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Economic Evaluation

# Cost-Effectiveness of Multigene Pharmacogenetic Testing in Patients With Acute Coronary Syndrome After Percutaneous Coronary Intervention

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## ABSTRACT

*Objective:* To evaluate the cost-effectiveness of multigene testing (*CYP2C19, SLCO1B1, CYP2C9, VKORC1*) compared with single-gene testing (*CYP2C19*) and standard of care (no genotyping) in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) from Medicare's perspective.

*Methods:* A hybrid decision tree/Markov model was developed to simulate patients post-PCI for ACS requiring antiplatelet therapy (*CYP2C19* to guide antiplatelet selection), statin therapy (*SLCO1B1* to guide statin selection), and anticoagulant therapy in those that develop atrial fibrillation (*CYP2C9/VKORC1* to guide warfarin dose) over 12 months, 24 months, and lifetime. The primary outcome was cost (2016 US dollar) per quality-adjusted life years (QALYs) gained. Costs and QALYs were discounted at 3% per year. Probabilistic sensitivity analysis (PSA) varied input parameters (event probabilities, prescription costs, event costs, health-state utilities) to estimate changes in the cost per QALY gained.

*Results:* Base-case–discounted 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. PSA-discounted results indicated that, at the $50 000/QALY gained willingness-to-pay threshold, multigene testing had the highest probability of cost-effectiveness in the majority of simulations at 24 months (61%) and over the lifetime (81%).

*Conclusions:* On the basis of projected simulations, multigene testing for Medicare patients post-PCI for ACS has a higher probability of being cost-effective over 24 months and the lifetime compared with single-gene testing and standard of care and could help optimize medication prescribing to improve patient outcomes.

*Keywords:* acute coronary syndrome, multigene testing, pharmacogenetics, precision medicine.

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## Introduction

Approximately 7% of the 1200 FDA-approved medications have pharmacogenetic guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC), which involves genetic information for 17 genes.[1] Integrating pharmacogenetic information in the drug-prescribing process can help optimize medication selection to achieve better patient outcomes through better drug efficacy and avoiding unwanted side effects.

Clinical incorporation of pharmacogenetic testing is typically completed for the immediate drug being prescribed. For patients receiving a percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS), single-gene testing for *CYP2C19* has been implemented at multiple centers to guide selection of antiplatelet therapy. CPIC guidelines recommend use of prasugrel or ticagrelor for patients with *CYP2C19* variants (*2 to *8) to reduce their increased risk for cardiovascular events on clopidogrel, the most commonly prescribed antiplatelet therapy.[2] Approximately 30% of US patients have these *CYP2C19* variants and could benefit from pharmacogenetic testing before antiplatelet therapy selection.[3,4]

Multigene testing, a strategy that tests for multiple pharmacogenetic genes, provides information for multiple drugs and has

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been proposed as an alternative to single-gene testing.[5,6] The shift toward multigene testing is driven by multiple factors, including more efficient and less expensive genetic testing options.[7] In addition, the availability of comprehensive pharmacogenetic results allows clinicians to incorporate genetic information into future prescribing decisions immediately.[8]

Patients undergoing a PCI for ACS could potentially benefit from multigene testing rather than *CYP2C19* testing alone. These patients often have comorbidities that necessitate frequent use of additional drugs that have associated CPIC guidelines[8]; for example, a long-term statin therapy post-ACS as secondary prevention is recommended, and lower simvastatin doses or alternative statin use for patients with *SLCO1B1* variants (rs4149056 C allele) avoids an increased risk of myopathy.[9] Approximately 25% of US patients have *SLCO1B1* variants and could benefit from pharmacogenetic testing before statin therapy selection.[9] Additionally, patients with ACS are at higher risk to develop atrial fibrillation during their lifetime compared with the general population, and CPIC guidelines for *CYP2C9* and *VKORC1* can help optimize warfarin dosing to help prevent thromboembolic and bleeding events. Specifically, reduced warfarin doses should be used for patients with various *CYP2C9* (*2, *3) and *VKORC1* (rs9923231 A allele) variant combinations because of an increased risk of bleeding at standard warfarin dosing.[10–12] Approximately 40% of patients have *CYP2C9/VKORC1* variant combinations and could benefit from pharmacogenetic testing to determine optimal warfarin dosing.[13]

Although there are advantages to multigene testing over single-gene testing, the benefits of having comprehensive genetic information available for future drug prescribing in patients post-PCI for ACS have not been investigated to inform insurance reimbursement decisions.[14] Pharmacogenetic health economic evaluations in patients post-PCI with ACS are limited to evaluating single-gene *CYP2C19* testing in antiplatelet therapy selection.[15]

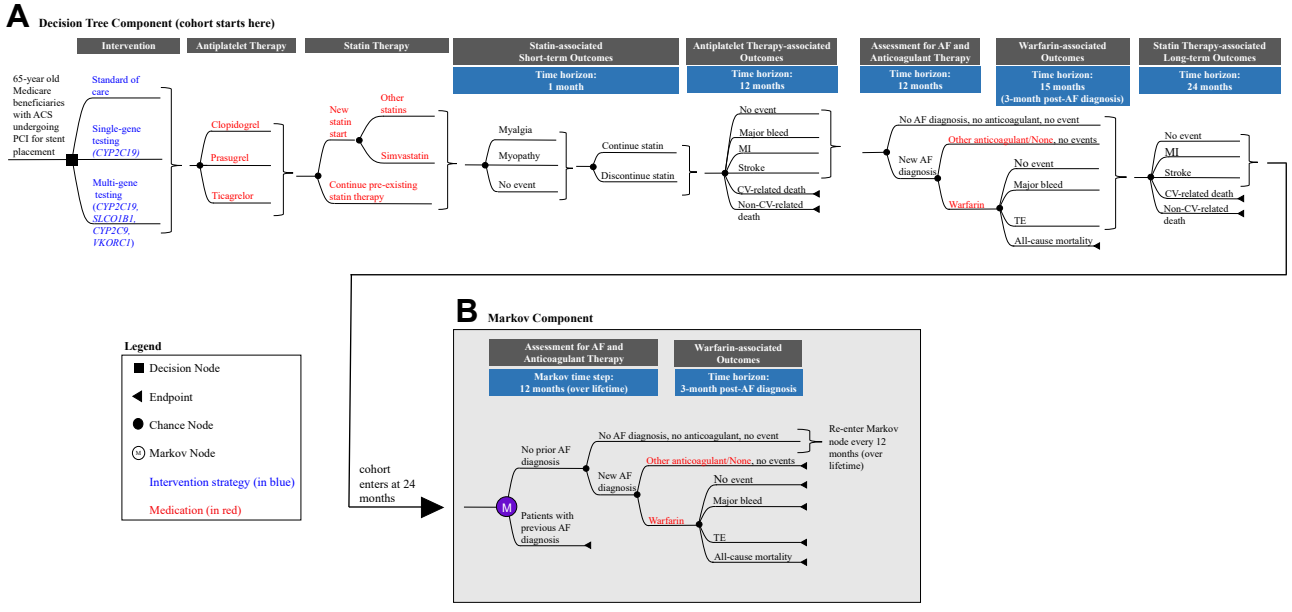
To this end, the objective of this study was to conduct a cost-effectiveness analysis to investigate the cost and potential health benefits associated with providing a multigene test for Medicare patients post-PCI for ACS. The gene-drug pairs included in the multigene testing strategy were limited to major cardiovascular therapeutic agents these patients are at a higher risk of being prescribed, including *CYP2C19* for antiplatelet therapy selection, *SLCO1B1* for statin selection, and *CYP2C9/VKORC1* for warfarin dosing.

## Methods

### Model Structure

A hybrid decision tree/Markov model (Fig. 1) was developed in Microsoft Excel, version 14.7.7 (Redmond, WA), to evaluate the cost-effectiveness of 3 genotyping strategies for Medicare patients post-PCI for ACS from the perspective of Medicare: (1) standard of care (no genotyping), (2) single-gene testing (*CYP2C19* for antiplatelet therapy selection), and (3) multigene testing (*CYP2C19* for

**Figure 1.** Structure of the hybrid decision tree/Markov model. Part A of the model is the decision tree component where 300 000 patients with ACS with PCI enter and are assigned to each of the 3 interventions: standard of care, single-gene testing, and multigene testing. Patients are first prescribed antiplatelet and statin therapies. Adverse outcomes related to statin therapy are assessed at 1 month. At 12 months antiplatelet-therapy-associated outcomes and the development of atrial fibrillation are assessed, and individuals prescribed warfarin are followed for 3-month post–atrial-fibrillation-associated outcomes. Then, the cohort is assessed for statin-therapy-associated long-term outcomes at 24 months. At 24 months, the cohort also enters part B of the model, the Markov component, where the development of atrial fibrillation is assessed each year until the end of life and individuals prescribed warfarin are followed for 3-month post–atrial-fibrillation-associated outcomes. The brackets in the figure indicate that the proceeding chance node branches to the right apply to each of the encompassing branches to the left of the bracket.




ACS indicates acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; other statins, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, and rosuvastatin; PCI, percutaneous coronary intervention; pre-existing statins, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin; standard of care, no genotyping; TE, thromboembolic events.

antiplatelet therapy selection, *SLCO1B1* for statin selection, and *CYP2C9/VKORC1* for warfarin dosing). Three time horizons were investigated: 12 months, 24 months, and lifetime. Patients entered one of the 3 interventions and remained on an antiplatelet therapy for 12 months. Cardiovascular outcomes associated with antiplatelet therapy were reported at 12 months and included no event, stroke, myocardial infarction (MI), major bleed, cardiovascular-related death, and non-cardiovascular-related death. A long-term statin was prescribed at the time of the PCI, and events associated with statin therapy were considered only for statin initiators. Statin-related outcomes at 1 month included myalgia and myopathy, which affected long-term adherence to statin therapy and associated cardiovascular outcomes.[16] Cardiovascular outcomes based on statin adherence were reported at 24 months, which included no event, stroke, MI, cardiovascular-related death, and non-cardiovascular-related death. Development of new-onset atrial fibrillation was assessed at 12 months in the decision tree and then every 12 months during the lifetime of the patient population using a Markov node starting at 24 months. Three-month outcomes after atrial fibrillation diagnosis and initiation of warfarin included no event, major bleed, thromboembolic event, and all-cause mortality.

## Model Cohort

A closed cohort of 300 000 Medicare beneficiaries 65 years old post-PCI for ACS was simulated in the model and assigned to each intervention strategy. Institutional review board approval was not required for this study.

## Model Input Parameters

Model inputs are summarized in Table 1.

### Antiplatelet therapy selection and associated events

Patients were assigned to antiplatelet therapies based on recent (2013) national rates of prescription use in individuals aged 65 years and older (75% clopidogrel, 10% prasugrel, 15% ticagrelor).[17] Cardiovascular event probabilities associated with antiplatelet therapies were approximated using the TRITON-TIMI 38 and PLATO trials, 2 major international randomized controlled trials (RCTs) investigating cardiovascular outcomes in patients post-PCI for ACS randomized to clopidogrel and prasugrel or ticagrelor.[23,24] Patients with *CYP2C19* variants prescribed clopidogrel have higher rates of stroke, MI, and death.[44,45] The event probabilities for patients on clopidogrel were further delineated by *CYP2C19* variant carrier status using 2 meta-analyses that investigated cardiovascular outcomes based on *CYP2C19* variant carrier status in patients receiving clopidogrel for coronary artery disease and with some undergoing a PCI.[25,26] For the 2 genotype-guided strategies, patients with *CYP2C19* variants originally prescribed clopidogrel were switched to prasugrel. Patients could develop only one cardiovascular outcome associated with antiplatelet therapy over the first 12 months.

### Statin therapy selection and associated events

The 45.7% of Medicare patients post-MI with no prior statin therapy were considered statin initiators in the simulated cohort with 13% prescribed simvastatin and 87% prescribed other statins.[18] Patients with *SLCO1B1* variants and prescribed simvastatin are at higher risk of statin-associated muscle symptoms (SAMS).[9] Statin-associated muscle symptoms include myopathy and myalgia and were assessed 1 month after initiating statin therapy. Adherence to statin therapy and its associated long-term cardiovascular protection is affected by myopathy and myalgia. It is estimated that among simvastatin users, 60% of myopathies are caused by *SLCO1B1* variants and 40% are caused by other factors. This breakdown in the cause of myopathies was applied to myopathies (11 to 26 cases per 10 000 patients per year[21]) and myalgias (prevalence of 4.7% to 9.5%[16,19]) to estimate cases that are caused by *SLCO1B1* at-risk genotypes or other factors. Approximately 26% of statin users who experience myalgias and 40% of users who experience myopathies discontinue their statin therapy long-term.[20,46] Long-term cardiovascular event probabilities for statin adherence and nonadherence were approximated using 24-month follow-up data from the Phase Z of the A to Z Trial, an RCT of patients post-ACS who either received an intensive or less intensive/placebo statin therapy.[27] Nonadherence to statin therapy in post-ACS patients increases their risk of MI, stroke, and death.[27] Only patients with *SLCO1B1* variants (~25% of the population) in the multigene testing strategy and assigned to receive simvastatin were switched to an alternative statin and were no longer at risk for myopathies/myalgias caused by *SLCO1B1* variants. Patients remained on their assigned statin for the entire simulation.

### Warfarin use for atrial fibrillation and associated events

Clinical guidelines recommend a long-term anticoagulant for patients with atrial fibrillation to prevent thromboembolic events,[12] and based on national prescribing for Medicare patients, about 30% receive warfarin.[10] Only patients receiving warfarin as an anticoagulant for the treatment of atrial fibrillation were followed in the model, and patients remained on warfarin long-term. Dose selection for warfarin can be optimized using *CYP2C9/VKORC1* genetic information to achieve the target international normalized ratio (INR).[11] Cardiovascular event probabilities for patients on warfarin to treat atrial fibrillation were approximated using 2 meta-analyses, which included RCTs comparing cardiovascular outcomes in patients on standard warfarin dosing to pharmacogenetic-guided warfarin dosing for a variety of diagnoses.[28,29] Patients with *CYP2C9/VKORC1* variants prescribed standard warfarin dosing have increased risk of major bleeds and thromboembolic events.[28,29] Patients on the standard of care or single-gene testing do not have *CYP2C9/VKORC1* information and received standard warfarin dosing. Patients in the multigene testing intervention group received *CYP2C9/VKORC1* testing, and their warfarin dose was tailored based on genetic results.

### Costs

*CYP2C19* single-gene testing cost was approximated using the Centers for Medicare and Medicaid Services 2016 Clinical Diagnostic Laboratory Fee Schedule.[31] Multigene testing cost was approximated from peer-reviewed studies and expert opinion.[6,14] Medication costs were estimated by averaging 6 months of recently reported monthly costs in the GoodRx database. Event costs associated with MI, stroke, and major bleed were derived from the Centers for Medicare and Medicaid Services 2015 Inpatient Charge Data.[34] Costs for events that were not available in the Medicare Inpatient Charge Data were derived from published cost-effectiveness analyses.[33,35,36] The medical care expenditure component of the consumer price index (CPI) from the US Bureau of Labor Statistics[47] was used to convert prices from various base years to 2016 US dollars, the last full year of available CPI data.[47] Costs were discounted at 3% per year.[48]

### Quality of life estimates

Health utility values and ranges were obtained from recently published cost-effectiveness analyses conducted in patients with similar cardiovascular diagnoses.[15,35,39-43] Health utilities for antiplatelet- and statin-associated cardiovascular events were

**Table 1.** Model inputs: event probabilities, cost, and health utilities.

| Parameter | Base case | One-way sensitivity analysis values: min, max* | Distribution (parameters)† | Ref. |
|---|---|---|---|---|
| **Annual Prescription Proportion Breakdown** | | | | |
| Antiplatelet Therapy | | | | |
| Clopidogrel | 0.75 | — | — | 17 |
| Prasugrel | 0.10 | — | — | 17 |
| Ticagrelor | 0.15 | — | — | 17 |
| New statin start | 0.46 | — | — | 18 |
| Statin Therapy | | | | |
| Simvastatin | 0.13 | — | — | 18 |
| Other statins | 0.87 | — | — | 18 |
| Warfarin Prescription | 0.30 | — | — | 10 |
| **Disease State Probabilities, 30 days** | | | | |
| Myalgia | | | | |
| *SLCO1B1*-induced | 0.0426 | 0.0347, 0.0486 | Beta ($\alpha$ = 182, $\beta$ = 4222) | 16,19,20 |
| Non-*SLCO1B1*-induced | 0.0284 | 0.0223, 0.0338 | Beta ($\alpha$ = 122, $\beta$ = 4282) | 16,19,20 |
| Myopathy | | | | |
| *SLCO1B1*-induced | 0.00111 | 0.00048, 0.00203 | Beta ($\alpha$ = 11.1, $\beta$ = 9989) | 20,21 |
| Non-*SLCO1B1*-induced | 0.00074 | 0.00044, 0.00104 | Beta ($\alpha$ = 7.4, $\beta$ = 9992.6) | 20,21 |
| Atrial fibrillation, 12 months | 0.0274 | 0.0168, 0.0408 | Beta ($\alpha$ = 27.4, $\beta$ = 972.6) | 22 |
| **Antiplatelet Therapy Event Probabilities, 12 months** | | | | |
| Stroke | | | | |
| Clopidogrel, no variants in *CYP2C19* | 0.0029 | 0.0014, 0.0051 | Beta ($\alpha$ = 14, $\beta$ = 4743) | 23,24,25 |
| Clopidogrel, variants in *CYP2C19* | 0.017 | 0.011, 0.024 | Beta ($\alpha$ = 34, $\beta$ = 2005) | 23,24,25 |
| Prasugrel | 0.0072 | 0.0050, 0.0098 | Beta ($\alpha$ = 49, $\beta$ = 6746) | 23 |
| Ticagrelor | 0.0082 | 0.0059, 0.011 | Beta ($\alpha$ = 56, $\beta$ = 6739) | 24 |
| Myocardial Infarction | | | | |
| Clopidogrel, no variants in *CYP2C19* | 0.059 | 0.053, 0.069 | Beta ($\alpha$ = 288, $\beta$ = 4469) | 23,24,25 |
| Clopidogrel, variants in *CYP2C19* | 0.097 | 0.087, 0.118 | Beta ($\alpha$ = 208, $\beta$ = 1831) | 23,24,25 |
| Prasugrel | 0.054 | 0.049, 0.062 | Beta ($\alpha$ = 377, $\beta$ = 6418) | 23 |
| Ticagrelor | 0.060 | 0.055, 0.068 | Beta ($\alpha$ = 417, $\beta$ = 6378) | 24 |
| Major bleed | | | | |
| Clopidogrel, no variants in *CYP2C19* | 0.013 | 0.0099, 0.018 | Beta ($\alpha$ = 89, $\beta$ = 6627) | 23,24 |
| Clopidogrel, variants in *CYP2C19* | 0.013 | 0.0099, 0.018 | Beta ($\alpha$ = 89, $\beta$ = 6627) | 23,24 |
| Prasugrel | 0.017 | 0.014, 0.02 | Beta ($\alpha$ = 117, $\beta$ = 6678) | 23 |
| Ticagrelor | 0.016 | 0.013, 0.02 | Beta ($\alpha$ = 111, $\beta$ = 6795) | 24 |
| CV-related death | | | | |
| Clopidogrel, no variants in *CYP2C19* | 0.013 | 0.0099, 0.018 | Beta ($\alpha$ = 64, $\beta$ = 4693) | 23,24,25 |
| Clopidogrel, variants in *CYP2C19* | 0.027 | 0.020, 0.037 | Beta ($\alpha$ = 56, $\beta$ = 1983) | 23,24,25 |
| Prasugrel | 0.016 | 0.012, 0.019 | Beta ($\alpha$ = 107, $\beta$ = 6688) | 23 |
| Ticagrelor | 0.014 | 0.011, 0.018 | Beta ($\alpha$ = 96, $\beta$ = 6699) | 24 |
| Non-CV-related death | | | | |
| Clopidogrel, no variants in *CYP2C19* | 0.0045 | 0.0025, 0.0070 | Beta ($\alpha$ = 21, $\beta$ = 4736) | 23,24,26 |
| Clopidogrel, variants in *CYP2C19* | 0.0080 | 0.0040, 0.013 | Beta ($\alpha$ = 16, $\beta$ = 2023) | 23,24,26 |
| Prasugrel | 0.0063 | 0.0043, 0.0088 | Beta ($\alpha$ = 43, $\beta$ = 6752) | 23 |
| Ticagrelor | 0.0039 | 0.0024, 0.0060 | Beta ($\alpha$ = 27, $\beta$ = 6768) | 24 |
| Event-free | | | | |
| Clopidogrel, no variants in *CYP2C19* | 0.91 | 0.88, 0.93 | — | — |
| Clopidogrel, variants in *CYP2C19* | 0.84 | 0.80, 0.89 | — | — |
| Prasugrel | 0.90 | 0.89, 0.92 | — | — |
| Ticagrelor | 0.90 | 0.89, 0.92 | — | — |
| **Statin-Associated Cardiovascular Event Probabilities, 24 months** | | | | |
| Discontinue statin long-term after myalgia | 0.266 | — | — | 16 |
| Discontinue statin long-term after myopathy | 0.403 | — | — | 16 |
| Myocardial infarction | | | | |
| Adherent to statin | 0.064 | 0.055, 0.079 | Beta ($\alpha$ = 151, $\beta$ = 2114) | 27 |
| Nonadherent to statin | 0.067 | — | — | 27 |
| Stroke | | | | |
| Adherent to statin | 0.012 | 0.008, 0.018 | Beta ($\alpha$ = 28, $\beta$ = 2237) | 27 |
| Nonadherent to statin | 0.016 | — | — | 27 |

*continued on next page*

**Table 1.** Continued

| Parameter | Base case | One-way sensitivity analysis values: min, max* | Distribution (parameters)† | Ref. |
|---|---|---|---|---|
| CV-related death | | | | |
| Adherent to statin | 0.036 | 0.028, 0.046 | Beta ($\alpha$ = 83, $\beta$ = 2182) | 27 |
| Nonadherent to statin | 0.048 | — | | 27 |
| Non-CV-related death | | | | |
| Adherent to statin | 0.009 | 0.005, 0.015 | Beta ($\alpha$ = 21, $\beta$ = 2244) | 27 |
| Nonadherent to statin | 0.009 | — | — | 27 |
| Event-free | | | | |
| Adherent to statin | 0.88 | 0.84, 0.91 | — | — |
| Nonadherent to statin | 0.86 | — | — | — |
| **Atrial Fibrillation Event Probabilities for Warfarin, 3 months** | | | | |
| Major bleed | | | | |
| Pharmacogenetic intervention | 0.006 | 0.002, 0.013 | Beta ($\alpha$ = 6, $\beta$ = 982) | 28 |
| Standard dosing | 0.017 | — | — | 28 |
| Thromboembolic events | | | | |
| Pharmacogenetic intervention | 0.006 | 0.002, 0.013 | Beta ($\alpha$ = 6, $\beta$ = 1012) | 29 |
| Standard dosing | 0.019 | — | — | 29 |
| All-cause mortality | | | | |
| Pharmacogenetic intervention | 0.011 | 0.005, 0.021 | Beta ($\alpha$ = 10, $\beta$ = 894) | 28 |
| Standard dosing | 0.011 | 0.005, 0.021 | Beta ($\alpha$ = 10, $\beta$ = 894) | 28 |
| Event-free | | | | |
| Pharmacogenetic intervention | 0.98 | 0.94, 0.99 | — | — |
| Standard dosing | 0.95 | 0.94, 0.96 | — | — |
| **Prescription Cost, Annual (2016 USD)** | | | | |
| Antiplatelet Therapy | | | | |
| Clopidogrel, maintenance dose, 75 mg per day | $108 | $80, $142 | Gamma (location = 0, scale = 1.63, shape = 66.3) | 30 |
| Prasugrel, maintenance dose, 10 mg per day | $474 | $468, $480 | Gamma (location = 0, scale = 0.015, shape = 31888) | 30 |
| Ticagrelor, maintenance dose, 90 mg twice a day | $4080 | $4007, $4153 | Gamma (location = 0, scale = 0.24, shape = 16785.9) | 30 |
| Statin Therapy | | | | |
| Statin initiators | $89 | $76, $104 | Gamma (location = 0, scale = 0.43, shape = 209) | 30 |
| Simvastatin, long-term dose, 20 to 40 mg per day | $133 | $107, $189 | Gamma (location = 0, scale = 2.13, shape = 68.04) | 30 |
| Other statins (atorvastatin, rosuvastatin, pravastatin, lovastatin), long-term dose, doses vary by agent | $116 | $102, $132 | Gamma (location = 0, scale = 0.36, shape = 327.55) | 30 |
| On pre-existing statin (simvastatin, atorvastatin, rosuvastatin, pravastatin, lovastatin), long-term dose, doses vary by agent | | | | |
| Anticoagulant | | | | |
| Warfarin, maintenance dose, 5 mg per day | $112 | $109, $115 | Gamma (location = 0, scale = 0.013, shape = 8649) | 30 |
| **Genetic Testing Costs (2016 USD)** | | | | |
| Single-gene testing (*CYP2C19*) | $292 | $162, $465 | Gamma (location = 0, scale = 14.6, shape = 20) | 31,32 |
| Multigene testing (*CYP2C19, SLCO1B1, CYP2C9, VKORC1*) | $250 | $146, $386 | Gamma (location = 0, scale = 10.7, shape = 23.4) | Expert opinion, 6,14 |
| **Events (2016 USD)** | | | | |
| Myopathy/myalgia | $398 | $236, $606 | Gamma (location = 0, scale = 15.9, shape = 25) | 33 |
| Nonfatal stroke | $13 874 | $6770, $23 398 | Gamma (location = 0, scale = 974.1, shape = 14.2) | 34 |
| Nonfatal myocardial infarction | $8518 | $3306, $16 504 | Gamma (location = 0, scale = 953.1, shape = 8.9) | 34 |
| Nonfatal major bleed | $7785 | $2570, $16 264 | Gamma (location = 0, scale = 1125.6, shape = 6.9) | 34 |
| Thromboembolic events | $8339 | $4954, $12 700 | Gamma (location = 0, scale = 333.5, shape = 25) | 35 |

*continued on next page*

**Table 1.** Continued

| Parameter | Base case | One-way sensitivity analysis values: min, max* | Distribution (parameters)† | Ref. |
|---|---|---|---|---|
| CV-related mortality | $15 181 | $8856, $23 398 | Gamma (location = 0, scale = 645.9, shape = 23.5) | 36 |
| Non-CV-related mortality | $14 019 | $8329, $21 353 | Gamma (location = 0, scale = 560.8, shape = 25) | 36 |
| All-cause mortality (average of CV-related and non-CV-related mortality) | $14 600 | $8674, $22 237 | Gamma (location = 0, scale = 584, shape = 25) | 36 |
| **Health State Utilities (12 months)** | | | | |
| Antiplatelet-associated and statin-associated CVD outcomes | | | | |
| Acute coronary syndrome, event-free survival, 65 to 74 years old | 0.88 | — | — | 37 |
| Acute coronary syndrome, event-free survival, 75 to 84 years old | 0.84 | — | — | 37 |
| Acute coronary syndrome, event-free survival, ≥85 years old | 0.80 | — | — | 37 |
| Nonfatal stroke | 0.77 | 0.74, 0.80 | Beta ($\alpha$ = 776.87, $\beta$ = 234.68) | 15 |
| Nonfatal myocardial infarction | 0.70 | 0.52, 0.85 | Beta ($\alpha$ = 28.11, $\beta$ = 12.05) | 38 |
| Nonfatal major bleed | 0.63 | 0.55, 0.70 | Beta ($\alpha$ = 141.23, $\beta$ = 84.38) | 39 |
| Atrial fibrillation | | | | |
| No event | 0.75 | 0.66, 0.82 | Beta ($\alpha$ = 127.94, $\beta$ = 43.79) | 40 |
| Thromboembolic events | 0.62 | 0.55, 0.69 | Beta ($\alpha$ = 155.26, $\beta$ = 95.16) | 35 |
| Major bleed | 0.60 | 0.53, 0.67 | Beta ($\alpha$ = 153.06, $\beta$ = 102.04) | 41 |
| Death | | | | |
| CV-related mortality | 0 | — | — | 42 |
| Non-CV-related mortality | 0 | — | — | 42 |
| All-cause mortality | 0 | — | — | 42 |
| **Health State Disutility (12 months)** | | | | |
| Myopathy/myalgia | 0.017 | 0.0033, 0.043 | Beta ($\alpha$ = 3.76, $\beta$ = 217.38) | 43 |

CV indicates cardiovascular; CVD, cardiovascular disease.
*Minimum and maximum values represent the 1st and 99th percentiles of the distribution range that were used in the one-way sensitivity analyses.
†Sensitivity analyses were defined by the distribution values listed in this column. Some distributions had infinite tails; therefore, the 1st and 99th percentiles of ranges were used as minimum and maximum values that were tested in the one-way sensitivity analyses.

applied for 1 year and then patients returned to an event-free ACS health utility value in subsequent years. If patients developed atrial fibrillation and experienced an adverse outcome while on warfarin (ie, thromboembolic events, major bleed), the associated health utility values were assigned for 1 year and then patients returned to an event-free atrial fibrillation health state utility in subsequent years. Quality-adjusted life years (QALYs) were discounted at 3% per year.[48]

### *Life expectancy*

Life expectancy estimates for the cohort were based on a study that constructed period life tables based on comorbid conditions present in a nationally representative sample of Medicare beneficiaries.[49] On the basis of this retrospective cohort study, the type and number of cardiovascular outcomes accumulated over time were used to estimate life expectancy for the lifetime time horizon (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.08.002).

Additional details about input parameters and assumptions are included in the Supplemental Methods (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.08.002).

## *Base-Case and Sensitivity Analyses*

Reported point estimates or midpoint values of ranges were used as the base-case value at 12 months, 24 months, and over the lifetime.[48] The uncertainty of the parameter estimates on costs and health outcomes was investigated in one-way and probabilistic sensitivity analyses using Oracle® Crystal Ball Classroom Edition, Release 11.1.2.4 (Redwood City, CA). Event probabilities, cost, and health state utilities estimates were parameterized using beta, gamma, and beta distributions, respectively.[48] Input parameters were varied one at a time according to their minimum and maximum values for the one-way sensitivity analyses, and 10 000 Monte Carlo simulations were completed for the probabilistic sensitivity analyses (PSA) using the parameters listed in Table 1.

Outcomes include myopathy/myalgia, number of discontinued statin therapies, stroke, MI, major bleed, thromboembolic events, deaths, life years, and QALYs. Interventions were rank-ordered by total cost and then sequentially compared to determine the incremental cost and gain in QALYs. The primary outcome, cost per QALY gained, was summarized as incremental cost-effectiveness ratios (ICER) and graphed as ICER planes.[48] Tornado diagrams summarized the one-way sensitivity analyses and identified the top 10 input parameters that have the greatest impact on the ICER, and an alternate scenario using the same methodology outlined for the primary analysis was completed to explore the uncertainty of the variable that had the greatest impact on the ICER. Cost-effectiveness acceptability curves were constructed as part of the PSA to compare the probability of cost-effectiveness at various WTP thresholds ($0 to $150 000) for the cost per QALY gained.[48,50] Cost-effectiveness was evaluated using $50 000 and $100 000 per QALY gained as the willingness-to-pay (WTP) thresholds, 2 commonly accepted cutoffs the United States is willing to spend on improvements in health.

## Results

### Base-Case Scenario

Tables 2 and 3 summarize the event outcomes and ICERs for the simulated cohort of 300 000 Medicare beneficiaries post-PCI for ACS.

#### Twelve-month outcomes

Overall, multigene testing resulted in the fewest events. There were 638 strokes, 2915 MIs, and 904 deaths avoided and a gain in 451 life years at the expense of an increase in 279 major bleeds for patients on either genotyping strategies in comparison to standard of care. Multigene testing had 195 fewer myalgia/myopathy cases and 53 fewer patients who discontinued their statins long term in comparison to single-gene testing and standard of care. The number of myalgia/myopathy cases and statin discontinuations are included in longer time horizons but do not change because they are not assessed beyond this time horizon.

Comparing the interventions sequentially by increasing discounted cost resulted in an ICER ($/QALY gained) of $59 876 for multigene testing when compared with standard of care, and single-gene testing was dominated by multigene testing. Multigene testing compared with standard of care (no genotyping) was only cost-effective at the $100 000/QALY gained WTP threshold.

#### Twenty-four-month outcomes

Overall, multigene testing resulted in the fewest events. There were 627 strokes and 2857 MIs avoided, and 1335 more life years for patients either of the genotyping strategies when compared with standard of care. Multigene testing had the lowest number of major bleeds and thromboembolic events out of the 3 interventions. The number of strokes and that of MIs are included in longer time horizons but do not change because they are not assessed beyond this time horizon.

Comparing the interventions sequentially by increasing discounted cost resulted in an ICER ($/QALY gained) of $33 512 for multigene testing when compared with standard of care, and single-gene testing was dominated by multigene testing. At both WTP thresholds, multigene testing compared with standard of care was cost-effective.

#### Lifetime outcomes

Overall, multigene testing resulted in the fewest events. Development of atrial fibrillation is the only new condition assessed annually during the remaining years. Out of the 3 interventions, multigene testing had the highest number of life years and the lowest number of outcomes associated with atrial fibrillation (ie, major bleeds and thromboembolic events).

Comparing the interventions sequentially by increasing discounted cost resulted in an ICER ($/QALY gained) of $3780 for multigene testing when compared with standard of care, and single-gene testing was dominated by multigene testing. At both WTP thresholds, multigene testing compared with standard of care was cost-effective.

### One-Way Sensitivity Analysis

The most impactful input parameter across all time horizons comparisons, as indicated by the tornado plots (see Appendix Figs. 1 to 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.08.002), was the cost of single-gene and multigene testing.

### Probabilistic Sensitivity Analysis

Figure 2 shows the cost-effectiveness plane for the 10 000 Monte Carlo simulations estimating the discounted cost per QALY gained for multigene testing versus standard of care and single-gene versus multigene testing. For the 3 time horizons, the majority of simulations for multigene testing compared with standard of care were in the northeast quadrant, indicating that genotyping results in higher QALYs at an increasing cost. At the $100 000/QALY WTP threshold, multigene testing compared with standard of care was cost-effective in 87.4% (12 months), 98.7% (24 months), and 99.9% (lifetime) of simulations. At the $50 000/QALY gained WTP threshold, multigene testing compared with standard of care was cost-effective in 42.1% (12 months), 82.0% (24 months), and 99.8% (lifetime) of simulations. At all time horizons for single-gene testing in comparison to multigene testing, the

**Table 2.** Base-case results: events for genotype strategies per 300 000 Medicare beneficiaries after acute coronary syndrome with percutaneous coronary intervention for stent placement.*

| | Myalgia and myopathy | Discontinue statin long-term | Stroke | MI | Major bleed | TE | Deaths | Total life years | Average life years per person |
|---|---|---|---|---|---|---|---|---|---|
| 12 months | | | | | | | | | |
| Standard of care | 4774 | 1287 | 2165 | 20 096 | 4219 | NA | 6645 | 296 678 | 0.989 |
| Multigene testing | 4579 | 1234 | 1527 | 17 181 | 4498 | NA | 5741 | 297 129 | 0.990 |
| Single-gene testing | 4774 | 1287 | 1527 | 17 181 | 4498 | NA | 5741 | 297 129 | 0.990 |
| 24 months | | | | | | | | | |
| Standard of care | 4774 | 1287 | 5773 | 39 018 | 4260 | 45 | 19 948 | 583 381 | 1.945 |
| Multigene testing | 4579 | 1234 | 5146 | 36 161 | 4513 | 14 | 19 085 | 584 716 | 1.949 |
| Single-gene testing | 4774 | 1287 | 5146 | 36 161 | 4540 | 45 | 19 086 | 584 716 | 1.949 |
| Lifetime | | | | | | | | | |
| Standard of care | 4774 | 1287 | 5773 | 39 018 | 4900 | 737 | NA | 6 438 455 | 21.46 |
| Multigene testing | 4579 | 1234 | 5146 | 36 161 | 4738 | 233 | NA | 6 462 435 | 21.54 |
| Single-gene testing | 4774 | 1287 | 5146 | 36 161 | 5182 | 739 | NA | 6 461 650 | 21.54 |

*Note.* Standard of care resulted in the overall most number of events and lowest total life years across all time horizons when compared with single-gene testing and multigene testing. Multigene testing resulted in an overall lower number of events when compared with single-gene testing at all time horizons.
MI indicates myocardial infarction; TE, thromboembolic events; standard of care, no genotyping; single-gene testing: *CYP2C19*; multigene testing: *CYP2C19, SLCO1B1, CYP2C9,* and *VKORC1*.
*Numbers represent the total number of each event over the indicated time horizon.

**Table 3.** Base-case league table results: incremental cost-effectiveness ratio of genotype strategies in 300 000 Medicare beneficiaries after acute coronary syndrome with percutaneous coronary intervention for stent placement.*

| | Total cost (2016 USD) | Cost per person (2016 USD) | Total Outcome (QALY) (n) | Outcome (QALY) per person (n) | Incremental total cost (2016 USD) | Incremental total QALYs (n) | ICER (Incremental total cost [2016 USD]/ Incremental total QALY [n]) |
|---|---|---|---|---|---|---|---|
| 12 months | | | | | | | |
| Standard of care | 590 844 110 | 1969 | 254 983 | 0.850 | — | — | — |
| Multigene testing | 645 404 459 | 2151 | 255 894 | 0.853 | 54 560 349 | 911 | 59 876 |
| Single-gene testing | 657 885 201 | 2193 | 255 891 | 0.853 | 12 480 742 | −3 | Dominated |
| 24 months | | | | | | | |
| Standard of care | 1 023 694 372 | 3412 | 497 265 | 1.658 | — | — | — |
| Multigene testing | 1 079 307 542 | 3598 | 498 925 | 1.663 | 55 613 171 | 1659 | 33 512 |
| Single-gene testing | 1 092 068 491 | 3640 | 498 919 | 1.663 | 12 760 948 | −5 | Dominated |
| Lifetime | | | | | | | |
| Standard of care | 1 574 907 720 | 5250 | 3 949 926 | 13.166 | — | — | — |
| Multigene testing | 1 630 140 791 | 5434 | 3 964 538 | 13.215 | 55 233 072 | 14 612 | 3780 |
| Single-gene testing | 1 645 260 453 | 5484 | 3 963 752 | 13.213 | 15 119 662 | −786 | Dominated |

*Note.* At all 3 time horizons, single-gene testing is dominated (worse outcomes, higher costs) by multigene testing. The cost per QALY gained was $59 876, $33 512, and $3780 at 12 months, 24 months, and lifetime, respectively, for multigene testing when compared with standard of care. In comparison to standard of care, multigene testing is cost-effective at all 3 time horizons at a WTP threshold of $100 000/QALY and cost-effective only at 24 months and lifetime at a WTP threshold of $50 000/QALY gained.

QALY indicates quality-adjusted life year; ICER, incremental cost-effectiveness ratio; standard of care, no genotyping; single-gene testing, *CYP2C19*; multigene testing: *CYP2C19, SLCO1B1, CYP2C9,* and *VKORC1*; WTP, willingness-to-pay.

*Cost and QALY discounted at 3% per year; interventions are rank-ordered by total cost and sequentially compared.

majority of simulations (53% to 56%) were dominated. At both WTP thresholds at 12 and 24 months, single-gene testing compared with multigene testing was cost-effective in approximately 30% of simulations. Over the lifetime, single-gene testing compared with multigene testing was cost-effective at both WTP thresholds in approximately 20% of simulations. For both comparisons across all time horizons, there is more variability in the QALYs gained than in the cost, and this variability increases at longer time horizons.

Figure 3 uses discounted costs and QALYs and compares the probability of cost-effectiveness for each intervention at each time horizon. At all time points, the most cost-effective intervention initially starts with standard of care and then switches to multigene testing at a WTP threshold starting at $58 000 (12 months), $33 000 (24 months), and $4000 (lifetime). At a $100 000/QALY gained WTP threshold, there was a greater probability that multigene testing was cost-effective in the majority of simulations across the 12-month, 24-month, and lifetime time horizons (64%, 70%, and 80%, respectively). At the WTP threshold of $50 000/QALY gained, there was a greater probability that multigene testing was a cost-effective strategy in the majority of simulations only at the 24-month and lifetime time horizons (61% and 81%, respectively). Standard of care had the highest probability of cost-effectiveness (52%) at the12-month time horizon under the $50 000/QALY gained WTP threshold. Single-gene testing was not a preferred strategy in most simulations at any time point across any of the WTP thresholds.

### *Alternate Scenario*

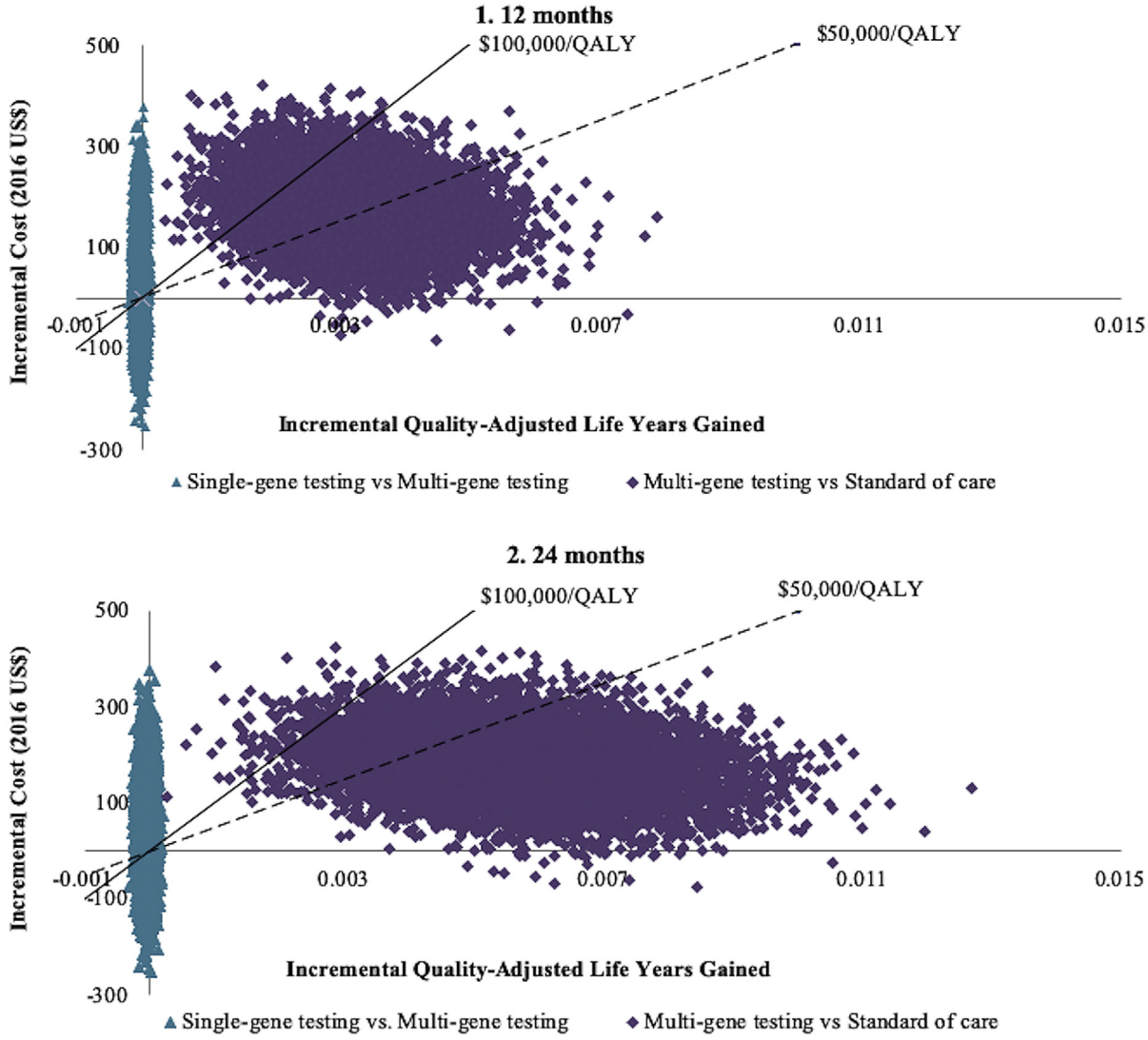
The ICER was most sensitive to genotyping costs across all time horizons, and given the likelihood that genetic costs will decrease in the future, an alternate scenario changing only the cost of single-gene testing to match multigene testing was completed (see Supplemental Results in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.08.002). Results of the alternate scenario were similar to the primary scenario with the exception that simulations indicated that multigene testing did not have a higher chance of being cost-effective until the lifetime time horizon when compared with single-gene testing.

## Discussion

Approximately 300 000 US Medicare beneficiaries undergo a PCI for ACS annually. In this analysis, the projected health and cost benefits of providing multigene testing (*CYP2C19* to guide antiplatelet therapy selection, *SLCO1B1* to guide statin selection, and *CYP2C9/VKORC1* to guide warfarin dosing) for Medicare beneficiaries aged 65 years post-PCI for ACS were simulated and compared with single-gene testing (*CYP2C19*) and standard of care (no genotyping). Pharmacogenetic cost-effectiveness analyses have traditionally focused on a single gene-drug pair.[15,51] Therefore, this analysis provides novel insight into the potential benefits multigene testing may afford this high-risk patient population in the short- (12 months) and long-term (24 months and lifetime).

The base-case scenario indicates that multigene testing is associated with the highest number of events avoided and the highest discounted QALYs gained, although these gains are small when compared with single-gene testing and standard of care over all time horizons. Single-gene testing was dominated by multigene testing at all time horizons. At a WTP threshold of $100 000/QALY gained, multigene testing compared with standard of care was cost-effective at 12 months, 24 months, and over the lifetime; however, at a WTP threshold of $50 000/QALY gained, cost-effectiveness was indicated only at 24 months and over the lifetime. The PSA cost-effectiveness acceptability curves indicate that, at a $100 000/QALY gained WTP threshold, there was a greater probability that multigene testing was cost-effective in the majority of simulations across the 12-month, 24-month, and lifetime time horizons (64%, 70%, and 80%, respectively). At the WTP threshold of $50 000/QALY gained, multigene testing had a greater probability of being cost-effective in the majority of simulations only at the 24-month and lifetime time horizons (61% and 81%, respectively). Taken together, the base-case scenario and PSA indicate that the probability of multigene testing being

**Figure 2.** Probabilistic sensitivity analysis results: incremental cost-effectiveness plane for 10 000 Monte Carlo simulations estimating the cost per QALYs gained per person at (1) 12 months, (2) 24 months, and (3) lifetime for Medicare beneficiaries with ACS undergoing a PCI for stent placement. Cost and QALYs are discounted at 3% per year. *Notes: Single-gene testing versus multigene testing:* At all time horizons, 53% to 56% of simulations were dominated, 7% to 8% of simulations were dominant, 15% to 16% of simulations were in the northeast quadrant, and 21% to 24% of simulations were in the southwest quadrant. At the $100 000 and $50 000 per QALY gained WTP thresholds at 12 and 24 months, single-gene testing was cost-effective in approximately 30% of simulations (majority in southwest quadrant). Over the lifetime, single-gene testing was cost-effective at both WTP thresholds in approximately 20% of simulations (majority in northeast quadrant). *Multigene versus standard of care:* At the $100 000/QALY WTP threshold, multigene testing was cost-effective in 87.4% (12 months), 98.7% (24 months), and 99.9% (lifetime) of simulations. At the $50 000/QALY gained WTP threshold, multigene testing was cost-effective in 42.1% (12 months), 82.0% (24 months), and 99.9% (lifetime) of simulations.

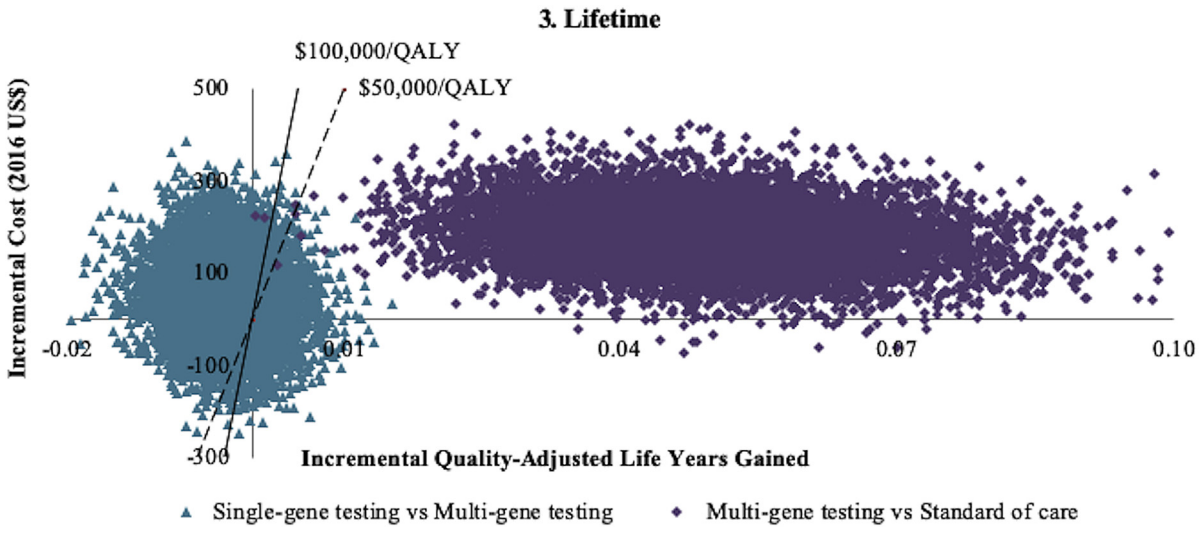



ACS indicates acute coronary syndrome; multigene testing, *CYP2C19, SLCO1B1, CYP2C9,* and *VKORC1*; PCI, percutaneous coronary intervention; QALY, quality-adjusted life year; single-gene testing: *CYP2C19*; standard of care, no genotyping.

cost-effective at both WTP thresholds increases at longer time horizons. This finding was confirmed even when accounting for variation in genetic testing cost, the input parameter that affected the ICER most per one-way sensitivity analyses. Longer time horizons allow the discounted cost and health benefits of multigene testing to accrue beyond what is offered with just single-gene testing of *CYP2C19*, although these gains are slight given the low proportion of patients prescribed simvastatin and warfarin.

The results of the single-gene testing of *CYP2C19* in this analysis are in line with the results of a recently published review of cost-effectiveness analyses evaluating *CYP2C19* testing to guide antiplatelet therapy selection for ACS patients, which found genotype-guided selection of antiplatelet therapies to be a cost-effective strategy when compared with universal use of antiplatelet therapies.[15] There are no published cost-effectiveness analyses investigating the role of *SLCO1B1* genotyping to guide

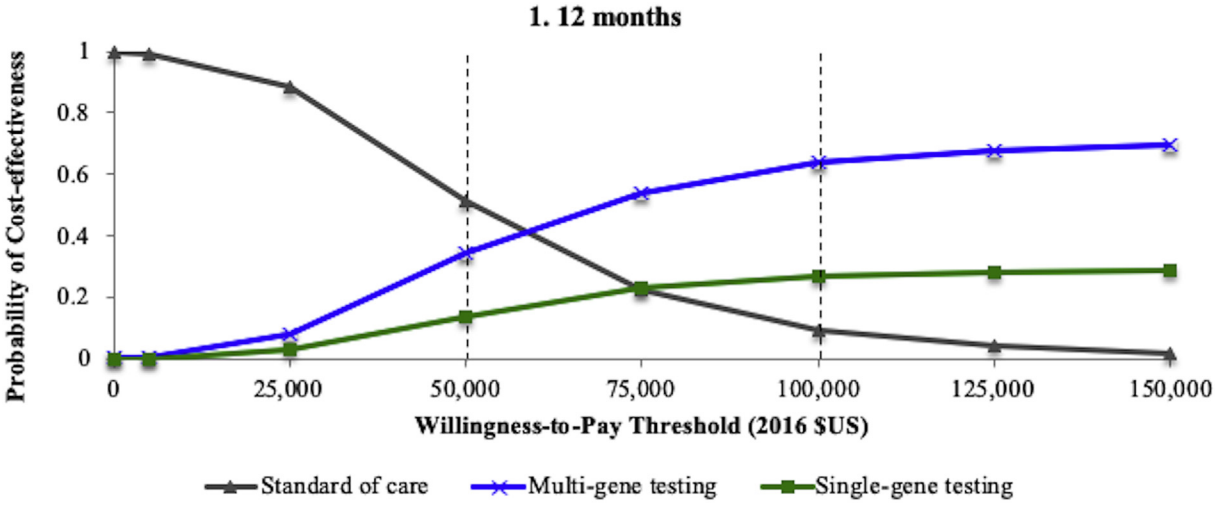
**Figure 2.** Continued.




statin therapy selection. The cost-effectiveness of *CYP2C9/VKORC1* genotyping for warfarin dosing in patients with atrial fibrillation is limited to specific subpopulations; for instance, one study concluded cost-effectiveness of *CYP2C9/VKORC1* genotyping for warfarin dosing among patients with atrial fibrillation only if a high hemorrhage risk was present,[51] whereas another study concluded cost-effectiveness only in patients if it lowers out-of-range INR values by more than 5-9 percentage points.[52]

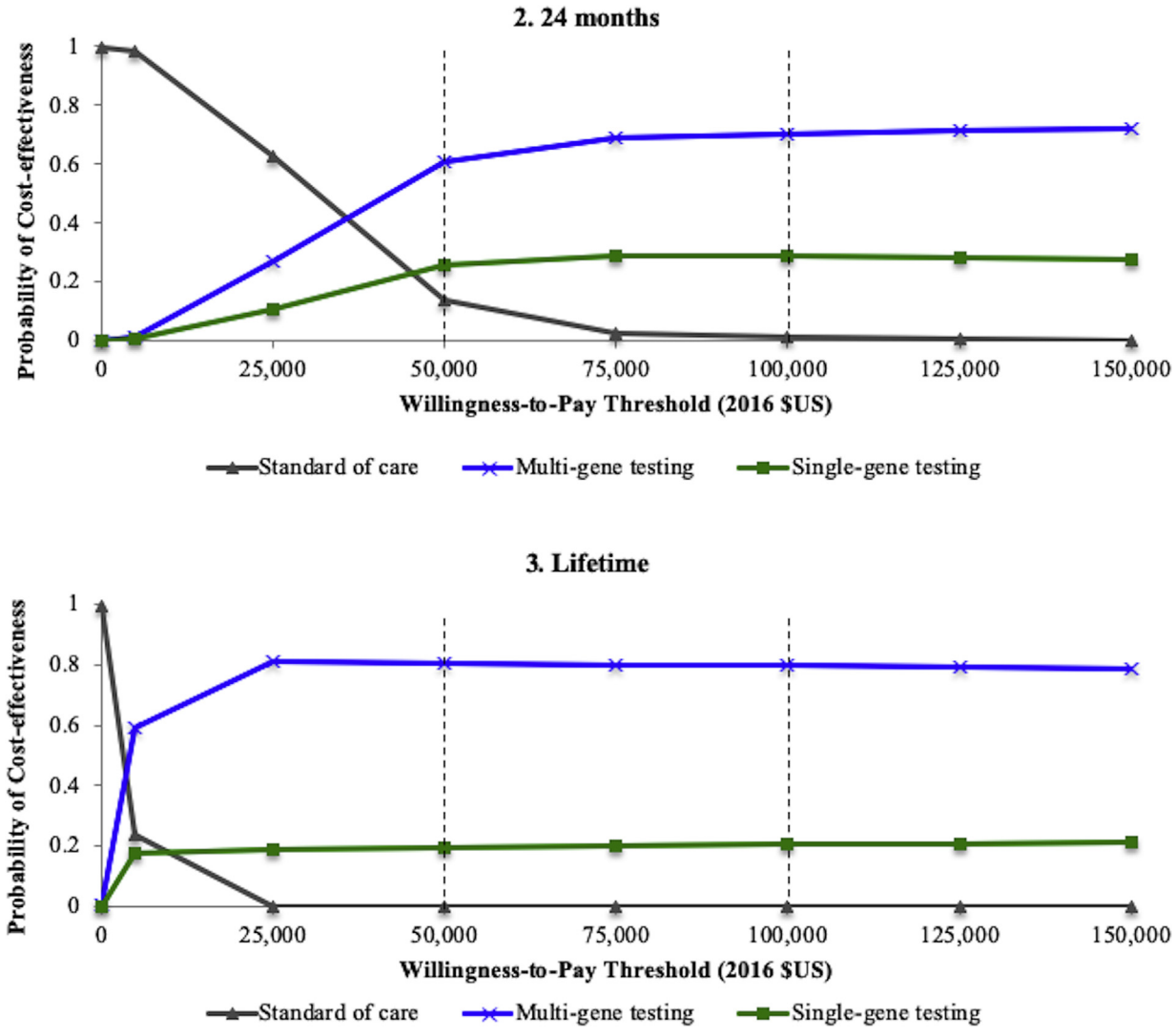
The results of these cost-effectiveness analyses suggest that cost-effectiveness depends on the gene-drug pair being considered and can be limited to specific subpopulations. In this analysis, the cost-effectiveness of multigene testing was largely driven by *CYP2C19* genotype-guided antiplatelet therapy selection, and provided an avenue for the incremental benefits of *SLCO1B1*, *CYP2C9*, and *VKORC1* testing to be used in the drug-prescribing process for patients post-PCI for ACS. The prescribing patterns of

**Figure 3.** Probabilistic sensitivity analysis: cost-effectiveness acceptability curves comparing the probability of cost-effectiveness per QALY gained at various WTP thresholds for standard of care, single-gene testing, and multigene testing at (1) 12 months, (2) 24 months, and (3) lifetime for Medicare beneficiaries with ACS undergoing a PCI for stent placement. Cost and QALYs are discounted at 3% per year. Dashed lines in graph indicate the $50 000 and $100 000 WTP thresholds. Multigene testing had the highest probability of being the most cost-effective strategy starting at a WTP threshold of approximately $58 000 at 12 months, approximately $33 000 at 24 months, and approximately $4000 over the lifetime. Multigene testing remained the strategy with the highest probability of being cost-effective at increasing WTP thresholds across all time horizons.




ACS indicates acute coronary syndrome; multigene testing, *CYP2C19, SLCO1B1, CYP2C9,* and *VKORC1*; PCI, percutaneous coronary intervention; QALY, quality-adjusted life year; single-gene testing, *CYP2C19*; standard of care, no genotyping; WTP, willingness-to-pay.

**Figure 3.** Continued.




antiplatelet therapies may differ from this simulation in the future, and as the main driver of cost-effectiveness, the benefits of the genetic testing interventions are likely to be lower if prescribing rates of clopidogrel decrease.

Although there are 84 drugs in various therapeutic areas with actionable pharmacogenetic guidance,[40] this analysis was limited to 3 major cardiovascular medications that have associated pharmacogenetic guidance and are likely to be prescribed to patients post-PCI for ACS. The benefits of multigene testing are likely underestimated in this analysis because these patients will likely require additional drugs with CPIC guidance beyond cardiovascular medications, such as antidepressants.[8] Future cost-effectiveness analyses investigating additional relevant gene-drug pairs beyond the cardiovascular therapeutic area are needed to understand the comprehensive benefits multigene testing can provide this population.

Additional limitations must be considered when interpreting the results given the simplifications that were made to project future cost and health consequences for this cohort. First, because there are limited data on the health state utilities for multiple comorbidities, health utilities for single comorbidities were used in the model. This may underestimate the actual health states of patients in this cohort who experienced multiple comorbidities and, as a result, underestimate the number of QALYs gained in the genotyping interventions where events were avoided. In addition, because this population starts out with reduced QALYs because of comorbidities, gains in QALYs are not as pronounced as they would be if healthier populations were simulated. To estimate the event probabilities from studies, a fixed event rate was assumed over time for the entire cohort because patient-level time-to-event data are not available to estimate the change in event risk over time more accurately. Additionally, generalizations beyond US Medicare beneficiaries post-PCI for ACS are limited, and findings are not tailored to reflect subgroups within this patient population. A major assumption in this analysis was successful interoperability in the healthcare system that ensured pharmacogenetic results remained accessible for patients over time to guide future treatment decisions. Lastly, it was assumed that

genetic information was used 100% of the time to guide drug-prescribing decisions, which may overestimate use in clinical practice.

Despite these limitations, this analysis offers valuable insight into the potential benefits that multigene testing could provide for Medicare beneficiaries post-PCI for ACS. The added *SLCO1B1* and *CYP2C9/VKORC1* information was relevant in achieving better cardiovascular outcomes and indicates that information gained from multigene testing is beneficial for this population. The findings from this analysis highlight the importance of infrastructure within the healthcare system to store these results in the EHR and allow pharmacogenetic test results to follow patients across time. A mechanism to alert future clinicians that pharmacogenetic testing has been completed in their patients to ensure that the information is accessible is needed for successful implementation and has been a key component of pharmacogenetic studies at major medical centers that have already implemented multigene testing.[5,53-55]

## Conclusions

On the basis of projected simulations, the results suggest that multigene testing (*CYP2C19*, *SLCO1B1, CYP2C9, VKORC1*) is a potentially cost-effective strategy that may help optimize medication selection for Medicare beneficiaries post-PCI for ACS. This was the case when multigene testing was compared with standard of care (no genotyping) and single-gene testing (*CYP2C19*) at 12 months, 24 months, and over the lifetime if the WTP threshold is $100 000/QALY gained, and over 24 months and the lifetime if the WTP threshold is $50 000/QALY gained.

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## Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.08.002.

## REFERENCES

1. Relling MV, Evans WE. Pharmacogenomics in the clinic. *Nature*. 2015;526(7573):343–350.
2. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther*. 2013;94(3):317–323.
3. Lee JA, Lee CR, Reed BN, et al. Implementation and evaluation of a CYP2C19 genotype-guided antiplatelet therapy algorithm in high-risk coronary artery disease patients. *Pharmacogenomics*. 2015;16(4):303–313.
4. Weitzel KW, Elsey AR, Langaee TY, et al. Clinical pharmacogenetics implementation: approaches, successes, and challenges. *Am J Med Genet C Semin Med Genet*. 2014;166C(1):56–67.
5. Pulley JM, Denny JC, Peterson JF, et al. Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project. *Clin Pharmacol Ther*. 2012;92(1):87–95.
6. Johnson JA, Burkley BM, Langaee TY, Clare-Salzler MJ, Klein TE, Altman RB. Implementing personalized medicine: development of a cost-effective customized pharmacogenetics genotyping array. *Clin Pharmacol Ther*. 2012;92(4):437–439.
7. Hayden EC. Technology: the $1,000 genome. *Nature*. 2014;507(7492):294–295.
8. Dong OM, Li A, Suzuki O, et al. Projected impact of a multigene pharmacogenetic test to optimize medication prescribing in cardiovascular patients. *Pharmacogenomics*. 2018;19(9):771–782.
9. Ramsey LB, Johnson SG, Caudle KE, et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. *Clin Pharmacol Ther*. 2014;96(4):423–428.
10. Hernandez I, Saba S, Zhang Y. Geographic variation in the use of oral anticoagulation therapy in stroke prevention in atrial fibrillation. *Stroke*. 2017;48(8):2289–2291.
11. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. *Clin Pharmacol Ther*. 2017;102(3):397–404.
12. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):e199–e267.
13. Mega JL, Walker JR, Ruff CT, et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet*. 2015;385(9984):2280–2287.
14. Keeling NJ, Rosenthal MM, West-Strum D, Patel AS, Haidar CE, Hoffman JM. Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers. *Genet Med*. October 2017. https://doi.org/10.1038/gim.2017.181.
15. Jiang M, You JH. Review of pharmacoeconomic evaluation of genotype-guided antiplatelet therapy. *Expert Opin Pharmacother*. 2015;16(5):771–779.
16. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med*. 2013;158(7):526–534.
17. Kim K, Lee TA, Touchette DR, DiDomenico RJ, Ardati AK, Walton SM. Contemporary trends in oral antiplatelet agent use in patients treated with percutaneous coronary intervention for acute coronary syndrome. *J Manag Care Spec Pharm*. 2017;23(1):57–63.
18. Rosenson RS, Farkouh ME, Mefford M, et al. Trends in use of high-intensity statin therapy after myocardial infarction, 2011 to 2014. *J Am Coll Cardiol*. 2017;69(22):2696–2706.
19. Danik JS, Chasman DI, MacFadyen JG, Nyberg F, Barratt BJ, Ridker PM. Lack of association between SLCO1B1 polymorphisms and clinical myalgia following rosuvastatin therapy. *Am Heart J*. 2013;165(6):1008–1014.
20. Group SC, Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy—a genomewide study. *N Engl J Med*. 2008;359(8):789–799.
21. Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D, Ebrahim S. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. *BMC Med*. 2014;12:51.
22. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes*. 2012;5(1):85–93.
23. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001–2015.
24. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045–1057.
25. Jin B, Ni HC, Shen W, Li J, Shi HM, Li Y. Cytochrome P450 2C19 polymorphism is associated with poor clinical outcomes in coronary artery disease patients treated with clopidogrel. *Mol Biol Rep*. 2011;38(3):1697–1702.
26. Hulot JS, Collet JP, Silvain J, et al. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. *J Am Coll Cardiol*. 2010;56(2):134–143.
27. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292(11):1307–1316.
28. Shi C, Yan W, Wang G, Wang F, Li Q, Lin N. Pharmacogenetics-based versus conventional dosing of warfarin: a meta-analysis of randomized controlled trials. *PLoS One*. 2015;10(12):e0144511.
29. Li X, Yang J, Wang X, Xu Q, Zhang Y, Yin T. Clinical benefits of pharmacogenetic algorithm-based warfarin dosing: meta-analysis of randomized controlled trials. *Thromb Res*. 2015;135(4):621–629.
30. Good Rx. https://www.goodrx.com/. Accessed July 23, 2018.
31. Centers for Medicare and Medicaid Services. Clinical Laboratory Fee Schedule Files. Clinical Laboratory Fee Schedule. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Inpatient2015.html. Accessed June 7, 2018.
32. Borse MS, Dong OM, Polasek MJ, Farley JF, Stouffer GA, Lee CR. CYP2C19-guided antiplatelet therapy: a cost–effectiveness analysis of 30-day and 1-year outcomes following percutaneous coronary intervention. *Pharmacogenomics*. 2017;18(12):1155–1166.
33. Jarmul J, Pletcher MJ, Hassmiller Lich K, et al. Cardiovascular genetic risk testing for targeting statin therapy in the primary prevention of atherosclerotic cardiovascular disease: a cost-effectiveness analysis. *Circ Cardiovasc Qual Outcomes*. 2018;11(4):e004171.
34. Centers for Medicare and Medicaid Services. Inpatient Charge Data FY 2015. Medicare Provider Utilization and Payment Data. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Inpatient2015.html. Accessed May 24, 2018.
35. Hernandez I, Smith KJ, Zhang Y. Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial

fibrillation at high risk of bleeding and normal kidney function. *Thromb Res*. 2017;150:123–130.
36. Choudhry NK, Patrick AR, Antman EM, Avorn J, Shrank WH. Cost-effectiveness of providing full drug coverage to increase medication adherence in post-myocardial infarction Medicare beneficiaries. *Circulation*. 2008;117(10):1261–1268.
37. Cowper PA, Pan W, Anstrom KJ, et al. Economic analysis of ticagrelor therapy from a U.S. perspective: results from the PLATO study. *J Am Coll Cardiol*. 2015;65(5):465–476.
38. Lala A, Berger JS, Sharma G, Hochman JS, Scott Braithwaite R, Ladapo JA. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a cost-effectiveness analysis. *J Thromb Haemost*. 2013;11(1):81–91.
39. Jiang M, You JH. Cost-effectiveness analysis of personalized antiplatelet therapy in patients with acute coronary syndrome. *Pharmacogenomics*. 2016;17(7):701–713.
40. Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. *Pharmacoeconomics*. 2006;24(10):1021–1033.
41. Ademi Z, Pasupathi K, Liew D. Clinical and cost effectiveness of apixaban compared to aspirin in patients with atrial fibrillation: an Australian perspective. *Appl Health Econ Health Policy*. 2017;15(3):363–374.
42. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *Br Med Bull*. 2010;96:5–21.
43. Pletcher MJ, Pignone M, Earnshaw S, et al. Using the coronary artery calcium score to guide statin therapy: a cost-effectiveness analysis. *Circ Cardiovasc Qual Outcomes*. 2014;7(2):276–284.
44. Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2018;11(2):181–191.
45. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA*. 2010;304(16):1821–1830.
46. Zhang H, Plutzky J, Shubina M, Turchin A. Continued statin prescriptions after adverse reactions and patient outcomes: a cohort study. *Ann Intern Med*. 2017;167(4):221–227.
47. United States Department of Labor Bureau of Labor Statistics. Consumer Price Index (CPI) Database. https://www.bls.gov/cpi/data.htm. Accessed July 23, 2018.
48. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press; 2007.
49. DuGoff EH, Canudas-Romo V, Buttorff C, Leff B, Anderson GF. Multiple chronic conditions and life expectancy: a life table analysis. *Med Care*. 2014;52(8):688–694.
50. Barton GR, Briggs AH, Fenwick EA. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). *Value Health*. 2008;11(5):886–897.
51. Eckman MH, Rosand J, Greenberg SM, Gage BF. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Ann Intern Med*. 2009;150(2):73–83.
52. Patrick AR, Avorn J, Choudhry NK. Cost-effectiveness of genotype-guided warfarin dosing for patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2009;2(5):429–436.
53. Hoffman JM, Haidar CE, Wilkinson MR, et al. PG4KDS: a model for the clinical implementation of pre-emptive pharmacogenetics. *Am J Med Genet C Semin Med Genet*. 2014;166C(1):45–55.
54. Gottesman O, Scott SA, Ellis SB, et al. The CLIPMERGE PGx Program: clinical implementation of personalized medicine through electronic health records and genomics-pharmacogenomics. *Clin Pharmacol Ther*. 2013;94(2):214–217.
55. Bielinski SJ, Olson JE, Pathak J, et al. Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time-using genomic data to individualize treatment protocol. *Mayo Clin Proc*. 2014;89(1):25–33.