype*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
22	MeSH DESCRIPTOR Phenotype EXPLODE ALL TREES IN NHSEED,HTA
23	MeSH DESCRIPTOR Genetic Variation EXPLODE ALL TREES IN NHSEED,HTA
24	MeSH DESCRIPTOR Genomics EXPLODE ALL TREES IN NHSEED,HTA
25	((((Genet*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
26	((((Pharmacogen*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
27	((((genetic* marker*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
28	((((genomic* marker*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA

29	((((genetic* analys*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
30	((((genetic* variation*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
31	((((genomic*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
32	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
33	((((cardiovascular disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
34	MeSH DESCRIPTOR Cardiovascular Diseases EXPLODE ALL TREES IN NHSEED,HTA
35	((((coronary arter* disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
36	MeSH DESCRIPTOR Coronary Artery Disease EXPLODE ALL TREES IN NHSEED,HTA
37	((((Coronary Arteriosclero*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
38	((((Angina Pectoris)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
39	MeSH DESCRIPTOR Angina Pectoris EXPLODE ALL TREES IN NHSEED,HTA
40	((((Myocardial Infarct*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
41	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES IN NHSEED,HTA
42	MeSH DESCRIPTOR Myocardial Reperfusion EXPLODE ALL TREES IN NHSEED,HTA

43	((((Myocardium)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
44	MeSH DESCRIPTOR Myocardium EXPLODE ALL TREES IN NHSEED,HTA
45	((((Heart Attack*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
46	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES IN NHSEED,HTA
47	((((Heart Failure*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
48	MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES IN NHSEED,HTA
49	((((Hypertensi*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
50	MeSH DESCRIPTOR Familial Primary Pulmonary Hypertension EXPLODE ALL TREES IN NHSEED,HTA
51	MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES IN NHSEED,HTA
52	MeSH DESCRIPTOR Hypertension, Malignant EXPLODE ALL TREES IN NHSEED,HTA
53	MeSH DESCRIPTOR Hypertension, Portal EXPLODE ALL TREES IN NHSEED,HTA
54	MeSH DESCRIPTOR Hypertension, Pregnancy-Induced EXPLODE ALL TREES IN NHSEED,HTA
55	MeSH DESCRIPTOR Hypertension, Pulmonary EXPLODE ALL TREES IN NHSEED,HTA
56	MeSH DESCRIPTOR Hypertension, Renal EXPLODE ALL TREES IN NHSEED,HTA
57	MeSH DESCRIPTOR Hypertension, Renovascular EXPLODE ALL TREES IN NHSEED,HTA
58	MeSH DESCRIPTOR Intracranial Hypertension EXPLODE ALL TREES IN NHSEED,HTA
59	MeSH DESCRIPTOR Masked Hypertension EXPLODE ALL TREES IN NHSEED,HTA
60	MeSH DESCRIPTOR White Coat Hypertension EXPLODE ALL TREES IN NHSEED,HTA
61	((((high blood pressure)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
62	((((Rheumatic Heart Disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and

	Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
63	MeSH DESCRIPTOR Rheumatic Heart Disease EXPLODE ALL TREES IN NHSEED,HTA
64	((((Cardiomyopath*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
65	MeSH DESCRIPTOR Cardiomyopathies EXPLODE ALL TREES IN NHSEED,HTA
66	MeSH DESCRIPTOR Cardiomyopathy, Dilated EXPLODE ALL TREES IN NHSEED,HTA
67	MeSH DESCRIPTOR Cardiomyopathy, Hypertrophic EXPLODE ALL TREES IN NHSEED,HTA
68	MeSH DESCRIPTOR Cardiomyopathy, Hypertrophic, Familial EXPLODE ALL TREES IN NHSEED,HTA
69	MeSH DESCRIPTOR Cardiomyopathy, Restrictive EXPLODE ALL TREES IN NHSEED,HTA
70	MeSH DESCRIPTOR Diabetic Cardiomyopathies EXPLODE ALL TREES IN NHSEED,HTA
71	((((Heart Valve Disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
72	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES IN NHSEED,HTA
73	((((Myocarditis)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
74	MeSH DESCRIPTOR Myocarditis EXPLODE ALL TREES IN NHSEED,HTA
75	((((Aortic Aneurysm*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
76	MeSH DESCRIPTOR Aortic Aneurysm EXPLODE ALL TREES IN NHSEED,HTA
77	((((Peripheral Arterial Disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
78	MeSH DESCRIPTOR Peripheral Arterial Disease EXPLODE ALL TREES IN NHSEED,HTA
79	((((Peripheral Vascular Disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and

	Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
80	MeSH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES IN NHSEED,HTA
81	((((Coronary Disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
82	MeSH DESCRIPTOR Coronary Disease EXPLODE ALL TREES IN NHSEED,HTA
83	MeSH DESCRIPTOR Arteriosclerosis EXPLODE ALL TREES IN NHSEED,HTA
84	MeSH DESCRIPTOR Intracranial Arteriosclerosis EXPLODE ALL TREES IN NHSEED,HTA
85	((((Arterioscleros?s)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
86	((((Venous Thrombo*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
87	MeSH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES IN NHSEED,HTA
88	MeSH DESCRIPTOR Venous Thromboembolism EXPLODE ALL TREES IN NHSEED,HTA
89	((((Acute rheumatic fever)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
90	MeSH DESCRIPTOR Rheumatic Fever EXPLODE ALL TREES IN NHSEED,HTA
91	((((pericarditis)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
92	MeSH DESCRIPTOR Pericarditis EXPLODE ALL TREES IN NHSEED,HTA
93	((((endocarditis)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
94	MeSH DESCRIPTOR Endocarditis EXPLODE ALL TREES IN NHSEED,HTA
95	((((Heart Disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA

96	MeSH DESCRIPTOR Heart Diseases EXPLODE ALL TREES IN NHSEED,HTA
97	MeSH DESCRIPTOR Pulmonary Heart Disease EXPLODE ALL TREES IN NHSEED,HTA
98	((((chronic rheumatic heart disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
99	((((isch?emic heart disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
100	MeSH DESCRIPTOR Myocardial Ischemia EXPLODE ALL TREES IN NHSEED,HTA
101	((((cerebrovascular disease*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
102	((((cerebrovascular disorder*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
103	MeSH DESCRIPTOR Cerebrovascular Disorders EXPLODE ALL TREES IN NHSEED,HTA
104	((((phlebitis)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
105	MeSH DESCRIPTOR Phlebitis EXPLODE ALL TREES IN NHSEED,HTA
106	MeSH DESCRIPTOR Thrombophlebitis EXPLODE ALL TREES IN NHSEED,HTA
107	((((thrombophlebitis)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
108	((((hypotension)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
109	MeSH DESCRIPTOR Hypotension EXPLODE ALL TREES IN NHSEED,HTA
110	MeSH DESCRIPTOR Hypotension, Controlled EXPLODE ALL TREES IN NHSEED,HTA
111	MeSH DESCRIPTOR Hypotension, Orthostatic EXPLODE ALL TREES IN NHSEED,HTA
112	MeSH DESCRIPTOR Intracranial Hypotension EXPLODE ALL TREES IN NHSEED,HTA

113	((((Rheumatic chorea)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
114	MeSH DESCRIPTOR Chorea EXPLODE ALL TREES IN NHSEED,HTA
115	((((chorea)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
116	((((Coronary thrombo*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
117	MeSH DESCRIPTOR Coronary Thrombosis EXPLODE ALL TREES IN NHSEED,HTA
118	((((embolism*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
119	MeSH DESCRIPTOR Embolism EXPLODE ALL TREES IN NHSEED,HTA
120	MeSH DESCRIPTOR Embolism and Thrombosis EXPLODE ALL TREES IN NHSEED,HTA
121	MeSH DESCRIPTOR Embolism, Air EXPLODE ALL TREES IN NHSEED,HTA
122	MeSH DESCRIPTOR Embolism, Cholesterol EXPLODE ALL TREES IN NHSEED,HTA
123	MeSH DESCRIPTOR Embolism, Fat EXPLODE ALL TREES IN NHSEED,HTA
124	MeSH DESCRIPTOR Embolism, Paradoxical EXPLODE ALL TREES IN NHSEED,HTA
125	MeSH DESCRIPTOR Intracranial Embolism EXPLODE ALL TREES IN NHSEED,HTA
126	MeSH DESCRIPTOR Intracranial Embolism and Thrombosis EXPLODE ALL TREES IN NHSEED,HTA
127	MeSH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES IN NHSEED,HTA
128	MeSH DESCRIPTOR Thromboembolism EXPLODE ALL TREES IN NHSEED,HTA
129	((((Atheroscleros*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
130	MeSH DESCRIPTOR Atherosclerosis EXPLODE ALL TREES IN NHSEED,HTA
131	MeSH DESCRIPTOR Carotid Artery Diseases EXPLODE ALL TREES IN NHSEED,HTA
132	MeSH DESCRIPTOR Intracranial Arteriosclerosis EXPLODE ALL TREES IN NHSEED,HTA

133	((((Mitral steno*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
134	MeSH DESCRIPTOR Mitral Valve Stenosis EXPLODE ALL TREES IN NHSEED,HTA
135	((((Myocardial Reperfusion*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
136	((((Stroke*)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
137	((Atrial Fibrillation)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
138	MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES IN NHSEED,HTA
139	((Atrial Flutter)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
140	MeSH DESCRIPTOR Atrial Flutter EXPLODE ALL TREES IN NHSEED,HTA
141	((LPAF OR LSP-AF OR PsAF or Ps-AF OR R-AF OR PerAF OR Per-Af OR CPAF)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN NHSEED, HTA
142	MeSH DESCRIPTOR Arrhythmias, Cardiac EXPLODE ALL TREES IN NHSEED,HTA
143	MeSH DESCRIPTOR Tachycardia, Ectopic Atrial EXPLODE ALL TREES IN NHSEED,HTA
144	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143
145	#32 AND #144

Table S3. Summary of included studies.

Study 1/35

First Author (Year)	SR8175 Hart et al 2019 [33]
URL	https://doi.org/10.1016/j.jval.2019.05.015
Stated Study Objectives	To estimate the cost-effectiveness associated with a multi-gene panel pre-emptively testing two genes providing CYP2C19 genotype-guided strategy for antiplatelet therapy, with CYP2D6 genotype-guided pain management, compared to single gene test for CYP2C19 with random assignment for pain treatment, and to no testing (empiric clopidogrel with random assignment for pain treatment)
Sample Characteristics	Patients with Non-STE ACS at 55 years old undergoing PCI and treated with mild to moderate pain management in US.
Intervention	The study has two intervention arms – (i) multigene test for specific genetic locations within CYP2C19 and CYP2D6 that are clinically actionable, followed by prasugrel for CYP2C19 LOF carriers and clopidogrel for CYP2C19 non-LOF carriers, or acetaminophen for CYP2D6 LOG carriers or tramadol for CYP2D6 non-LOF carriers; (ii) single gene test for CYP2C19 only.
Comparator	The study has one comparator arm – no genetic test.
Type of study design	Model - Decision Tree (DT) on Microsoft Excel 2016; RStudio
Time horizon	15 months
Perspective	US payer perspective
Currency (year)	USD 2016, discounted at 3% annually
Outcome measures	QALY gained, discounted at 3% annually
Willingness-to-pay threshold	USD 100,000 per QALY gained
Main findings & conclusion	Over 15 months, multi-gene testing was least costly and yielded more QALYs compared to both single gene and no testing; total incremental costs were $1646 lower with incremental gains of 0.04 QALYs for multi-gene compared with single gene and $11 368 lower with 0.17 QALY gains compared to no test. Base case analyses revealed multi gene was dominant compared to both single gene and no test, as it demonstrated cost savings with increased QALYs.
Findings of sensitivity analysis	One-way sensitivity analyses revealed the model was most sensitive to the probability of ADE associated with both acetaminophen and tramadol, not genotype-guided and the cost of the composite ADE from acetaminophen. In probabilistic analysis of 1000 replications, multigene testing was less costly and more effective than single gene testing in 73% simulations.
Funding source	No declaration.
Competing interest	This work was conducted as part of the dissertation M.R.H. completed. The authors have no relevant conflict of interest to disclose.
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 2/35

First Author (Year)	SR8017 Dong et al 2019 [34]
URL	https://doi.org/10.1016/j.jval.2019.08.002
Stated Study Objectives	To evaluate the cost-effectiveness of multigene testing (CYP2C19, SLCO1B1, CYP2C9, VKORC1) compared with singlegene testing (CYP2C19) and standard of care (no genotyping) in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) from Medicare's perspective.
Sample Characteristics	ACS patients aged 65 years old in US who underwent PCI and were to remain on warfarin for long term.
Intervention	The study has two intervention arms – (i) single gene testing, with CYP2C19 testing and prescribed with warfarin standard dosing; (ii) multigene testing, with CYP2C19 testing (patients would initially be prescribed clopidogrel, and those with variants would switch to prasugrel later), SLCO1B1 for statin selection (patients would initially be prescribed simvastatin, and those with variants would switch to other statins), and CYP2C9/VKORC1 testing where warfarin dose would be tailored based on the variants.
Comparator	The study has one comparator arm – standard of care (no gene testing).
Type of study design	Model - Markov cohort ± DT on Microsoft Excel 1 year cycle length; no mention of half cycle correction.
Time horizon	12 months / 24 months and lifetime in sensitivity analyses.
Perspective	Healthcare sector (US Medicare)
Currency (year)	USD (2016), discounted at 3% annually
Outcome measures	QALY gained, discounted at 3% annually
Willingness-to-pay threshold	USD 50,000 and USD 100,000 per QALY gained
Main findings & conclusion	Base-case results indicated that the cost per QALY gained was $59 876, $33 512, and $3780 at 12 months, 24 months, and lifetime, respectively, for multigene testing compared with standard of care. Single-gene testing was dominated by multigene testing at all time horizons.
Findings of sensitivity analysis	In deterministic analyses, the most impactful input parameter across all time horizons comparisons was the cost of single-gene and multigene testing. The probabilistic analyses (10,000 simulations) indicated that, at the $50 000/QALY gained willingness-to-pay threshold, multigene testing had the highest probability of cost-effectiveness in majority simulations at 24 months (61%) and over the lifetime (81%).
Funding source	American Heart Association grant to O.M. Dong and a UNC Eshelman Institute for Innovation grant to T. Wiltshire
Competing interest	No competing interest statements.
Methodological quality	17/20 "Yes / Rather Yes", 3/20 "No / Rather No", 0/20 "Unclear"

Study 3/35

First Author (Year)	SR0067 Jiang et al 2015 [35]
URL	https://journals.lww.com/jpharmacogenetics/Abstract/2015/12000/CYP2C19_genotype_plus_platelet_reactivity_guided.4.aspx
Stated Study Objectives	To evaluate the potential clinical and economic outcome of genotype plus platelet reactivity-guided antiplatelet therapy (PG-PRT) compared with universal clopidogrel and universal alternative antiplatelet therapy for ACS patients undergoing PCI
Sample Characteristics	Patient with ACS (mean age 60 years old) in US who underwent PCI
Intervention	The study has 1 intervention arm - genotype and platelet reactivity-guided antiplatelet therapy i.e., CYP2C19 testing, followed by (a) clopidogrel 75mg for ultrarapid metabolisers or extensive metabolisers, (b) alternative antiplatelet (prasugrel or ticagrelor) for poor metabolisers, (c) clopidogrel 225mg for intermediate metabolisers for 24-48 hours, after which those with high on-treatment platelet reactivity would transition to alternative antiplatelet while the others stayed on clopidogrel 225mg.
Comparator	The study has 2 comparator arms – (I) universal clopidogrel 75mg daily; (ii) universal alternative antiplatelet therapy (prasugrel or ticagrelor).
Type of study design	Model – Markov cohort +/- DT on TreeAge Pro 2014 and Microsoft Excel 2010. 1 year cycle length; no mention of half-cycle correction
Time horizon	40 years
Perspective	Healthcare sector
Currency (year)	USD (2015), discounted at 3% annually.
Outcome measures	QALY gained, discounted at 3% annually
Willingness-to-pay threshold	USD 50,000 per QALY gained
Main findings & conclusion	In base-case analysis, the intervention was the less costly (USD 71 887) strategy with higher QALYs gained (7.886 QALYs). The intervention seems to be cost saving.
Findings of sensitivity analysis	Universal clopidogrel would be the preferred strategy if the prevalence of the CYP2C19 LOF allele was <2.6% or the incidence of HTPR in IM patients was >82.8%. In 10 000 Monte Carlo simulations, PG-PRT was less costly than universal clopidogrel, with higher QALYs. Compared with universal alternative antiplatelet therapy, PG-PRT was less costly, with higher QALYs.
Funding source	Not reported
Competing interest	Declared no competing interest
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 4/35

First Author (Year)	SR9334 Kim et al 2021 [36]
URL	https://doi.org/10.1038/s41397-020-00204-6
Stated Study Objectives	To evaluate the cost-effectiveness of a genotype-guided strategy among patients with acute coronary syndromes using adecision-tree model based on the Singapore healthcare payer's perspective over a 1-year time horizon.
Sample Characteristics	Patients in Singapore (mean age 62 years old) with ACS undergoing PCI
Intervention	The study has one intervention arm – CYP2C19 testing, followed by ticagrelor among carriers of at least one LOF alleles, or clopidogrel among non-carriers.
Comparator	The study has two comparator arms – no testing, with (i) universal clopidogrel, (ii) universal ticagrelor.
Type of study design	Model - Decision Tree (DT) on Microsoft Excel 2011
Time horizon	1 year
Perspective	Healthcare sector
Currency (year)	SGD (2019)
Outcome measures	QALY gained
Willingness-to-pay threshold	SGD 88,991 per QALY gained (1 x GDP)
Main findings & conclusion	Both genotype-guided (72,158 SGD/QALY) and universal ticagrelor (82,269 SGD/QALY) were considered cost-effective based on a WTP threshold of SGD 88,991. In our secondary analysis, the ICER for universal ticagrelor was 114,998 SGD/QALY vs testing.
Findings of sensitivity analysis	In deterministic analyses, probability of death among LOF-clopidogrel was the most sensitive for testing vs universal clopidogrel as well as for universal ticagrelor vs testing. In probabilistic analyses (1000 replications), genotype-guided treatment was the most cost-effective strategy when the WTP threshold was between SGD 70,000 to 100,000.
Funding source	No declaration.
Competing interest	Declared no competing interest.
Methodological quality	16/20 "Yes / Rather Yes", 3/20 "No / Rather No"/20 "Unclear"

Study 5/35

First Author (Year)	SR8044 Limdi et al 2020 [37]
URL	https://doi.org/10.1038/s41397-020-0162-5
Stated Study Objectives	(1) To conduct CEA of genotype-guided dual-antiplatelet therapy (DAPT) versus empiric DAPT following acute coronary syndrome (ACS) and PCI using real-world effectiveness data. (2) To explore secondary strategies informed by clinical praxtice wherein treatment is modified at 30 days post-PCI (de-escalation).
Sample Characteristics	2,000,000 hypothetical high-risk patients with acute coronary syndrome (ACS) in the US.
Intervention	The study has two intervention arms – (i) genotype-guided escalation, where patients were genotyped at time of PCI, followed by ticagrelor for carriers of LOF allele and clopidogrel for carriers of non-LOF alleles, (ii) genotype-guided de-escalation, where all patients are prescribed ticagrelor for the first 30 days post PCI, followed by de-escalation to clopidogrel among those with non-LOF alleles.
Comparator	The study has three comparator arms – no testing, with (i) universal clopidogrel, (ii) universal ticagrelor, or (iii) non-guided de-escalation, where all patients are prescribed ticagrelor for the first 30 days post PCI, followed by universal de-escalation to clopidogrel.
Type of study design	Model - Discrete event sim ± DT on R (Version 3.6.3)
Time horizon	1 year
Perspective	US healthcare payer
Currency (year)	USD 2016
Outcome measures	QALY gained
Willingness-to-pay threshold	USD 100,000 per QALY gained
Main findings & conclusion	Compared with universal clopidogrel, both universal ticagrelor and genotype-guided escalation had higher quality-adjusted life years (QALY's). Only genotype-guided escalation was cost-effective ($42,365/QALY) and demonstrated the highest probability of being cost-effective across conventional willingness-to-pay thresholds. Compared with the nonguided de-escalation strategy, although genotype-guided de-escalation and universal ticagrelor were more effective, with ICER of $188,680/QALY and $678,215/QALY, respectively, they were not cost-effective.
Findings of sensitivity analysis	In sensitivity analyses, variation in CYP2C19 LOF allele frequency and variation in acceptance of genotype-based recommendations did not alter the preferred strategy. In probabilistic sensitivity analyses, genotype-guided escalation had the highest probability of being cost-effective compared with universal clopidogrel or universal ticagrelor across all conventional WTP thresholds.
Funding source	National Institute of Health, various academic institutions, and anonymous donor
Competing interest	JFP is a consultant for Color Genomics Inc. No other authors have any conflicts of interest to declare.
Methodological quality	16/20 "Yes / Rather Yes", 4/20 "No / Rather No", 0/20 "Unclear"

Study 6/35

First Author (Year)	SR8462 Marrero et al 2019 [38]
URL	https://ieeexplore.ieee.org/document/9004735
Stated Study Objectives	(1) To determine the potential public health impact of large-scale genetic testing to inform the use of cholesterol-lowering drugs (2) To evaluate how the cost-effectiveness of genetic testing changes with respect to the population tested
Sample Characteristics	Patients (aged between 40 – 75 years old) with no history of atherosclerotic CVD and a low-density lipoprotein (LDL)
Intervention	The study has one intervention arm – prescribing statins based on clinical + genetic risk factors (GenePCE risk score). May also have a "no treatment" arm but the simulation of this arm is not described in the methods section.
Comparator	The study has one comparator arm – prescribing statins based on clinical risk factors only (PCE risk score).
Type of study design	Model - Markov microsim ± DT on R (v3.5.0) 1 year cycle length; no mention of half-cycle correction
Time horizon	10 years
Perspective	Not stated
Currency (year)	USD (cost year not stated)
Outcome measures	CHD events averted, QALY gained
Willingness-to-pay threshold	Not stated (but cited Neumann et al 2014)
Main findings & conclusion	Both treatment strategies are well below the commonly used cost effectiveness thresholds for all populations and testing costs, compared to no treatment. Policies informed with clinical and genetic information are cost-saving compared to the policies informed with clinical information only if there is no cost associated with genetic testing. Genetic testing is most cost-effective if performed on people who are less than 50 years old. It is least cost-effective if performed on female individuals only. However, the ICER of the policies informed with clinical and genetic information compared to the policies derived with clinical information only is considerably higher than the regularly used cost-effectiveness thresholds in all scenarios.
Findings of sensitivity analysis	No sensitivity analysis reported.
Funding source	NSF grants and United States Department of Veteran Affairs grants
Competing interest	No competing interest statement
Methodological quality	6/20 "Yes / Rather Yes", 8/20 "No / Rather No", 6/20 "Unclear"

Study 7/35

First Author (Year)	SR9315 Jung et al 2021 [39]
URL	https://doi.org/10.2217/epi-2021-0021
Stated Study Objectives	To conduct cost-utility analysis of the Epi+Gen CHD™ test compared with the current 'standard tool', atherosclerotic cardiovascular disease (ASCVD) risk calculator.
Sample Characteristics	Individuals in US (age 40 – 79 years old) with ASCVD low risk (10-year risk of CHD<5%) and CHD free with LDL levels<190 mg/dl, systolic blood pressure<140 mm Hg at the age of 40 years, without diabetes.
Intervention	The study has one intervention arm – Epi + Gen CHD screening to estimate 10-year risk of ASCVD, followed by statin prevention therapy for those at "high risk"
Comparator	The study has one comparator arm – standard practice using ACC/AHA pooled cohort equation to estimate 10-year risk of ASCVD, followed by statin prevention therapy for those at "high risk".
Type of study design	Model - Markov cohort ± DT on R (heemod package) 1 year cycle length; no mention of half-cycle correction.
Time horizon	35 years
Perspective	Not specified
Currency (year)	USD (2020), discounted at 3% annually.
Outcome measures	QALY gained, discounted at 3% annually.
Willingness-to-pay threshold	USD 150,000 per QALY gained
Main findings & conclusion	Epi + Gen CHD screening accrued higher QALYs and lower cost compared to ASCVD equations, regardless of whether clinicians undertake secondary test (coronary calcium screening, ECG or exercise stress test) before initiating the statin therapy.
Findings of sensitivity analysis	In deterministic sensitivity analyses, ICER values were most sensitive to variations in estimates of the cost of post-CHD care The cost of statin and the cost of post-CHD care had greater impacts on cost for men than for women. In probabilistic analyses (10,000 replications), Epi + Gen CHD showed that Epi + Gen CHD tests was the dominant strategy more than 90% of the simulations.
Funding source	No declaration.
Competing interest	The University of Iowa has filed intellectual property claims related to the integrated genetic/epigenetic technology described in this communication on behalf of two authors. Three authors and Cardio Diagnostics Inc. have filed intellectual property claims related to the integrated genetic/epigenetic technology described in this communication. One author is the Chief Executive Officer and stockholder of Cardio Diagnostics Inc.; one is the Chief Medical Officer and stockholder of Cardio Diagnostics Inc.; one author is an employee and stockholder of Cardio Diagnostics Inc.
Methodological quality	15/20 "Yes / Rather Yes", 5/20 "No / Rather No", 0/20 "Unclear"

Study 8/35

First Author (Year)	SR6178 Hynninen et al 2019 [40]
URL	https://doi.org/10.1371/journal.
Stated Study Objectives	To optimize the population-level use and targeting of genetic testing alongside traditional risk factors in the prevention of CHD events and thereby, to assess the cost-benefit of genetic testing.
Sample Characteristics	Patients with ACS (at least 45 years old) in Finland
Intervention	The study has six intervention arms – (i) genetic risk score (GRS) for all, (ii) GRS optimised (use GRS for an optimal patient segment to determine whether to treat), (iii) traditional risk score (TRS) and GRS optimised, where GRS is carried out optionally after having observed the result of optimally targeted TRS, (iv) GRS and TRS optimised, (v) TRS for all and GRS for patients with updated risk between 10-20%, (vi) TRS & GRS for all.
Comparator	The study has four comparator arms – (i) no treatment (Do not test or treat any patient), (ii) treatment optimised (use prior risk to determine who to treat with statin medication), (iii) TRS optimised (use TRS for an optimal patient segment to determine whether to treat), (iv) TRS for all.
Type of study design	Model - Decision Tree (DT)
Time horizon	10 years
Perspective	Healthcare sector
Currency (year)	Euro (2015), discounted at 3% annually
Outcome measures	QALY gained.
Willingness-to-pay threshold	EUR 50,000 per QALY gained
Main findings & conclusion	Strategy 'TRS & GRS optimised' has the highest NMB of 379,786 € = 7.6292 QALYs × 50,000 €/QALY– 1,674 € and is therefore optimal. Strategy 'TRS optimized' has the second highest NMB = 379,784 €. The remaining strategies have lower NMBs than 'TRS & GRS optimized' - either (i) a substantial increase in costs relative to the increase in health outcomes (strategies 'TRS for all & GRS for 10–20%', 'TRS for all', and 'TRS & GRS for all'), (ii) a substantial decrease in health outcomes relative to the decrease in costs (strategy 'No treatment'), or (iii) a decrease in health outcomes and an increase in costs (dominated strategies 'GRS & TRS optimized', 'GRS optimized', 'Treatment optimized', and 'GRS for all').
Findings of sensitivity analysis	In one-way sensitivity analysis, the net monetary benefit of strategy 'TRS & GRS optimized' is most sensitive to changes in (i) the probability of death in case of a CHD event, (ii) risk reduction by statins, and (iii) the cost of a non-fatal CHD event. In probabilistic analysis, the probability of strategy 'TRS & GRS optimized' being optimal is 80%.
Funding source	The Finnish Funding Agency for Technology and Innovation, the Academy of Finland's IMPRO project, the Strategic Research Council of the Academy of Finland
Competing interest	Declared no competing interests.
Methodological quality	16/20 "Yes / Rather Yes", 4/20 "No / Rather No", 0/20 "Unclear"

Study 9/35

First Author (Year)	SR0328 Jarmul et al 2018 [41]
URL	https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.117.004171
Stated Study Objectives	To estimate the cost-effectiveness of cGRS testing to inform clinical decision making about statin initiation in individuals with low-to-intermediate (2.5%–7.5%) 10-year predicted risk of ASCVD
Sample Characteristics	Patients with CAD (mean age 57 years old) in US
Intervention	The study has two intervention arms – (i) cGRS testing / treat if cGRS = intermediate or high, (ii) cGRS testing / treat if cGRS = high.
Comparator	The study has two comparator arms – (i) test none / treat none, (ii) test none / treat all.
Type of study design	Model - Markov cohort ± DT 1 year cycle length; no mention of half-cycle correction
Time horizon	Lifetime
Perspective	Healthcare sector
Currency (year)	USD (2016), discounted at 3% annually.
Outcome measures	QALY gained, discounted at 3% annually. Life years gained.
Willingness-to-pay threshold	USD 50,000 per QALY gained
Main findings & conclusion	In base case analyses, the preferred strategy is to treat all patients with ASCVD risk >2.5% without cGRS testing. For certain clinical scenarios, such as a 57-year-old man with a 10-year ASCVD risk of 7.5%, cGRS testing can be cost-effective under a limited set of assumptions e.g., when statins cost $15 per month and statin disutility is 0.013, the preferred strategy (at WTP $50 000 per QALY gained) is to test and treat if cGRS is intermediate or high.
Findings of sensitivity analysis	Overall, the results were not sensitive to assumptions about statin efficacy and harms In probabilistic analysis, when statin disutility and statin cost were set at their base case assumptions (base case, scenarios 1, 5, and 6), the probability of cost-effectiveness for the preferred strategy (assuming a WTP threshold of $50 000 per QALY gained) of treat all was either at or close to 100%. For the scenarios in which a cGRS testing strategy was preferred, the probability of cost-effectiveness for that strategy ranged from 43% to 91%, indicating substantial parameter uncertainty even for this most favorable scenario for cGRS testing.
Funding source	NIH T32 GM008719 (Medical Scientist Training Program; PI: Mohanish Deshmukh, PhD)
Competing interest	Declared no competing interest.
Methodological quality	18/20 “Yes / Rather Yes”, 2/20 “No / Rather No”, 0/20 “Unclear”

Study 10/35

First Author (Year)	FC9001 Mujwara et al 2022 [42]
URL	https://www.ahajournals.org/doi/10.1161/JAHA.121.025236
Stated Study Objectives	To project health benefits and health care costs associated with including polygenic risk score for CAD (CAD-PRS) as a risk- enhancing factor among individuals with borderline or intermediate risk of atherosclerotic cardiovascular disease (ASCVD) derived from the pooled cohort equation (PCE)
Sample Characteristics	Individuals in the United States (40 – 75 years old) with borderline or intermediate 10- year risk of ASCVD
Intervention	The study has one intervention arm – using PCE-CAD-PRS) that included conventional risk factors (sex, race, age, blood pressure, lipids, diabetes, and smoking status) and CAD-PRS to determine 10-year risk for a first AS-CVD event, with those at "high-risk" (≥20%) receiving statin prevention therapy.
Comparator	The study has one comparator arm – using PCE alone comprising conventional risk factors to determine 10-year risk for a first AS-CVD event, with those at "high-risk" (≥20%) receiving statin prevention therapy.
Type of study design	Model - Markov cohort ± DT on TreeAge Pro Software 2021 1 year cycle length; no mention of half-cycle correction.
Time horizon	5 and 10 years old and lifetime
Perspective	Healthcare sector
Currency (year)	USD (2019), discounted at 3% annually.
Outcome measures	QALY gained, discounted at 3% annually.
Willingness-to-pay threshold	USD 50,000 per QALY gained
Main findings & conclusion	In base-case analyses, PCE+CAD-PRS was dominant compared with PCE alone in the 5-and 10-year time horizons. We found that, respectively, PCE+CAD-PRS had 0.003 and 0.011 higher mean quality-adjusted life-years and $40 and $181 lower mean costs per person screened, with 29 and 50 fewer events of CAD and ischemic stroke in a cohort of 10 000 individuals compared with PCE alone.
Findings of sensitivity analysis	In deterministic sensitivity analyses, the risk of developing CAD, the effectiveness of statin prevention therapy, and the cost of treating CAD had the largest impact on the cost per quality-adjusted life-year gained. However, this cost remained below the $50 000 willingness-to-pay threshold except when the annual risk of developing CAD was <0.006 in the 5-year time horizon. In probabilistic analyses (10,000 replications), results from Monte Carlo simulation indicated that PCE+CAD-PRS would be cost-effective, with the probability of 94% and 99% at $50 000 willingness-to-pay threshold in the 5-and 10-year time horizon, respectively.
Funding source	Allelica, Inc (medical device company)
Competing interest	Dr Mujwara, P. Di Domenico, Dr Busby, and Dr Bottà are employees of Allelica, Inc. G. Henno is an employee of Pacific Biosciences of California, Inc., and a former employee of Illumina Inc. S. Peng and Dr Schroeder are employees of Illumina, Inc.
Methodological quality	17/20 "Yes / Rather Yes", 3/20 "No / Rather No", 0/20 "Unclear"

Study 11/35

First Author (Year)	SR0123 Ramirez et al 2013 [43]
URL	https://link.springer.com/article/10.1007/s40258-013-0053-x
Stated Study Objectives	To perform a cost-effectiveness analysis of evaluating the risk of suffering a CHD event in Spain using Cardio inCode compared with the standard method (using Framingham or REGICOR functions alone).
Sample Characteristics	Two population-based cohorts were used in this model - REGICOR cohort (Spain, aged 53,9 years old) and Framingham cohort (USA, aged 56 years old)
Intervention	The study has one intervention arm – Cardio inCode testing that incorporates genetic risk of CHD reclassifies the CHD event risk based on REGICOR and Framingham risk equations, where patients reclassified at high risk received treatment with statins and antihypertensive drugs.
Comparator	The study has one comparator arm – standard care, where patients classified at high risk based on REGICOR or Framingham risk equations, received treatment with statins and antihypertensive drugs.
Type of study design	Model - Markov cohort ± DT on TreeAge Pro Healthcare Module 2009 1 year cycle length; no mention of half-cycle correction.
Time horizon	Lifetime
Perspective	Healthcare sector
Currency (year)	Euro (2011), discounted at 3.5% annually
Outcome measures	QALY gained, discounted at 3.5% annually
Willingness-to-pay threshold	EURO 30,000 per QALY gained
Main findings & conclusion	At a price of €400, Cardio inCode compared to standard care, the ICER was €12,969 in the REGICOR cohort and €21,385 in the Framingham cohort. The threshold price of Cardio in-Code to reach the ICER threshold generally accepted in Spain (€30,000/QALY) would range between €668 and €836. The greatest benefit occurred in the subgroup of patients with moderate-high risk (22.8% patients, ICER €1,652/QALY) in the REGICOR cohort, or with high-risk (12% patients, ICER €5,884/QALY) in the Framingham cohort.
Findings of sensitivity analysis	In deterministic analysis, the model was most sensitive to the utilities of moderate, low, and high CHD risk health states (for REGICOR cohort) and the CHD event probability (moderate risk), CHD event cost, and CHD death probability (for Framingham cohort). In probabilistic analysis (1000 replications), Cardio inCode was the most cost-effective option compared with the standard method in 82.0% simulations in the REGICOR cohort, or 65.7% simulations in the Framingham cohort.
Funding source	Grant from Ferrer for studies in connection with this publication
Competing interest	Four authors were employees of the company Ferrer Incode and two authors were employees of the company Gendiag at the time of preparation of the manuscript. Two authors received a research grant from Ferrer for studies in connection with the development of this manuscript. Two authors received an honorarium from Ferrer Internacional in connection with the development of this manuscript.
Methodological quality	16/20 “Yes / Rather Yes”, 4/20 “No / Rather No”, 0/20 “Unclear”

Study 12/35

First Author (Year)	SR0045 Oemrawsingh et al 2016 [44]
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4943245/
Stated Study Objectives	To examine the potential cost-effectiveness of the combined clinical risk score and PGXscore.
Sample Characteristics	Patients with stable coronary artery disease (CAD), aged 59.8±9.3 years old but without overt heart failure or uncontrolled hypertension in the Netherlands. The study is a sub-study of the EUROPA trial.
Intervention	The study has three interventional arms, all involving testing for three single nucleotide polymorphism (SNPs) found to be significant modifiers of perindopril treatment effect: rs275651 and rs5182 in the AT1 receptor gene and rs12050217 in the BK1 receptor gene that generated a PGXscore ranging between 0 and 6 – (i) testing only in patients with a high clinical risk score (≥10) and perindopril treatment only if PGXscore=0 to 2, (ii) testing only in patients with a medium or high clinical risk score (≥7) and perindopril treatment only if PGXscore=0 to 2, (iii) testing in all patients and perindopril treatment only if PGXscore=0 to 2.
Comparator	The study has one comparator arm – Perindopril treatment in all patients irrespective of PGXscore.
Type of study design	EE alongside RCT with simple Excel model, based on data from the RCT.
Time horizon	4.2 years
Perspective	Healthcare sector (Not stated explicitly; inferred based on list of cost stated in Page 3)
Currency (year)	Euro (cost year not stated)
Outcome measures	Life years gained.
Willingness-to-pay threshold	Not stated.
Main findings & conclusion	Strategies (iii) generated the highest number of life-years gained (0.0040), which dominated perindopril treatment in all patients which gave 0.035 life years gained at higher incremental cost ($232 vs $147).
Findings of sensitivity analysis	No sensitivity analysis reported.
Funding source	The Netherlands Heart Foundation (Grant No.: NHS2005B219).
Competing interest	Declared no competing interests. Also declared that the sponsor of the EUROPA trial, Servier, had no role in the design, conduct, analysis, or interpretation of this sub-study, nor in the preparation, review, or approval of the manuscript.
Methodological quality	8/20 “Yes / Rather Yes”, 12/20 “No / Rather No”, 0/20 “Unclear”

Study 13/35

First Author (Year)	SR9025 AlMukdad et al 2021 [45]
URL	https://www.sciencedirect.com/science/article/pii/S0167527321001261
Stated Study Objectives	To assess the utilization cost of CYP2C19 genotype-guided antiplatelet therapy, universal use of clopidogrel, and ticagrelor against their outcomes as first-line therapies in patients with ACS who underwent PCI in Qatar
Sample Characteristics	ACS patients in Qatar who underwent PCI
Intervention	The study has one intervention arm – CYP2C19 testing, followed by ticagrelor for carriers of CYP2C19*2 or *3 alleles, or clopidogrel for non-carriers.
Comparator	The study has two comparator arms – (i) universal clopidogrel 75mg oral tablet daily, (ii) universal ticagrelor 90mg oral tablet twice daily.
Type of study design	Model - Markov cohort ± DT 1 year cycle length; no mention of half-cycle correction.
Time horizon	20 years
Perspective	Hospital perspective (HMC, Hamad Medical Corporation)
Currency (year)	USD (2019/2020), discounted at 3.5% annually.
Outcome measures	QALY gained, discounted at 3.5% annually.
Willingness-to-pay threshold	USD 150,000 per QALY gained
Main findings & conclusion	Against universal clopidogrel, genotype-guided therapy was cost-effective over the one-year duration (ICER, USD 6102 /success), and dominant over the long-term. Genotype-guided therapy was dominant against universal ticagrelor over the one-year duration, and cost-effective over the long term (ICUR, USD 1383 /QALY). Universal clopidogrel was dominant over ticagrelor for the short term, and cost-effective over the long-term (ICUR, USD 10,616 /QALY).
Findings of sensitivity analysis	In deterministic and probabilistic sensitivity analyses, testing remained either dominant or cost-effective compared to no-testing across all plausible ranges.
Funding source	Qatar National Research Fund, Qatar Foundation
Competing interest	No competing interest reported.
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 14/35

First Author (Year)	SR0010 Deiman et al 2016 [46]
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5039130/
Stated Study Objectives	(1) To examine the outcome of changing from clopidogrel to prasugrel for CYP2C19 poor metabolisers; (2) To examine potential cost-effectiveness of genotype-guided post-PCI treatment.
Sample Characteristics	3260 patients (mean age 64.6 ± 10.8 years old) with ST-segment elevation myocardial infarction (STEMI) who are scheduled to receive percutaneous coronary intervention (PCI) in the Netherlands.
Intervention	The study has three interventional arms: all involved testing for CYP2C19 metaboliser status, followed by (i) prasugrel for poor metaboliser, (ii) prasugrel for intermediate or poor metaboliser, (iii) ticagrelor for intermediate or poor metaboliser.
Comparator	The study has three comparator arms, which has no testing followed by (i) universal clopidogrel, (ii) universal prasugrel, (iii) universal ticagrelor.
Type of study design	Economic evaluation alongside observational study
Time horizon	1 year
Perspective	Healthcare
Currency (year)	Euro (cost year not stated)
Outcome measures	QALY gained
Willingness-to-pay threshold	EUR 65,000 per QALY gained
Main findings & conclusion	CYP2C19-related poor metabolisers prasugrel may be more effective than clopidogrel to prevent major adverse cardiovascular events after PCI and this approach could be cost-effective.
Findings of sensitivity analysis	No sensitivity analysis reported.
Funding source	Declared no funding
Competing interest	B.A.L.M. Deiman, P.A.L. Tonino, K. Kouhestani, C.E.M. Schrover, V. Scharnhorst, L.R.C. Dekker and N.H.J. Pijls declared that they have no competing interest.
Methodological quality	11/20 “Yes / Rather Yes”, 7/20 “No / Rather No”, 2/20 “Unclear”

Study 15/35

First Author (Year)	SR6116 Fragoulakis et al 2019 [47]
URL	https://doi.org/10.1038/s41397-019-0069-1
Stated Study Objectives	To estimate the cost-effectiveness of a pharmacogenomics versus a non-pharmacogenomics-guided treatment of clopidogrel for patients diagnosed with CAD undergoing PCI.
Sample Characteristics	557 patients with coronary artery disease in Spain (≥18 years old) who underwent PCI with stent implantation, excluding those requiring oral anticoagulation, or presenting contraindication for taking acetylsalicylic acid / clopidogrel / prasugrel or displaying high risk of bleeding.
Intervention	The study has one intervention arm (named “Prospective”), where patients initially started on clopidogrel while CYP2C19 testing is undertaken, after which those found with >1 CYP2C19 alleles were switched to prasugrel.
Comparator	The study has one comparator arm (named “Retrospective”), where all patients had clopidogrel based on routine clinical practice.
Type of study design	EE alongside observational study.
Time horizon	1 year
Perspective	Healthcare sector
Currency (year)	Euro (2017)
Outcome measures	QALY gained
Willingness-to-pay threshold	Not stated
Main findings & conclusion	The analysis predicts a survival of 0.9446 QALYs in the pharmacogenomics arm and 0.9379 QALYs in the non-pharmacogenomics arm within a 1-year horizon. The cumulative costs per patient were €2971 and €3205 for the Prospective and Retrospective groups, respectively. The main cost driver of total cost in both arms was hospitalization costs. The ICER indicated that PGx was a dominant option. Our data show that pharmacogenomics-guided clopidogrel treatment strategy may represent a cost-effective choice compared with non-pharmacogenomics-guided strategy for patients undergoing PCI.
Findings of sensitivity analysis	In probabilistic analysis with 5000 replications, majority simulations fell into the South-East quadrant indicating that the Prospective group was less expensive but also more effective than the Retrospective group.
Funding source	Genomic Medicine Alliance Health Economics Working Group. The laboratory of B.R.A. is funded by UAEU grant.
Competing interest	Declared no competing interest.
Methodological quality	15/20 “Yes / Rather Yes”, 4/20 “No / Rather No”, 1/20 “Unclear”

Study 16/35

First Author (Year)	SR4350 Phelps et al 2014 [48]
URL	https://doi.org/10.1016/j.ahj.2014.02.005
Stated Study Objectives	To estimate the cost effectiveness of CAD diagnostic strategies including “no test”, a gene expression score (GES) test, MPI, and sequential strategies combining GES and MPI
Sample Characteristics	Non-diabetic patients (starting age 57 years old) presenting in primary care for the diagnosis of obstructive coronary artery disease (CAD), excluding patients with a previous history of myocardial infarction (MI) and patients with a previous history of revascularization
Intervention	The study has three intervention arms – (i) commercially available gene expression score (GES) alone where patients with score >15 would undergo invasive coronary angiography, (ii) GES where patients with score >15 would undergo myocardial perfusion imaging (MPI); those tested positive with MPI will undergo invasive coronary angiography, (iii) GES where patients with score≥28 or those with score 16-27 and tested positive with MPI would undergo invasive coronary angiography.
Comparator	The study has two comparator arms – (i) no test; (ii) MPI alone.
Type of study design	Model - Markov cohort ± DT 1 year cycle length; no mention of half-cycle correction.
Time horizon	Lifetime
Perspective	Societal
Currency (year)	USD (2012), discounted at 3% annually
Outcome measures	QALY gained, discounted at 3% annually
Willingness-to-pay threshold	USD 100,000 per QALY gained
Main findings & conclusion	In base case analysis, the 2-threshold GES strategy is the most cost-effective strategy at a threshold of $100,000 per QALY gained, with an ICER of approximately $72,000 per QALY gained relative to no testing. Myocardial perfusion imaging alone and the 1-threshold strategy are weakly dominated.
Findings of sensitivity analysis	In sensitivity analysis, ICERs fall as the probability of oCAD increases from the base case value of 15%. The ranking of ICERs among strategies is sensitive to test costs, including the time cost for testing.
Funding source	No declaration.
Competing interest	No competing interest statement
Methodological quality	15/20 “Yes / Rather Yes”, 5/20 “No / Rather No”, 0/20 “Unclear”

Study 17/35

First Author (Year)	SR0172 Crespin et al 2011 [49]
URL	https://doi.org/10.1016/j.jval.2010.11.012
Stated Study Objectives	To determine the cost-effectiveness of universal ticagrelor compared with a genotype-driven selection of antiplatelet agents.
Sample Characteristics	Patients with ACS (minimum age 66 and mean age 79 years old) and hospitalized in US
Intervention	The study has one intervention arm – CYP2C19 testing, followed by ticagrelor among carriers of CYP2C19*2 mutations or clopidogrel among non-carriers.
Comparator	The study has one comparator arm – no testing, with universal ticagrelor.
Type of study design	Model - Markov cohort ± DT on Microsoft Excel 2007 using Crystal Ball, Fusion Edition version 11.1.1.3. 1-month cycle length; no mention of half-cycle correction.
Time horizon	5 years
Perspective	Healthcare sector
Currency (year)	USD (2009), discounted at 3% annually.
Outcome measures	QALY gained, discounted at 3% annually. Life years gained.
Willingness-to-pay threshold	USD50,000 per QALY gained
Main findings & conclusion	The ICER for universal ticagrelor was $10,059 per QALY compared to genotype-driven treatment. The ICER increased for longer durations of therapy. A 15-month duration of therapy resulted in an ICER of $12,334 per QALY and at 24 months the ICER increased to $18,682 per QALY. Similar results were obtained in the analysis of life years gained, as expected given the survival benefit produced by ticagrelor. The ICER for universal ticagrelor was $7539 per life year compared to the genotype-driven treatment over the 5-year period.
Findings of sensitivity analysis	In one-way deterministic analysis, the ICER was most sensitive to the price of ticagrelor and the hazard ratio for death for ticagrelor compared with clopidogrel. The ICER remained below $50,000 per QALY until a monthly ticagrelor price of $693 or a 0.93 hazard ratio for death for ticagrelor relative to clopidogrel. In probabilistic analysis (1000 replications), universal ticagrelor was below $50,000 per QALY in 97.7% of simulations.
Funding source	National Institute on Aging and the National Institute of General Medical Sciences
Competing interest	Not reported
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 18/35

First Author (Year)	SR0155 Shiffman et al 2012 [50]
URL	https://doi.org/10.1016/j.clinthera.2012.04.004
Stated Study Objectives	To estimate the incremental cost-effectiveness of using genetic test results for 2 LPA variants to derive modified Framingham Risk Score estimates and to use these estimates to identify patients likely to benefit from aspirin use according to USPSTF guidelines for aspirin use in the primary prevention of CVD
Sample Characteristics	Patients with CHD in US (age 45 – 79 years old), whose risks are estimated using Framingham Risk Score
Intervention	The study has one intervention arm – LPA testing, followed by aspirin for carriers of LPA or no aspirin for non-carriers.
Comparator	The study has one comparator arm – no LPA testing.
Type of study design	Model – not specified
Time horizon	10 years
Perspective	Not specified
Currency (year)	USD (2009), discounted at 3.5% annually.
Outcome measures	QALY gained, discounted at 3.5% annually. CVD event averted.
Willingness-to-pay threshold	Not reported
Main findings & conclusion	The net incremental cost of LPA testing would be $2,009,953 over 10 years, or approximately $201,000 per year, resulting in an ICER of $30,846 per CVD event averted and $24,942 per QALY gained. Because the number of events prevented differed between men and women, the incremental cost per QALY would range from $13,283 in men to $58,193 in women.
Findings of sensitivity analysis	In deterministic sensitivity analyses, the cost of the test had the largest effect on the ICER. In probabilistic analyses (1000 replications), the cost of testing explained the highest percentage of the variability in the ICER.
Funding source	Berkeley HeartLab (medical device company)
Competing interest	Declared no competing interest.
Methodological quality	13/20 “Yes / Rather Yes”, 6/20 “No / Rather No”, 1/20 “Unclear”

Study 19/35

First Author (Year)	SR0138 Parthan et al 2013 [51]
URL	https://link.springer.com/article/10.1007/s40273-013-0054-5
Stated Study Objectives	To assess the cost effectiveness of testing for the KIF6 variant followed by targeted statin therapy (KIF6 Testing) versus not testing patients (No Test) and treating them with Pravastatin 40mg daily (P40) or Atorvastatin 80mg daily (A80)
Sample Characteristics	Patient in the US (mean age 58 years old), who had recently survived an ACS event
Intervention	The study has one intervention arm - Trp719Arg variant in kinesin family member 6 protein (KIF6) testing, followed by A80 among carriers of KIF6 and P40 among non-carriers.
Comparator	The study has two comparator arms – no testing, with (i) universal A80, (ii) universal P40.
Type of study design	Model - Markov cohort ± DT 1 year cycle length; no mention of half-cycle correction.
Time horizon	Lifetime
Perspective	Healthcare sector
Currency (year)	USD (2010), discounted at 3% annually.
Outcome measures	QALY gained, discounted at 3% annually
Willingness-to-pay threshold	USD100,000 per QALY gained
Main findings & conclusion	Lifetime costs were US$31,700; US$37,100 and US$41,300 for No Test P40, KIF6 Testing and No Test A80 strategies, respectively. The No Test A80 strategy was associated with more QALYs (9.71) than theKIF6 Testing (9.69) and No Test P40 (9.57) strategies. No Test A80 had an incremental cost-effectiveness ratio (ICER) of US$232,100 per QALY gained compared with KIF6 Testing. KIF6 Testing had an ICER of US$45,300 per QALY compared with No Test P40.
Findings of sensitivity analysis	In deterministic analyses, KIF6 testing vs No Test A80: findings are most sensitive to the probability of cardiovascular events in KIF6 noncarriers treated with A80, the proportion of untested patients who are adherent, the proportion of tested KIF6 carriers who are adherent, the probability of cardiovascular events in KIF6 noncarriers treated with P40, and the utility value for patients with stable CHD. KIF6 testing vs No Test P40: findings are most sensitive to the probability of cardiovascular events in carriers treated with P40, the utility value for patients with stable CHD, the probability of events in carriers treated with A80, and patient starting age in the model. In probabilistic analyses, KIF6 Testing is expected to be the most cost-effective strategy between thresholds of approximately US$46,000 and US$230,000 per QALY, followed by the No Test A80 strategy.
Funding source	Celera Corporations (a medical device company)
Competing interest	Three authors are employees of OptumInsight, Cambridge, MA, and were paid consultants to Celera and one author was a paid consultant to OptumInsight related with the development of this manuscript. Three authors are full-time employees of Celera, a wholly owned subsidiary of Quest Diagnostics. Two authors are inventors on patents related to the KIF6 719Arg variants.
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 20/35

First Author (Year)	SR3277 Wang et al 2018 [52]
URL	https://www.nature.com/articles/tpj201694
Stated Study Objectives	To evaluate the cost-effectiveness, from the Hong Kong health-care provider's perspective, of CYP2C19*2 genotype-guided selection of antiplatelet therapy compared with the universal use of clopidogrel or ticagrelor among ACS patients who undergo percutaneous coronary intervention (PCI)
Sample Characteristics	Hypothetical patients in Hong Kong (60 years old) with acute coronary syndrome who underwent PCI
Intervention	The study has one intervention arm – CYP2C19 testing, followed by ticagrelor for carriers of CYP2C19*2 alleles, or clopidogrel for non-carriers.
Comparator	The study has two comparator arms – without testing, (i) universal clopidogrel, (ii) universal ticagrelor
Type of study design	Model - Markov cohort ± DT on TreeAge and Microsoft Excel 2016. 1 year cycle length; no mention of half-cycle correction
Time horizon	25 years old
Perspective	Healthcare sector
Currency (year)	USD (2016), discounted at 3% annually.
Outcome measures	QALY gained, discounted at 3% annually.
Willingness-to-pay threshold	USD 42,423 per QALY gained (1 x GDP)
Main findings & conclusion	In base–case analyses, universal ticagrelor was cost-effective compared with universal clopidogrel but was dominated by genotype-guided treatment. Genotype-guided treatment was cost-effective compared with universal clopidogrel use (ICER of USD2560/QALY).
Findings of sensitivity analysis	In deterministic analysis, with the cost of genotype testing up to USD400, CYP2C19*2 genotype-guided antiplatelet treatment remained a cost-effective strategy compared with either universal use of generic clopidogrel or ticagrelor in post-PCI ACS patients in Hong Kong. The ICER for genotype testing was most sensitive to the hazard ratio of stroke between ticagrelor vs clopidogrel. In probabilistic analysis, genotype-guided strategy has 98.5% probability of being cost-effective compared with universal clopidogrel and ticagrelor.
Funding source	Hong Kong Research Grant Council General Research Fund
Competing interest	Declared no conflict of interest.
Methodological quality	17/20 "Yes / Rather Yes", 3/20 "No / Rather No", 0/20 "Unclear"

Study 21/35

First Author (Year)	SR0012 Patel et al 2014 [53]
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4161409/
Stated Study Objectives	To evaluate the cost-utility of genotype-guided treatment, compared with prasugrel or generic clopidogrel treatment without genotyping, from the US healthcare provider's perspective.
Sample Characteristics	Patients (mean age 61 years old) with moderate-to-high risk acute coronary syndrome and planned PCI in the US.
Intervention	The study has one interventional arm – genotype-guided therapy testing for CYP2C19, followed by prasugrel for those with reduced-function polymorphism and clopidogrel for those without.
Comparator	The study has two comparator arms – universal prasugrel (with aspirin) and universal clopidogrel (with aspirin).
Type of study design	Model - Decision Tree (DT) on TreeAge Pro 2014
Time horizon	15 months
Perspective	Healthcare sector
Currency (year)	USD (2011), discounted at 5% annually
Outcome measures	QALY gained, discounted at 5% annually
Willingness-to-pay threshold	USD 100,000 per QALY gained
Main findings & conclusion	Clopidogrel cost USD19,147 and provided 10.03 QALYs versus prasugrel (USD21,425, 10.04 QALYs) and genotype-guided therapy (USD19,231, 10.05 QALYs). The ICUR of genotype-guided therapy compared with clopidogrel was USD4,200. Genotype-guided therapy provided more QALYs at lower costs compared with prasugrel.
Findings of sensitivity analysis	Results were sensitive to the cost of clopidogrel and relative risk of myocardial infarction and stroke between CYP2C19 variant vs. non-variant. Net monetary benefit curves showed that genotype-guided therapy had at least 70% likelihood (from 10,000 replications in probabilistic analysis) of being the most cost-effective alternative at a willingness-to-pay of USD100,000/QALY. In comparison with clopidogrel, prasugrel therapy was more cost-effective with <21% certainty at willingness-to-pay of >USD170,000/QALY
Funding source	Declared no funding.
Competing interest	The study abstract was presented as a poster at the American College of Clinical Pharmacy Annual Meeting, October 21-24, 2012, Hollywood, Florida, USA.
Methodological quality	18/20 "Yes / Rather Yes", 2/20 "No / Rather No", 0/20 "Unclear"

Study 22/35

First Author (Year)	SR6008 An et al 2018 [54]
URL	https://www.proquest.com/openview/ce39ed20414b8c90a65d2c1fadaadbde/1.pdf?pq-origsite=gscholar&cbl=3912278
Stated Study Objectives	To evaluate the cost-effectiveness of CYP2C19 gene testing to guide antiplatelet therapy in patients with acute coronary syndrome in China
Sample Characteristics	Patient with acute coronary syndrome underwent bypass grafting or PCI in China.
Intervention	The study has one intervention – CYP2C19 testing, followed by ticagrelor for carriers of LOF alleles, or clopidogrel for non-carriers.
Comparator	The study has two comparators – no testing, with (i) universal clopidogrel, or (ii) universal ticagrelor.
Type of study design	Model - Markov cohort ± DT on TreeAge Pro 2012 1 year cycle length; no mention of half-cycle correction.
Time horizon	30 years
Perspective	Healthcare sector
Currency (year)	RMB (cost year not stated), discounted at 5% annually
Outcome measures	QALY gained, discounted at 5% annually
Willingness-to-pay threshold	RMB 149,976 per QALY gained (3 x GDP)
Main findings & conclusion	Base-case results showed that genotype-guided ticagrelor and universal ticagrelor were dominant compared with universal clopidogrel (ICER below WTP threshold). Universal ticagrelor was cost-effective when compared with universal clopidogrel.
Findings of sensitivity analysis	In one-way deterministic analyses, that findings were most sensitive to the cost of no-event state for ticagrelor, the cost of no-event state for clopidogrel, and death rate for ticagrelor. In probabilistic analyses (1000 simulations), genotype-guided ticagrelor was cost-effective in 73.9% simulations compared to universal ticagrelor, or 87.9% compared to universal clopidogrel.
Funding source	National Social Science Foundation of China
Competing interest	No competing interest statements.
Methodological quality	15/20 “Yes / Rather Yes”, 5/20 “No / Rather No”, 0/20 “Unclear”

Study 23/35

First Author (Year)	SR0397 Borse et al 2017 [55]
URL	https://doi.org/10.2217/pgs-2017-0075
Stated Study Objectives	To determine whether using a CYP2C19 genotype-guided strategy to optimize P2Y12 inhibitor selection in CAD patients is cost effective over the initial 30 days and 1 year following PCI.
Sample Characteristics	CAD patients in US undergoing PCI and treated with aspirin and a P2Y12 inhibitor for at least 12 months
Intervention	The study has one intervention arm – CYP2C19 testing, followed by prasugrel among carriers of 1 or 2 LOF alleles, or clopidogrel among non-carriers.
Comparator	The study has two comparator arms – no testing, (i) universal clopidogrel, (ii) universal prasugrel.
Type of study design	Model - Decision Tree (DT) on TreeAge Pro 2016
Time horizon	30 days and 12 months
Perspective	Healthcare sector
Currency (year)	USD (2014)
Outcome measures	Total adverse events – sum of major adverse cardiovascular events (MACE, composite of cardiovascular death, myocardial infarction, or ischemic stroke events), stent thrombosis, and major bleeding.
Willingness-to-pay threshold	USD 50,000 per major event avoided
Main findings & conclusion	In base-case analyses, at 30 days genotype-guided treatment had an incremental cost per major cardiovascular or bleeding event avoided of US$8525 vs universal clopidogrel and US$42,198 vs prasugrel. At 1 year, genotype-guided treatment dominates universal prasugrel, and had an incremental cost per major cardiovascular or bleeding event avoided of US$50,308 vs universal clopidogrel.
Findings of sensitivity analysis	In probabilistic analysis (10,000 replications), genotype-guided treatment was cost effective over 30 days in 62% simulation and over 1 year in 70% of simulations.
Funding source	No declaration.
Competing interest	Declared no competing interest.
Methodological quality	17/20 “Yes / Rather Yes”, 2/20 “No / Rather No”, 1/20 “Unclear”

Study 24/35

First Author (Year)	SR0108 Kazi et al 2014 [56]
URL	https://doi.org/10.7326/M13-1999
Stated Study Objectives	To determine the most cost-effective strategy for dual antiplatelet therapy after percutaneous coronary intervention for ACS (among drug-only strategies and genotype-guided strategies)
Sample Characteristics	Patients with ACS aged 65 years old, who received PCI with 1 or more drug-eluting stent in US
Intervention	The study has two intervention arms – (i) CYP2C19 testing, followed by prasugrel among carriers of 1 or 2 loss-of-function alleles (LOF), or clopidogrel among carriers of 2 gain-of-function (GOF) alleles, 1 GOF 1 wild-type or 2 wild-type alleles, (ii) CYP2C19 testing, followed by ticagrelor among carriers of 1 or 2 LOF, or clopidogrel among carriers of 2 GOF, 1 GOF 1 wild-type or 2 wild-type alleles.
Comparator	The study has three intervention arms – (i) generic clopidogrel, (ii) universal prasugrel, (iii) universal ticagrelor.
Type of study design	Model - Markov cohort ± DT on TreeAge Pro 2009; Microsoft Excel 2007 1-month cycle length; no mention of half-cycle correction
Time horizon	Lifetime
Perspective	Societal
Currency (year)	USD (2011), discounted at 3% annually
Outcome measures	QALY gained, discounted at 3% annually
Willingness-to-pay threshold	USD 50,000 per QALY gained
Main findings & conclusion	The clopidogrel strategy produced $179 301 in costs and 9.428 QALYs. Genotyping with prasugrel was superior to prasugrel alone, with an ICER of $35 800 per QALY relative to clopidogrel. Genotyping with ticagrelor was more effective than genotyping with prasugrel ($30 200 per QALY relative to clopidogrel). Ticagrelor was the most effective strategy ($52 600 per QALY relative to genotyping with ticagrelor). Assuming stronger associations between genotype and thrombotic outcomes (high-discrimination scenario), ticagrelor was substantially less cost-effective ($104 800 per QALY). Genotyping with prasugrel was the preferred therapy among patients who could not tolerate ticagrelor.
Findings of sensitivity analysis	In probabilistic analysis, in the low-discrimination scenario, genotyping with ticagrelor was the preferred strategy in 39% of the simulations and ticagrelor in 42% of the simulations. In the high-discrimination scenario, the preferred strategy was genotyping with ticagrelor in 63% of the simulations, ticagrelor in 19%, and genotyping with prasugrel in 13%. Ticagrelor was the preferred strategy in more than 50% of simulations at thresholds greater than $54 500 per QALY in the low-discrimination scenario and $98 000 per QALY in the high-discrimination scenario.
Funding source	American Heart Association, U.S. Department of Veterans Affairs, Stanford University, and University of California San Francisco.
Competing interest	Declared no competing interest.
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 25/35

First Author (Year)	SR8309 Kim et al 2019 [57]
URL	https://doi.org/10.1007/s10557-019-06896-8
Stated Study Objectives	To evaluate the cost-effectiveness of several strategies to personalize P2Y12 inhibitor selection in patients with ACS to identify a preferred strategy for personalizing P2Y12 inhibitor therapy.
Sample Characteristics	Patients at 62 years old with planned PCI performed in US
Intervention	The study has three intervention arms – (i) genotype + conservative ticagrelor i.e., CYP2C19 testing followed by ticagrelor for low metabolisers and clopidogrel for all others, (ii) genotype + liberal ticagrelor, i.e., CYP2C19 testing followed by ticagrelor for intermediate or low metabolisers and clopidogrel for all others, (iii) genotype + phenotype, i.e., CYP2C19 testing followed by ticagrelor for low metabolisers or intermediate metabolisers who are non-respondents (based on platelet reactivity testing, PRT).
Comparator	The study has three comparator arms – (i) universal clopidogrel, (ii) clopidogrel + phenotype, where patients started with clopidogrel and non-respondents (based on PRT) would transition to ticagrelor, (iii) universal ticagrelor.
Type of study design	Model - Markov cohort ± DT on TreeAge Pro 2013 1 year cycle length; no mention of half-cycle correction
Time horizon	Lifetime (exact time horizon not stated)
Perspective	Healthcare sector, includes formal health care sector costs paid by third-party payers
Currency (year)	USD (2017), discounted at 3% annually
Outcome measures	QALY gained, discounted at 3% annually
Willingness-to-pay threshold	USD 100,000 per QALY gained
Main findings & conclusion	In base case analysis, ICER for the clopidogrel + phenotype, genotype + liberal ticagrelor, and universal ticagrelor strategies were $12,119/QALY, 29,412/QALY, and $142,456/QALY, respectively. Genotype + conservative ticagrelor and genotype + phenotype were not cost-effective due to second-order dominance.
Findings of sensitivity analysis	In one-way sensitivity analyses, the alternative P2Y12 inhibitor selection strategies were sensitive to the risk ratios of the ischemic and bleeding events in the model. In probabilistic analysis (10,000 replications), the probability of being cost effective for the genotype + liberal ticagrelor was 63%, universal ticagrelor 33%, clopidogrel + phenotype 3%, and universal clopidogrel 1%.
Funding source	No declaration.
Competing interest	Dr. DiDomenico (1) received an honorarium from Amgen Inc. for preparation of a heart failure drug monograph (2) an Otsuka America Pharmaceuticals, Inc. heart failure advisory board member. Dr. Touchette (1) received an unrestricted grant from Cardinal Health, Sunovion Pharmaceuticals Inc; (2) a consultant to and Director of the American College of Clinical Pharmacy Practice Based Research Network on a study funded by Pfizer Inc.
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 26/35

First Author (Year)	SR2331 Okere et al 2018 [58]
URL	https://www.jmcp.org/doi/10.18553/jmcp.2018.24.2.142
Stated Study Objectives	To evaluate the cost-effectiveness of a pharmacist integration of medication therapy management (MTM) and point-of-care genotype-guided selection of antiplatelet therapy (POCP) compared with universal use of ticagrelor or clopidogrel combined with MTM.
Sample Characteristics	Patients with ACS in US (mean age 65 years old), who underwent PCI
Intervention	The study has two intervention arms – (i) point-of-care phenotypic and genetic testing, followed by ticagrelor for carriers of LOF alleles, or clopidogrel for non-carriers (POCP) (ii) POCP with face-to-face comprehensive medication therapy management (MTM) to improve healthcare utilisation (POCP-MTM).
Comparator	The study has two comparator arms – no testing, (i) MTM-clopidogrel, (ii) MTM-ticagrelor.
Type of study design	Model - Markov cohort ± DT 1 year cycle length with half cycle correction
Time horizon	Lifetime
Perspective	Healthcare sector
Currency (year)	USD (2016), discounted at 3.5% annually.
Outcome measures	QALY gained, discounted at 3.5% annually.
Willingness-to-pay threshold	USD50,000, USD100,000, USD150,000 or USD200,000 per QALY gained
Main findings & conclusion	PCOP (with dual antiplatelet therapy) resulted in 5.29 QALYs, at a cost of $50,207. MTM-clopidogrel resulted in 5.34 QALYs, at a cost of $50,011. POCP-MTM resulted in 5.36 QALYs, at a cost of $50,270. Finally, MTM-ticagrelor resulted in 5.42 QALYs, at a cost of $53,346. MTM-ticagrelor was found to be cost-effective compared with MTM-clopidogrel or MTM-POCP, irrespective of the willingness to pay.
Findings of sensitivity analysis	In probabilistic analyses (10,000 replications), MTM-ticagrelor has 93% probability of being cost-effective at a WTP of $200,000 per QALY and a 99% probability of being cost-effective at a WTP of $300,000 per QALY.
Funding source	No declaration.
Competing interest	Declared no competing interest.
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 27/35

First Author (Year)	SR0148 Panattoni et al 2012 [59]
URL	https://link.springer.com/article/10.2165/11595080-000000000-00000#author-information
Stated Study Objectives	To evaluate the cost effectiveness of generic clopidogrel in patients with ACS, compared with the use of prasugrel in all patients, and also of a genetically guided strategy, with*2 allele carriers receiving prasugrel and non-carriers receiving clopidogrel.
Sample Characteristics	Patients (between 45 – 80 years old) hospitalised due to acute coronary syndrome (ACS) in New Zealand
Intervention	The study has one intervention arm – CYP2C19 testing, followed by prasugrel among carriers of CYP2C19*2 alleles or clopidogrel among non-carriers.
Comparator	The study has two comparator arms – no testing, with (i) universal clopidogrel, (ii) universal prasugrel.
Type of study design	Model - Decision Tree (DT)
Time horizon	15 months and lifetime
Perspective	Healthcare sector
Currency (year)	NZD (2009), discounted at 3% annually.
Outcome measures	
Willingness-to-pay threshold	NZD 50,000 per QALY gained
Main findings & conclusion	A genetic test to guide the selected use of prasugrel was cost effective ($NZ8702/QALY versus $NZ24 617/QALY) for hospital and clinical trial incidence, respectively. Based on the hospital rates, the genetically guided strategy was especially cost effective for Maoris ($NZ7312/QALY) and Pacific Islanders ($NZ7041/QALY).
Findings of sensitivity analysis	Base-case findings were robust to the sensitivity analysis, except the genetically guided strategy under the 15-month clinical trial event rate scenario ($NZ168 748/QALY) did not remain cost effective under a $NZ50000 threshold. In probabilistic analyses, the genetically guided strategy reaches a 90% probability of being cost effective at a threshold less than $NZ10000 for the New Zealand hospital adverse rates, but not until over $NZ50 000 using the clinical trials rates.
Funding source	Auckland District Health Board A-Plus Trust, an organization of the New Zealand national public health system
Competing interest	Dr Patrick Gladding is the founder of and shareholder in the non-profit translational research company, Theranostics Laboratory (NZ) Ltd. Dr Patrick Gladding and Dr Mark Webster have an issued USPTO (US Patent and Trademark Office) patent 12/950,617 on treatment strategies related to clopidogrel pharmacogenetics. Dr Laura Panattoni, Dr Paul Brown and Braden Te Ao have no conflicts to disclose.
Methodological quality	18/20 “Yes / Rather Yes”, 2/20 “No / Rather No”, 0/20 “Unclear”

Study 28/35

First Author (Year)	SR0120 Sorich et al 2013 [60]
URL	https://doi.org/10.2217/pgs.13.164
Stated Study Objectives	To assess the cost–effectiveness of using CYP2C19 genotype to guide clopidogrel and ticagrelor therapy for the individuals who are most likely to benefit from CYP2C19 genotyping
Sample Characteristics	Patients with CAD in Australia & New Zealand (mean age 62 years old), likely to undergo coronary stenting.
Intervention	The study has one intervention arm – CYP2C19 testing followed by ticagrelor for carriers of LOF alleles or clopidogrel for carriers of non-LOF alleles.
Comparator	The study has two intervention arms – (i) universal clopidogrel, (ii) universal ticagrelor.
Type of study design	Model - Markov cohort ± DT on TreeAge Pro 2009; Microsoft Excel 2010. 1-year cycle length; no mention of half-cycle correction.
Time horizon	Lifetime (40 years)
Perspective	Healthcare sector
Currency (year)	AUD (2011), discounted at 5% annually.
Outcome measures	QALY gained, discounted at 5% annually.
Willingness-to-pay threshold	AUD 30,000 - 50,000 per QALY gained
Main findings & conclusion	In base case analyses, the use of the genotyping strategy, compared to universal clopidogrel resulted in a gain of 0.069 QALYs (i.e., 25 additional quality-adjusted life days) at the additional cost of AUS$435 per individual (ICER AUS$6000 per QALY gained). Meanwhile, use of universal ticagrelor, compared to genotyping strategy resulted in a gain of 0.033 QALYs (i.e., 12 additional quality-adjusted life days) at the additional cost of AUS$755 per individual (ICER AUS$23,000 per QALY gained).
Findings of sensitivity analysis	In deterministic analysis, the parameters with the greatest effect on cost–effectiveness were the estimates of comparative treatment effect for the CYP2C19 subgroups. In probabilistic analysis, genotype strategy was the most cost-effective strategy if society was willing to pay AUS$7000–21,000 per additional QALY, and the universal ticagrelor strategy was the most cost-effective option at a monetary value above AUS$21,000 per additional QALY.
Funding source	National Heart Foundation of Australia
Competing interest	Declared no competing interest.
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 29/35

First Author (Year)	SR0143 Lala et al 2013 [61]
URL	https://doi.org/10.1111/jth.12059
Stated Study Objectives	To evaluate the cost-effectiveness of a CYP2C19*2 genotype-guided strategy of antiplatelet therapy in ACS patients undergoing PCI, compared with two 'no testing' strategies (empiric clopidogrel or prasugrel).
Sample Characteristics	Patients with ACS in US (mean age 60 years old), undergoing PCI
Intervention	The study has one intervention arm – CYP2C19 testing, followed by prasugrel for carriers of LOF alleles or clopidogrel for non-carriers)
Comparator	The study has two comparator arms – no testing, with (i) universal clopidogrel, (ii) universal prasugrel.
Type of study design	Model - Markov cohort ± DT on TreeAge Pro 2010 30-day cycle length; no mention of half-cycle correction.
Time horizon	15 months & 10 years
Perspective	Healthcare sector
Currency (year)	USD (2010), discounted at 3% annually.
Outcome measures	QALY gained, discounted at 3% annually.
Willingness-to-pay threshold	USD 100,000 per QALY gained
Main findings & conclusion	In base case analyses, the genetic testing-guided strategy yielded the most QALYs and was the least costly. Over 15 months, total costs were $18 lower with a gain of 0.004 QALY in the genotype-guided strategy compared with empiric clopidogrel, and $899 lower with a gain of 0.0005 QALY compared with empiric prasugrel.
Findings of sensitivity analysis	In deterministic analyses, the relative risk of thrombotic events in carriers compared with wild-type individuals treated with clopidogrel was the most influential. In probabilistic analysis (10,000 replications), genetic testing to determine optimal antiplatelet strategy was cost-effective in 75% simulations at WTP threshold of $50000 and in 78% of the simulations at WTP threshold of $100000 per QALY.
Funding source	J. S. Berger was partially funded by an American Heart Association Fellow to Faculty Award (0775074N) and a Doris Duke Clinical Scientist Development Award (2010055)
Competing interest	Declared no competing interest.
Methodological quality	18/20 “Yes / Rather Yes”, 2/20 “No / Rather No”, 0/20 “Unclear”

Study 30/35

First Author (Year)	SR0156 Reese et al 2012 [62]
URL	https://doi.org/10.1002/j.1875-9114.2012.01048
Stated Study Objectives	To evaluate the cost-effectiveness of genotype-guided antiplatelet therapy compared with either clopidogrel or prasugrel for all patients irrespective of genotype.
Sample Characteristics	Patients with acute coronary syndrome in US scheduled for PCI
Intervention	The study has one intervention arm – CYP2C19 testing, followed by prasugrel among intermediate or poor metabolisers (at least one copy of CYP2C19 LOF alleles), or clopidogrel among ultrarapid or extensive metabolisers (two copies of fully-functional CYP2C19 allleles).
Comparator	The study has two comparator arms – no testing, with (i) universal clopidogrel, (ii) universal prasugrel.
Type of study design	Model - Decision Tree (DT) on TreeAge Pro 2009
Time horizon	12 months
Perspective	Private payer
Currency (year)	USD (2011), discounted at 5% annually.
Outcome measures	
Willingness-to-pay threshold	Not reported
Main findings & conclusion	Genotype-guided antiplatelet therapy was dominant, or more effective and less costly, when compared with the selection of clopidogrel (ICER $6760 [95% confidence interval (CI) $6720 to $6790]) or prasugrel (ICER $11,710 [95% CI $11,480 to $11,950]) for all patients without regard to genotype. Genotype-guided therapy that included generic clopidogrel was dominant to prasugrel for all patients (ICER $27,160 [95% CI $27,890 to $26,420]). Cost savings were not evident when genotype-guided therapy that included generic clopidogrel was compared with generic clopidogrel for all patients (ICER $2300 [95% CI $2290 to $2320]).
Findings of sensitivity analysis	In probabilistic analysis, if a private payer were willing to pay $9670/event avoided, the payer could be 95% certain to avoid one event when choosing between genotype-guided therapy and branded clopidogrel. However, when choosing between genotype-guided therapy and prasugrel, the payer could be 95% certain to avoid an event if willingness to pay is established at $225,500/event avoided.
Funding source	No declaration.
Competing interest	Dr. Mullins receives grant funding from GlaxoSmithKline, Novartis, Pfizer, and sanofi-aventis and consulting income from Amgen, Bayer, Bristol-Myers Squibb, Cubist, Eisai, Genentech, Novartis, Pfizer, and sanofi-aventis. Dr. Onukwugha receives grant funding from Bayer, Novartis and sanofi-aventis. Dr. Beitelshees is supported by a National Institutes of Health grant.
Methodological quality	15/20 “Yes / Rather Yes”, 5/20 “No / Rather No”, 0/20 “Unclear”

Study 31/35

First Author (Year)	SR0032 Jiang et al 2017 [66]
URL	https://link.springer.com/article/10.1007/s10557-016-6705-y
Stated Study Objectives	To examine the cost-effectiveness of CYP2C19 loss-of-function and gain-of-function allele guided (LOF/GOF-guided) antiplatelet therapy in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).
Sample Characteristics	60-year-old patients with ACS undergoing PCI for ischemic heart disease in US.
Intervention	The study has one intervention arm – CYP2C19 test, followed by clopidogrel for carriers of wild-type alleles (CYP2C19 *1) or alternative antiplatelet (prasugrel 10mg daily or ticagrelor 90mg twice daily) for carriers of loss-of-function (CYP2C19 *2, *3, *4, *5, *6, *7, and *8 variants) or gain-of-function (CYP2C19 *17 variants) alleles.
Comparator	The study has two comparator arms – no testing, with (i) clopidogrel 75mg daily, or (ii) alternative antiplatelet (prasugrel 10mg daily or ticagrelor 90mg twice daily).
Type of study design	Model - Markov cohort ± DT on Microsoft Excel 2013 1 year cycle length; no mention of half cycle correction
Time horizon	30 years
Perspective	US healthcare provider
Currency (year)	USD (2016), discounted at 3% annually
Outcome measures	QALY gained, discounted at 3% annually Event rates of nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, stent thrombosis, major bleeding.
Willingness-to-pay threshold	USD 50,000 per QALY gained
Main findings & conclusion	Base-case analysis found nonfatal myocardial infarction (5.62%) and stent thrombosis (1.2%) to be the lowest in universal alternative P2Y12 inhibitor arm, whereas nonfatal stroke (0.72%), cardiovascular death (2.42%), and major bleeding (2.73%) were lowest in LOF/GOF-guided group. LOF/GOF-guided arm gained the highest QALYs (7.5301 QALYs) at lowest life-long cost (USD 76,450). Using both CYP2C19 GOF and LOF alleles to select antiplatelet therapy appears to be the preferred antiplatelet strategy over universal clopidogrel and universal alternative P2Y12 inhibitor therapy for ACS patients with PCI.
Findings of sensitivity analysis	One-way sensitivity analysis showed base-case results were subject to the hazard ratio of cardiovascular death in carriers versus noncarriers of LOF allele and hazard ratio of cardiovascular death in non-carriers of LOF allele versus general patients. In probabilistic sensitivity analysis of 10,000 Monte Carlo simulations, at WTP of USD 50,000 per QALY gained, LOF/GOF-guided therapy was the preferred strategy in 99.07% simulations, over universal alternative P2Y12 inhibitor in 0.04% and universal clopidogrel in 0.89%.
Funding source	Declared no funding.
Competing interest	Declared no conflicts of interest.
Methodological quality	17/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 0/20 “Unclear”

Study 32/35

First Author (Year)	SR0041 Jiang et al 2016 [67]
URL	https://www.futuremedicine.com/doi/10.2217/pgs-2016-0008
Stated Study Objectives	To compare the clinical and economic outcomes of pharmacogenetic-guided (PG-guided) and platelet reactivity testing-guided antiplatelet therapy for patients with acute coronary syndrome undergoing percutaneous coronary intervention.
Sample Characteristics	A hypothetical cohort of 60-year-old ACS patients undergoing PCI in US
Intervention	The study has one intervention arm – CYP2C19 testing, followed by clopidogrel 75mg daily for carriers of wild-type alleles, or alternative P2Y12 inhibitors (prasugrel 10mg daily or ticagrelor 90mg twice daily) for carriers of LOF alleles.
Comparator	The study has three comparator arms – (i) universal clopidogrel 75mg daily, (ii) universal alternative P2Y12 inhibitors, (iii) platelet reactivity testing, where patients would initiate with clopidogrel loading dose, followed by an alternative P2Y12 inhibitors for low responders, or clopidogrel for normal responders.
Type of study design	Model - Markov cohort ± DT on TreeAge Pro 2014 and Microsoft Excel 2013. 1 year cycle length; no mention of half cycle correction
Time horizon	30 years
Perspective	US healthcare provider
Currency (year)	USD (2016), discounted at 3% annually
Outcome measures	QALY gained, discounted at 3% annually
Willingness-to-pay threshold	USD 50,000 per QALY gained
Main findings & conclusion	PG-guided therapy was the preferred option with lowest cost (US$75,208) and highest quality-adjusted life years gained (7.6249 quality-adjusted life years), compared to the other three strategies. PRT-guided therapy also dominated (less costly by US$421 and more effective by 0.0258 QALYs) the universal clopidogrel arm and extendedly dominated universal alternative agents (more costly and more effective, by ICER below threshold).
Findings of sensitivity analysis	PG-guided therapy was the preferred strategy throughout variation of all model inputs and no threshold value was identified. The most influential parameters were the transition probabilities from IHD to death and post-MI state to death, followed by cost of PCI and the utility value of IHD. In probabilistic analysis, of 10,000 simulations, PG-guided therapy gained higher QALYs with cost saving in 83.22% of time.
Funding source	No declaration.
Competing interest	Declared no competing interest.
Methodological quality	16/20 “Yes / Rather Yes”, 4/20 “No / Rather No”, 0/20 “Unclear”

Study 33/35

First Author (Year)	SR8093 Fu et al 2020 [68]
URL	https://doi.org/10.2217/pgs-2019-0050
Stated Study Objectives	To evaluate the cost–effectiveness ofCYP2C19 loss-of-function(LOF) allele-guided antiplatelet therapy compared with the universal use of clopidogrel or ticagrelor among Chinese patients with acute coronary syndrome undergoing PCI.
Sample Characteristics	ACS patients at 60 years old who underwent PCI in China
Intervention	The study has one intervention arm – CYP2C19 testing followed by ticagrelor among carriers of LOF alleles or clopidogrel among carriers of non-LOF alleles.
Comparator	The study has two comparator arms – (i) universal clopidogrel, (ii) universal ticagrelor.
Type of study design	Model - Markov cohort ± DT on TreeAge pro 2017 and Microsoft Excel 2016. 1 year cycle length; no mention of half-cycle correction
Time horizon	25 years
Perspective	Not stated
Currency (year)	RMB 2018, discounted at 5% annually
Outcome measures	QALY gained, discounted at 5% annually
Willingness-to-pay threshold	RMB 53,945 per QALY gained (1 x GDP)
Main findings & conclusion	Base-case analysis showed ‘universal ticagrelor use’ was cost–effective for an ICER of 33,875 yuan per QALY gained compared with ‘universal clopidogrel use’ of which gained a 1.6932 QALYs at lowest life-long cost of 2450 yuan. CYP2C19 LOF-guided therapy had an effectiveness of 1.6975 QALYs at a cost of 2812 yuan, for an ICER of 84,118 yuan per QALY gained relative to ‘universal clopidogrel use’
Findings of sensitivity analysis	Sensitivity analysis demonstrated that base-case results were significantly affected by five factors: the risk ratio of ‘non-fatal myocardial infarction’, ‘non-fatal stroke’ and ‘cardiovascular death’ in ticagrelor versus clopidogrel and the annual costs of clopidogrel and ticagrelor. According to probabilistic analyses, when willing to pay is about 32,000 yuan, patients willing to receive clopidogrel or ticagrelor are approximately equal.
Funding source	Beijing Natural Science Foundation to Nie Xiaoyan
Competing interest	Declared no competing interest.
Methodological quality	16/20 “Yes / Rather Yes”, 3/20 “No / Rather No”, 1/20 “Unclear”

Study 34/35

First Author (Year)	SR9140 Claassens et al 2022 [69]
URL	https://doi.org/10.1007/s40256-021-00496-4
Stated Study Objectives	To assess the cost efectiveness of the genotypeguided strategy compared with a standard treatment strategy with ticagrelor or prasugrel within the context of the Dutch healthcare system.
Sample Characteristics	Patients in the Netherlands (61 ± 11.1 years old, 25% female) and 10% had prior history of coronary artery disease / STEMI undergoing PCI.
Intervention	The study has one intervention arm – CYP2C19 testing, followed by ticagrelor or prasugrel among carriers of CYP2C19*2 or *3 LOF alleles, or clopidogrel among non-carriers.
Comparator	The study has one intervention arm – no testing, with standard treatment of ticagrelor 90 mg twice daily or prasugrel 5 or 10 mg once daily.
Type of study design	Model - Markov cohort ± DT on R and Microsoft Excel 1 year cycle length; no mention of half-cycle correction.
Time horizon	1, 5, 10 and 25 years (lifetime) until 100 years old
Perspective	Healthcare sector
Currency (year)	EUR (2020), discounted at 4% annually.
Outcome measures	QALY gained, discounted at 1.5% annually.
Willingness-to-pay threshold	EUR 20,000 per QALY gained
Main findings & conclusion	In base-case analysis, the genotype-guided strategy is dominant against standard treatment without genotyping, resulting in 8.98 QALYs gained and €725,550.69 in cost savings.
Findings of sensitivity analysis	In deterministic sensitivity analyses, the model is most sensitive to “hazard ratio” (not specified), but genotype-guided strategy remains dominant. In probabilistic sensitivity analysis, genotype-guided strategy remained cost saving in “almost” all iterations.
Funding source	ZonMw, a Dutch government agency
Competing interest	One author received grants from the University College London Hospitals National Institute for Health Research Biomedical Research Centre. One author received institutional grants from Medtronic, AstraZeneca, and Sanofi and personal fees from AstraZeneca and Amgen. One author received personal fees from Boston Scientifc, Abbott Vascular, and GE. One author received institutional grants from AstraZeneca and ZonMw and personal fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, the Medicines Company, Accumetrics, Boehringer-Ingelheim, Bayer, BMS, Pfzer, and Ferrer. One author received institutional grants from AstraZeneca, GSK, Pfzer, and Amgen and personal fees from AstraZeneca, Daiichi Sankyo, Boehringer-Ingelheim, Bayer, BMS, Pfzer, GSK, and Roche. Other authors declared no competing interest.
Methodological quality	18/20 “Yes / Rather Yes”, 2/20 “No / Rather No”, 0/20 “Unclear”

Study 35/35

First Author (Year)	SR9182 Dong et al 2022 [70]
URL	https://doi.org/10.1093/ehjqcco/qcac031
Stated Study Objectives	To evaluate the 12-month cost-effectiveness of P2Y12 inhibitor escalation and deescalation from the perspective of the Veterans Health Administration (VHA) of the US Department of Veterans Affairs
Sample Characteristics	Veteran patients in US with ACS receiving PCI
Intervention	The study has one intervention arm – CYP2C19 testing, where patients originally prescribed ticagrelor or prasugrel would be de-escalated to clopidogrel if CYP2C19 was functional, whereas patients originally prescribed clopidogrel would be escalated to prasugrel or ticagrelor if CYP2C19 LOF status was present.
Comparator	The study has one comparator arm – no testing, where patients remain in their original prescription.
Type of study design	Model - Decision Tree (DT) on Microsoft Excel
Time horizon	12 months
Perspective	Healthcare sector
Currency (year)	USD (2020)
Outcome measures	QALY gained
Willingness-to-pay threshold	USD 150,000 per QALY gained
Main findings & conclusion	Compared with no CYP2C19 testing, the CYP2C19 testing averted 33 CV events (1 non-fatal stroke, 27 non-fatal MI, and 8 CV-related deaths) and caused 3 additional bleeds. The cost/person for the CYP2C19 testing strategy was $527 lower (9.9%) than the no CYP2C19 testing strategy ($4785/person vs. $5311/person). CYP2C19 testing was dominant (health gains 0.0027 QALYs, cost savings $527 per person).
Findings of sensitivity analysis	In deterministic sensitivity analyses, 5/27 input parameters explained >75% of the variation in ICER – HSUV for MI, CYP2C19 LOF carrier prevalence, costs of CV-related death and MIs, and the probability of MI in patients who were de-escalated from ticagrelor to clopidogrel on the basis of CYP2C19 testing results. However, these variations did not affect the base-case finding. In probabilistic analyses (1000 replications), >97% simulations indicated CYP2C19 testing was dominant over no CYP2C19 testing across WTP $0–$175000.
Funding source	National Institute of Health (NIH)
Competing interest	One author was supported by the National Human Genome Research Institute of the NIH. One was supported by the National Heart, Lung, and Blood Institute of the NIH, received an honorarium from the American Heart Association, and received travel grants from the Society for Cardiovascular Angiography and Intervention and from Northwestern Cardiovascular Young Investigators' Forum. One was supported by the Department of Veterans Affairs and Sanford Health, received grants from the National Institutes of Health, received consulting fees from Sanford Health for serving on a scientific advisory board, and received honoraria from the Association for Molecular Pathway and Genome Medical.
Methodological quality	16/20 "Yes / Rather Yes", 3/20 "No / Rather No", 1/20 "Unclear"

Table S4. Methodological quality ratings of included studies (arranged in alphabetical order), based on CHEC-Extended

** Median number of items rated "Yes / Rather Yes" = 17 (85.0% items out of 20)*

	AlMukdad2021	An2018	Borse2017	Claassens2022	Crespin2011	Deiman2016	Dong2019	Dong2022	Fragoulakis2019	Fu2020	Hart2019	Hynninen2019	Jarmul2018	Jiang2015	Jiang2016	Jiang2017	Jung2021	Kazi2014
Item 1: Is the study population clearly described?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 2: Are competing alternatives clearly described?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 3: Is a well-defined research question posed in answerable form?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 4: Is the economic study design appropriate to the stated objective?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Unclr	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 5: Are the structural assumptions and the validation methods of the model properly reported?	N/RN	N/RN	Y/RY	N/RN	Y/RY	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	Y/RY	N/RN	N/RN	N/RN
Item 6: Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Y/RY	Y/RY	N/RN	Y/RY	N/RN	Unclr	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 7: Is the actual perspective chosen appropriate?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Unclr	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	N/RN
Item 8: Are all important and relevant costs for each alternative identified?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 9: Are all costs measured appropriately in physical units?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 10: Are costs valued appropriately?	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY

Item 11: Are all important and relevant outcomes for each alternative identified?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 12: Are all outcomes measured appropriately?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 13: Are outcomes valued appropriately?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 14: Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 15: Are all future costs and outcomes discounted appropriately?	Y/RY	Y/RY	Unclr	Y/RY	Y/RY	N/RN	Y/RY	Unclr	Unclr	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY
Item 16: Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 17: Do the conclusions follow from the data reported?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 18: Does the study discuss the generalizability of the results to other settings and patient/client groups?	N/RN	N/RN	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	N/RN	N/RN	Y/RY	N/RN	Y/RY	N/RN	N/RN	N/RN	N/RN	Y/RY
Item 19: Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Y/RY	N/RN	Y/RY	Y/RY	N/RN	Y/RY	N/RN	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY
Item 20: Are ethical and distributional issues discussed appropriately?	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN
Total "Yes / Rather Yes" (Y/RY)	17	15	17	18	17	11	17	16	15	16	17	16	18	17	16	17	15	17
Total "No / Rather No" (N/RN)	3	5	2	2	3	7	3	3	4	3	3	4	2	3	4	3	5	3
Total "Unclr" (Unclear)	0	0	1	0	0	2	0	1	1	1	0	0	0	0	0	0	0	0
% “Yes / Rather Yes” (Y/RY)	85%	75%	85%	90%	85%	55%	85%	80%	75%	80%	85%	80%	90%	85%	80%	85%	75%	85%

	Kim2019	Kim2021	Lala2013	Limdi2020	Marrero2019	Mujwara2022	Oemrawsingh2016	Oker e2018	Panattoni2012	Parthan2013	Patel 2014	Phelps2014	Ramirez2013	Reese 2012	Shiffman2012	Sorich2013	Wang 2018
Item 1: Is the study population clearly described?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 2: Are competing alternatives clearly described?	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 3: Is a well-defined research question posed in answerable form?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 4: Is the economic study design appropriate to the stated objective?	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 5: Are the structural assumptions and the validation methods of the model properly reported?	N/RN	N/RN	Y/RY	N/RN	Y/RY	Y/RY	N/RN	N/RN	Y/RY	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN
Item 6: Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	N/RN	Y/RY	Y/RY
Item 7: Is the actual perspective chosen appropriate?	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 8: Are all important and relevant costs for each alternative identified?	Y/RY	Y/RY	Y/RY	Y/RY	Unclr	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 9: Are all costs measured appropriately in physical units?	Y/RY	Y/RY	Y/RY	Y/RY	Unclr	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 10: Are costs valued appropriately?	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 11: Are all important and relevant outcomes for each alternative identified?	Y/RY	Y/RY	Y/RY	Y/RY	Unclr	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY

Item 12: Are all outcomes measured appropriately?	Y/RY	Y/RY	Y/RY	Y/RY	Unclr	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 13: Are outcomes valued appropriately?	Y/RY	Y/RY	Y/RY	Y/RY	Unclr	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Unclr	Y/RY	Y/RY
Item 14: Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	N/RN	Y/RY	Y/RY
Item 15: Are all future costs and outcomes discounted appropriately?	Y/RY	Unclr	Y/RY	N/RN	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 16: Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 17: Do the conclusions follow from the data reported?	Y/RY	Y/RY	Y/RY	Y/RY	Unclr	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY	Y/RY
Item 18: Does the study discuss the generalizability of the results to other settings and patient/client groups?	Y/RY	N/RN	N/RN	Y/RY	N/RN	N/RN	Y/RY	N/RN	N/RN	Y/RY	Y/RY	N/RN	N/RN	Y/RY	N/RN	N/RN	N/RN
Item 19: Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	N/RN	Y/RY	Y/RY	Y/RY	N/RN	N/RN	Y/RY	Y/RY	Y/RY	N/RN	Y/RY	N/RN	N/RN	N/RN	N/RN	Y/RY	Y/RY
Item 20: Are ethical and distributional issues discussed appropriately?	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN	N/RN
Total "Yes / Rather Yes" (Y/RY)	17	16	18	16	6	17	8	17	18	17	18	15	16	15	13	17	17
Total "No / Rather No" (N/RN)	3	3	2	4	8	3	12	3	2	3	2	5	4	5	6	3	3
Total "Unclr" (Unclear)	0	1	0	0	6	0	0	0	0	0	0	0	0	0	1	0	0
% "Yes / Rather Yes" (Y/RY)	85%	80%	90%	80%	30%	85%	40%	85%	90%	85%	90%	75%	80%	75%	65%	85%	85%

Yes / Rather Yes (Y/RY) No / Rather No (N/RN) Unclear

Table S5. Variation in economic evaluation findings based on study characteristics for the 147 comparisons.

Study Characteristics	Number of comparisons (n = 147)								p*
	Dominant (n_c = 44)		Cost-effective (n_c = 64)		Not cost-effective (n_c = 31)		Dominated (n_c = 8)		
	N	%	n	%	n	%	n	%	
Year of publication									
2011-2017	18	40.9	31	48.4	10	32.3	-	-	0.037
2018-2022	26	59.1	33	51.6	21	67.7	8	100	
Continent									
North America (US)	33	75.0	26	39.7	20	64.5	7	87.5	0.010
Europe (Netherlands, Spain, Finland)	6	18.2	21	32.8	7	22.6	1	12.5	
Asia (China, Hong Kong, Qatar, Singapore)	4	9.1	5	7.8	3	9.7	-	-	
Australia & New Zealand	1	2.3	12	18.8	1	3.2	-	-	
Funding									
Non-private (Public or non-profit)	17	38.6	35	54.7	14	45.2	4	50.0	0.115
Not specified	21	47.7	16	25.0	14	45.2	4	50.0	
Private	1	2.3	8	12.5	-	-	-	-	
None	5	11.4	5	7.8	3	9.7	-	-	
Any author affiliated to pharmaceutical / biotechnology industry									
No	30	68.2	49	77.8	25	78.1	4	50.0	0.287
Yes	14	31.8	14	22.2	7	21.9	4	50.0	
Perspective									
Healthcare system / provider	28	63.6	59	92.2	24	77.4	8	100.0	<0.001
Not stated	12	27.3	-	-	5	16.1	-	-	
Societal	2	4.5	5	7.8	2	6.5	-	-	
Private payer	2	4.5	-	-	-	-	-	-	
Type of economic evaluations									
Cost utility analysis only	33	75.0	49	76.6	27	87.1	6	75.0	0.581
Cost utility analysis & Cost effectiveness analysis	8	18.2	14	21.9	4	12.9	2	25.0	
Cost effectiveness analysis only	3	6.8	1	1.6	-	-	-	-	
Type of study design									
Model	41	93.2	59	93.8	28	90.3	8	100.0	0.908
Non-Model	3	6.8	4	6.2	3	9.7	-	-	
Time horizon									
Lifetime	12	27.3	39	60.9	19	61.3	6	75.0	0.001
Non-lifetime	32	72.7	25	39.1	12	38.7	2	25.0	
Age									
<65	35	79.5	47	73.4	17	54.8	3	37.5	0.002
Not stated	7	15.9	7	10.9	2	6.5	1	12.5	
=>65	2	4.5	9	15.6	12	38.7	4	50.0	

Gene tested									
CYP2C19 [a]	27	61.4	42	65.6	24	77.4	5	62.5	0.603
Not stated [b]	17	38.6	20	31.2	7	22.6	3	37.5	
Non-CYP2C19	-	-	2	3.1	-	-	-	-	
Purpose of genetic testing									
To stratify patients between medications (stratification)	27	61.4	44	68.8	24	77.4	5	62.5	0.496
To predict the risk of CAD (prognostic)	17	38.6	20	31.2	7	22.6	3	37.5	
How Economic Models accounted for the effect of PGx **									
Relative Risk Only	12	29.3	9	15.0	7	25.0	2	25.0	<0.001
Relative Risk & Probability / Rate	2	4.9	4	6.7	3	10.7	1	12.5	
Relative Risk & Accuracy	6	14.6	2	3.3	2	7.1	-	-	
Probability / Rate Only	8	19.5	41	68.3	13	46.4	5	62.5	
Probability / Rate & Accuracy	1	2.4	1	1.7	-	-	-	-	
Accuracy Only	12	29.3	3	5.0	3	10.7	-	-	
Sources of PGx effectiveness data **									
Systematic review or RCTs	22	53.7	37	61.7	17	60.7	3	37.5	0.545
Others	19	46.3	23	38.3	11	39.3	5	62.5	
Sources of PGx cost data									
Peer-reviewed literature	9	20.5	6	9.4	9	29.0	4	50.0	<0.001
Private lab	21	47.7	16	25.0	3	9.7	1	12.5	
Official document	4	9.1	15	23.4	12	38.7	-	-	
Official document & Private Lab	2	4.5	-	-	-	-	-	-	
Official document & Peer-reviewed literature	-	-	3	4.7	2	6.5	-	-	
Others	6	13.6	23	35.9	5	16.1	3	37.5	
Not reported	2	4.5	1	1.6	-	-	-	-	
Methodological quality rating (CHEC-Extended)[g]									
Median or above (≥ 85.0%)	21	47.7	33	51.6	17	54.8	6	75.0	0.578
Below median (< 85.0%)	23	52.3	31	48.4	14	45.2	2	25.0	

** Based on Fisher's exact test as all characteristics have cells with expected counts < 5.*

*** Sums less than total comparisons because these characteristics are only applicable for model-based economic evaluations.*

a. This includes testing CYP2C19 alone, or CYP2C19 with other genes.

b. These are studies that use a proprietary genetic test kit and / or proprietary genetic risk scores, which may specify the number of genes, but the exact genes are not stated.

Table S6. Findings from probabilistic sensitivity analysis, to examine possibility of misclassification of base-case conclusions in Table S5.

	Dominant (n_c = 44)	Cost-effective (n_c = 64)	Not cost-effective (n_c = 31)	Dominated (n_c = 8)
Did not perform PA	3	8	6	0
Performed but did not report PA findings	2	15	16	6
Performed and reported PA findings	39	41	9	2
% simulations dominant or cost-effective ≥ 75%	31	25	0	0
% simulations dominant or cost-effective < 75%	8	16	9	2
% simulations dominant or cost-effective ≥ 50%	36	33	0	1
% simulations dominant or cost-effective < 50%	3	8	9	1
Total number of comparisons	44	64	31	8

* We used the willingness-to-pay (WTP) thresholds reported by the respective studies, to determine whether an intervention is dominant, cost-effective, not cost-effective, or dominated.

PA = Probabilistic analysis is the analysis that draws randomly a set of input parameters from their respective distributions (Monte Carlo simulations) to generate outputs (cost and effectiveness). These are normally repeated between 1,000 and 10,000 times to give a range of cost and effectiveness values. These values are used to calculate the proportion of simulations that find an intervention cost saving (i.e., less costly, and more effective) or the proportion of simulations that find the intervention cost-effective (i.e., below the willingness-to-pay (WTP) threshold).

Figure S1. Study selection flow chart.