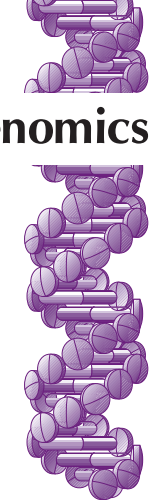
Research Article

Pharmacogenomics



Early health technology assessments in pharmacogenomics: a case example in cardiovascular drugs

Aim: To assess the required characteristics (cost, sensitivity and specificity) of a pharmacogenomic test for being a cost-effective prevention of angiotensin-converting enzyme inhibitors induced angioedema. Furthermore, we assessed the influence of only testing high-risk populations. **Materials & methods:** A decision tree was used. **Results:** With a willingness-to-pay threshold of €20,000 and €80,000 per quality adjusted life year, a 100% sensitive and specific test may have a maximum cost of €1.30 and €1.95, respectively. When only genotyping high-risk populations, the maximum test price would be €5.03 and €7.55, respectively. **Conclusion:** This theoretical pharmacogenomic test is only cost-effective at high specificity, high sensitivity and a low price. Only testing high-risk populations yields more realistic maximum test prices for cost–effectiveness of the intervention.

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The use of pharmacogenomics is becoming more common in daily clinical practice. In many cases it improves patient outcomes by predicting the response to drugs or adverse events, allowing healthcare providers to adjust treatment accordingly [1]. Recent literature shows variation in the performance of pharmacogenomics: it varies from a large effect with a large increase in efficiency to a large increase of costs per patient without much benefit [2]. Technology in pharmacogenomics is advancing and the number of known SNPs impacting pharmacological treatment is rapidly increasing.

Since both the advancement of technology as well as an aging population cause an increased pressure on healthcare budgets, cost–effectiveness of innovations is on the healthcare policy agenda of many countries. To determine the coverage of innovations from public funds, several countries use a threshold which indicates the maximum costs to be paid for the gain of one extra quality adjusted life year (QALY) by the new intervention [3]. For the UK for example, the threshold is indicated at £30,000 per QALY. For The Netherlands, the discussion on the threshold is ongoing. The current thresholds range from €20,000 to €80,000 per QALY gained, based on disease burden [4].

The price of testing as well as the effect of genetic variation on treatment response or adverse events is often unknown. From a health system perspective it is therefore important to assess, at an early stage, the impact of a test in daily practice. When price and the sensitivity (true positive rate) and specificity (true negative rate) of the test are still unknown, the estimation of cost–effectiveness is done in a turn-around analysis: investigate the

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required specifications that would make the test a cost-effective diagnostic. The threshold for costs per QALY is used as the basis of this evaluation. By evaluating an intervention at an early stage, its value becomes clear early and this can inform either further research, an implementation trajectory or an exit strategy.

In this study, we take a case example of an early HTA assessment of the prediction of angioedema caused by the use of angiotensin-converting enzyme inhibitors (ACEi). ACEis are among the most frequently prescribed drugs and serve as an important treatment modality for several, highly prevalent cardiovascular indications [5–7]. They are generally well tolerated. Nonproductive, persistent cough is the most common adverse drug reaction (ADR) and occurs in approximately 9% of ACEi users [8]. Besides this mild and well-known ADR, ACEis can cause the rare ACEi-induced angioedema, a serious and frightening sudden swelling of the upper airways that can be fatal [6,7,9–11].

ACEi-induced angioedema is characterized by a transient, localized swelling of the deep reticular dermis, subcutaneous or submucosal tissues of the head and neck region and occasionally the viscera [12]. It frequently affects the face, lips, tongue and upper airways and is usually accompanied by symptoms such as a lump in the throat, hoarse voice and difficulties in swallowing and breathing [12]. Typically, ACEi-induced angioedema develops over 4–6 h and resolves within 1–2 days [12,13]. Rare lethal cases with severe airway obstruction have also been reported [6,7]. The factors predisposing to ACEi-induced angioedema are not fully elucidated. Among clinical risk factors of ACEi-induced angioedema are female sex, age over 65 years, African–American ethnicity, local trauma, smoking, history of drug rash, Type 2 diabetes, seasonal allergies and ACEi-induced cough. The mechanism of ACEi-induced angioedema is thought to involve the accumulation of bradykinin, due to a dysregulation of its inactivation by ACE and alternative enzymes [14]. Genetic variants identified in the *MME* gene and the *XPNPEP2* gene, belonging to the bradykinin degradation pathway, could contribute to the development of angioedema (AE) in some of the patients [14]. However, the effect of genetic variation on the susceptibility to AE caused by ACE is is yet to be fully uncovered.

The identification of patients at risk of ACEi-induced angioedema using a pharmacogenomic test prior to treatment initiation could prevent harm caused by this ADR and reduce healthcare expenses.

Hence, the goal of this study is to assess required test characteristics (cost, sensitivity and specificity) in order for the test to be a cost-effective measure for preventing ACEi-induced angioedema. In addition, we investigate the benefits of only testing specific populations that are known to have an increased risk of developing this serious ADR.

Materials & methods

We used a decision-tree model to compare genotyping versus no genotyping prior to starting an ACEi. The model reflects the patient pathway and is depicted in Figure 1. In constructing the model we conformed to the ISPOR Modeling Good Research Practices [15]. As angioedema risk is greatest immediately after starting an ACEi and because of scarce data on angioedema risk in long-term ACEi use, a decision tree was the preferred model to simulate patient pathways.

Angioedema incidence

ACEi-induced angioedema incidence rates (per 1000 person-years) have been reported to be in the 1.97–4.38 range in observational studies by Miller *et al.* and Toh *et al.* [16,17]. The OCTAVE randomized controlled trial (omapatrilat vs enalapril) by Kostis *et al.* reported 0.68% of patients developing angioedema during 24 weeks of follow-up [18]. Cumulative incidence of 1.79 (1.73–71.85) per 1000 persons reported by Toh *et al.* was used for model input, based on 3301 events in 1,845,138 exposed persons. Three hundred and twenty-six (9.88%) of these events were classified as 'serious', indicating the need for in-patient care [17].

ACEi treatment characteristics

After the initial ACEi prescription, patients stop and/or switch to another drug class in up to 44% of cases [19,20]. However, it is unlikely that switching and discontinuation patterns are influenced by being genotyped for angioedema prior to starting an ACEi. We therefore assume that all patients stay on the ACEi for 1 year unless they develop angioedema or receive a positive diagnosis by genomic assay. In these cases, according to guidelines, they are switched to another antihypertensive. The price of 'other antihypertensive' is the weighed per person average of the cost per user × number of users of ATC-classes C03 (diuretics), C08 (calcium antagonists) and C07 (beta-blockers), yielding an average cost per user per year of €23.77. This is higher than the annual per user cost of ACEis at €13.62 [21,22]. The difference between these two treatments (€10.15) is used as model input. Supplementary Table 1 presents the data used for calculating treatment costs.

Subgroups

Subgroups of patients with an increased risk for developing ACEi-induced angioedema have been identified by Miller *et al.* [16]. People from African ancestry are at highest risk for developing ACEi-induced angioedema, as shown in Table 1.

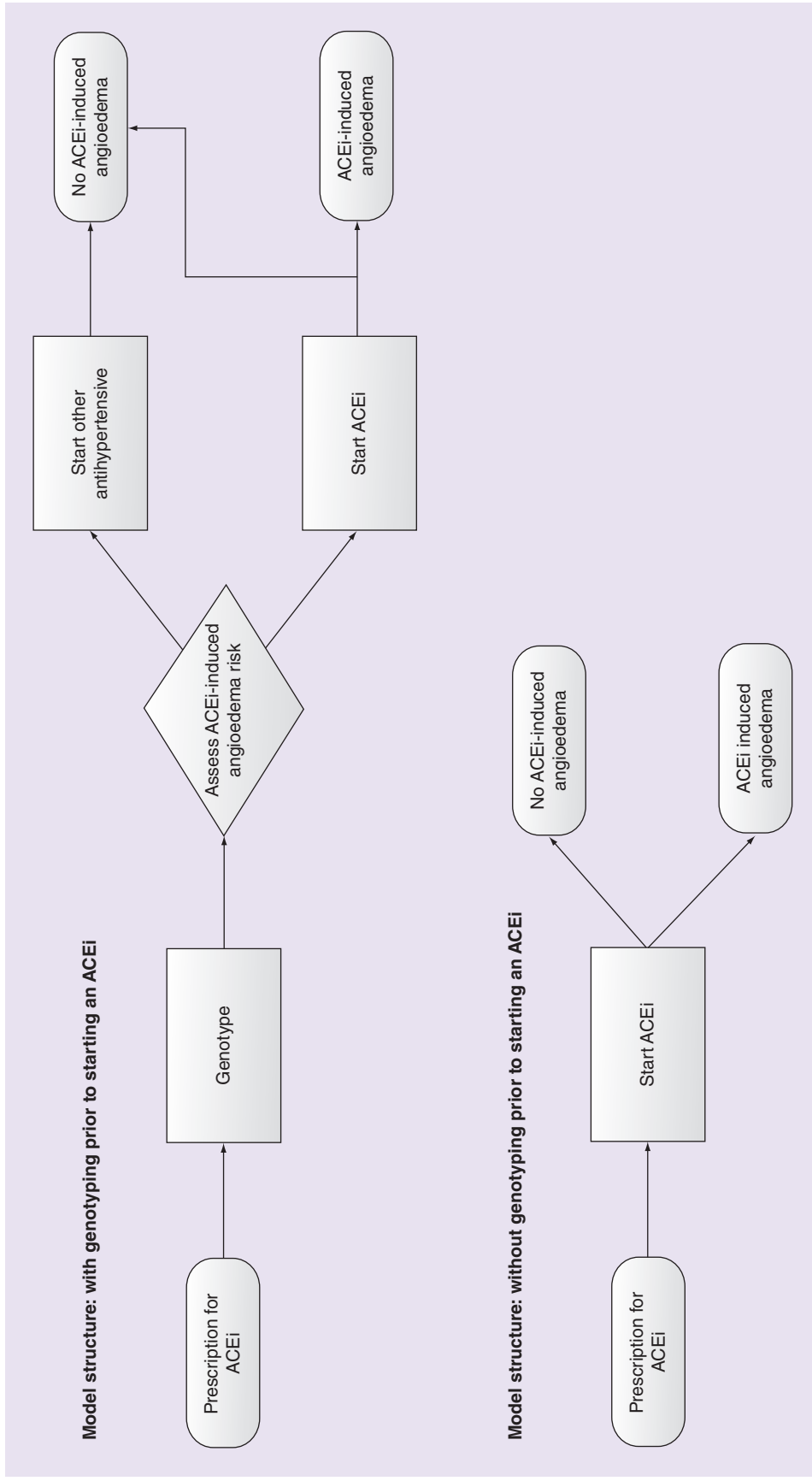

Figure 1. Model structures used.
ACEi: Angiotensin-converting enzyme inhibitors.

Table 1. Subgroups with increased risk of developing angiotensin-converting enzyme inhibitors induced angioedema.

Risk factor	OR/HR
African ancestry	RR: 3.88
Age 65–74	RR: 1.42
Female gender	RR: 1.45

Data taken with permission from [16].

Estimation of QALYs

Mortality due to ACEi-related angioedema is extremely rare but, per case, results in a large loss of QALYs. Evidence on mortality is scarce and is mainly available in the form of case reports. To estimate mortality risk, studies that recorded intensive care unit (ICU) admittance or direct mortality due to angioedema, were selected. The selected studies are shown in Supplementary Table 2. We assumed that all lethal cases would be admitted to the ICU. Then, lethal cases were divided by the total number of patients with angioedema admitted to the ICU to yield a mortality probability of 0.66% per ICU admittance. The average ACEi starter was 62 years old [23]. QALYs lost by premature mortality were calculated using life expectancy data from Statistics Netherlands and data on quality of life per age group, yielding 17.20 QALYs [24,25].

Utilities

By making assumptions regarding answers to the validated EQ5D questionnaire and using the Dutch value set to calculate utility scores, specific health state utilities were generated [26].

Costs – resource use

Banerji *et al.* assessed the percentage of ACEi-induced angioedema among all patients with angioedema presenting to the emergency department and described their healthcare requirements [27]. We combined these results with the data presented by Toh *et al.* to calculate the fraction of ICU stays of per total in-patient stays [17]. ICU stays were further specified

Table 2. Model parameters and probability distributions.

Parameter	Value	Distribution	EQ5D input
Probability of visiting ED†	0.4256	Fixed	
Probability of observational stay at ED†	0.0773	Beta	
Probability of patient stay (regular ward)†	0.0515	Beta	
Probability of ICU stay†	0.0472	Beta	
Probability of ambulance†	0.1141	Beta	
Probability of visiting GP†	0.574	Beta	
Incidence rate of angioedema (per 1000)	1.79	Beta	
Probability of mortality†	0.0004	Beta	
Cost of visiting ED (€)	170.59	Fixed	
Cost of observational stay at ED (€)	283.56	Fixed	
Cost of in-patient stay (regular ward) (€)	737.14	Fixed	
Cost of ICU stay (€)	8434.26	Fixed	
Cost of requiring ambulance (€)	331.00	Fixed	
Cost of visiting GP (€)	28.00	Fixed	
Additional cost on other antihypertensive (€)	10.15	Fixed	
Utility during ED visit	0.569	Fixed	33333
Utility during observational stay at ED	0.569	Fixed	33333
Utility during in-patient stay (regular ward)	0.569	Fixed	33333
Utility during ICU stay	0.115	Fixed	55533
Utility during GP visit	0.638	Fixed	22222
Quality of Life lost by fatal angioedema	17.78	Fixed	

†Probability is per angioedema event.
ED: Emergency department; GP: General practitioner; ICU: Intensive care unit.

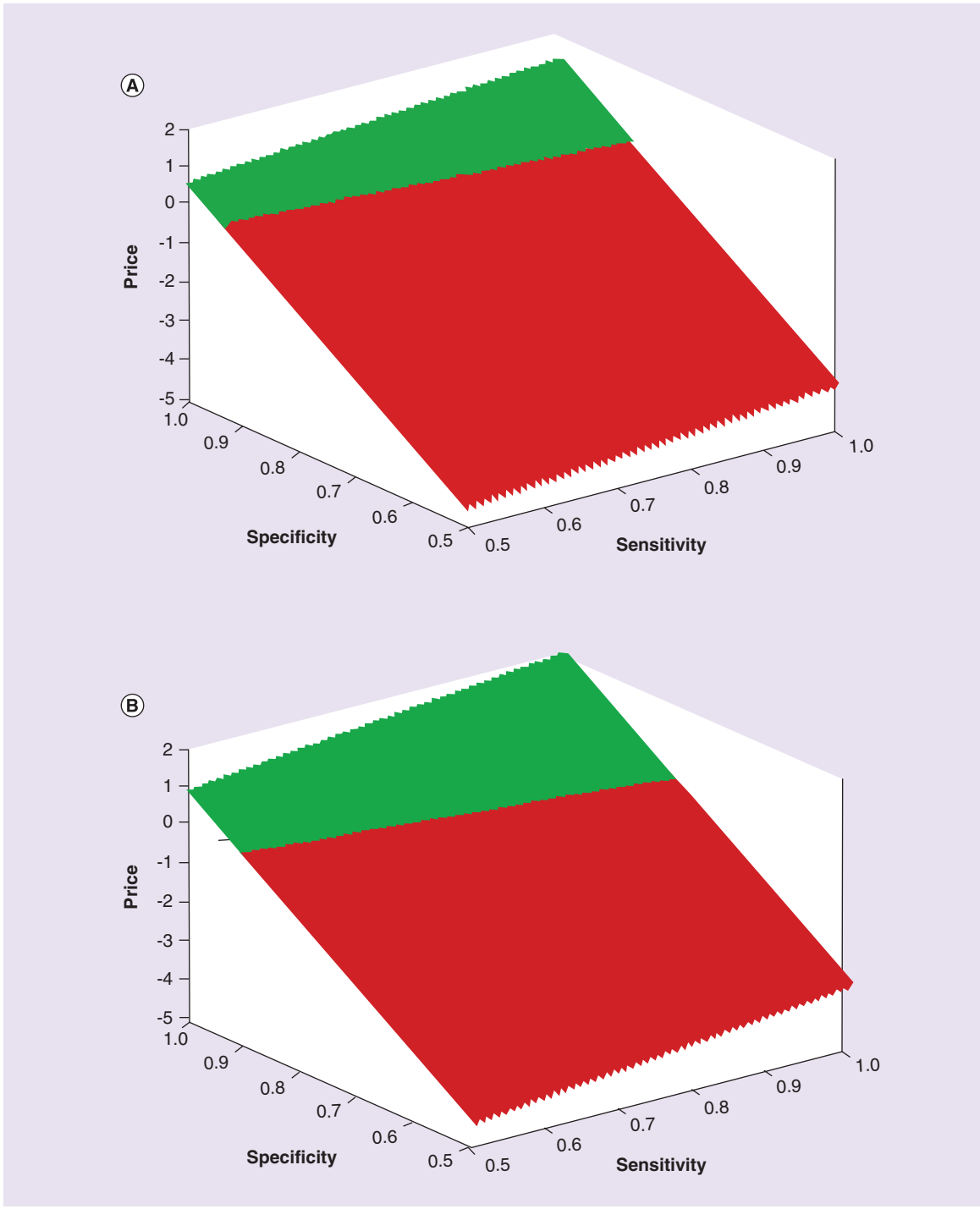

Figure 2. Base-case results. (A) Maximum test price to meet a willingness-to-pay threshold of €20,000. **(B)** Maximum test price to meet a willingness-to-pay threshold of €80,000.

using data from Soo Hoo *et al.* [28]. They investigated ACEi-induced angioedema requiring ICU admission, yielding data on hospitalization duration [28]. Drug utilization for the treatment of angioedema was not assessed as these costs are included in reference prices for hospital admittance.

Costs – prices

Costs for in-patient stays, general practitioner and emergency department visits and ambulance use were based on reference prices published by the Dutch Manual for Costing in Economic Evaluations [29]. Drug utilization and costs were retrieved from The Drug Information

System and The Pharmacy Purchase Price database of the Dutch National Healthcare Institute [21,22]. All costs are in Euros and, if applicable, indexed to 2016. Because of the 1-year time horizon, discounting of future costs and effects was not necessary.

Analysis

The main outcome was the incremental cost–effectiveness ratio (ICER) which is the ratio indicating the extra costs per QALY gained. In the OCTAVE-randomized controlled trial, significantly more patients experienced

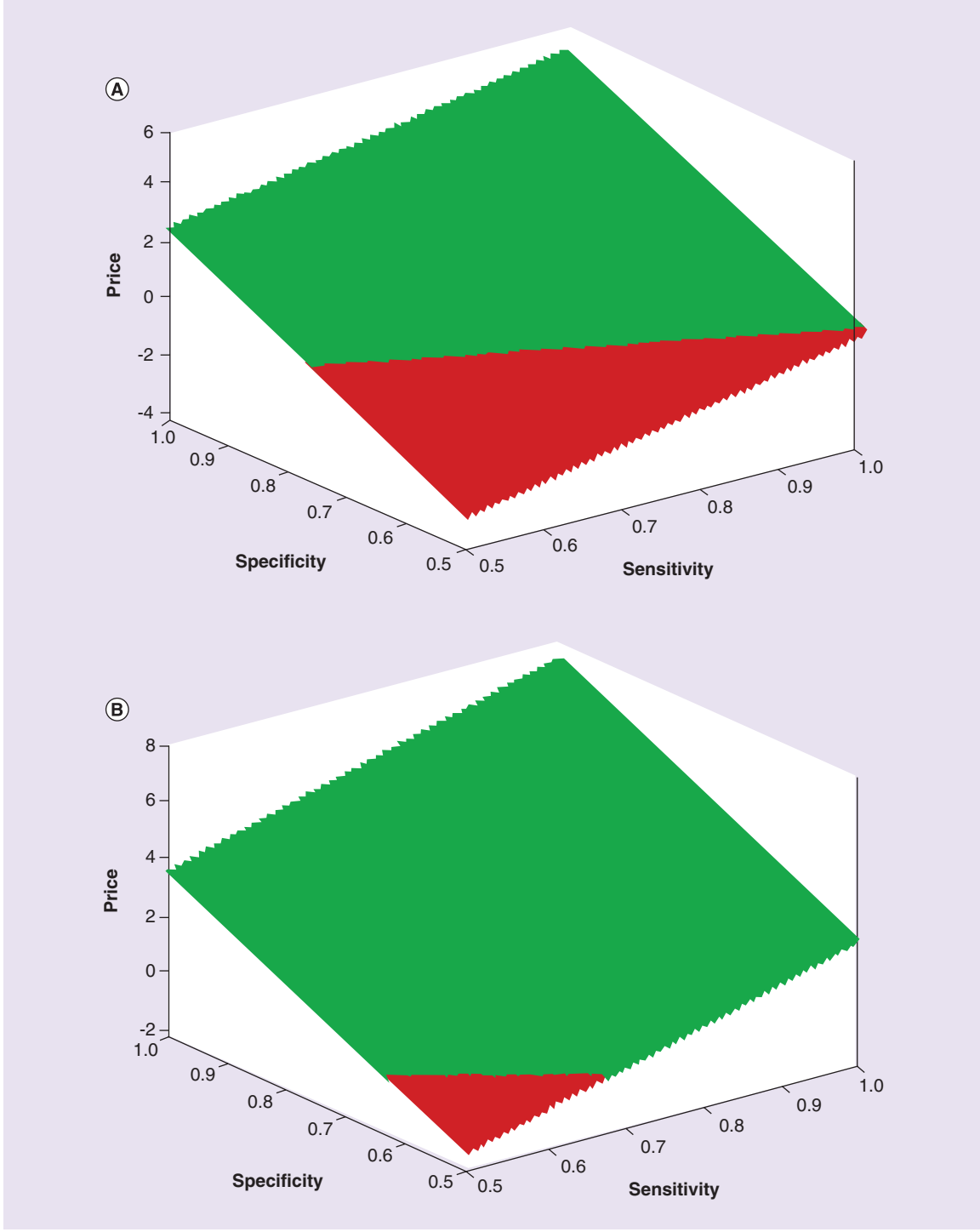

Figure 3. Subgroup results. (A) Maximum test price when only testing people of African ancestry (HR = 3.88) to meet a willingness-to-pay threshold of €20,000. **(B)** Maximum test price when only testing people of African ancestry (HR = 3.88) to meet a willingness-to-pay threshold of €80,000.

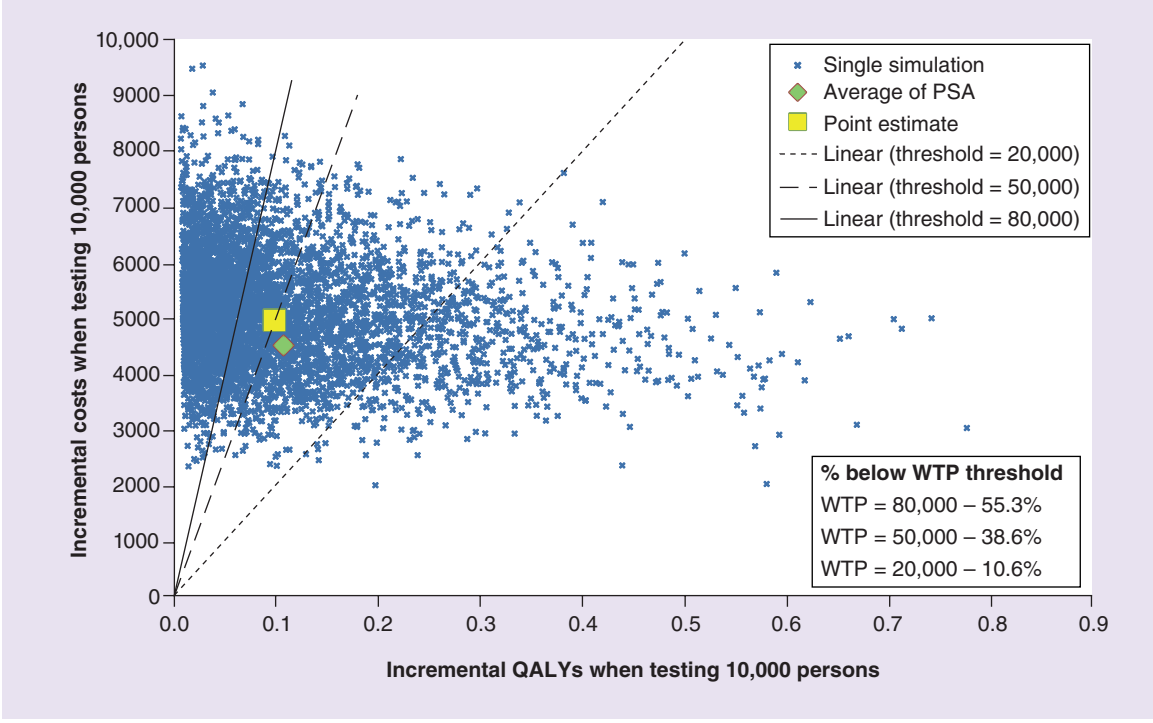

Figure 4. Probabilistic sensitivity analysis. Parameters used: 5000 simulations, fixed test price = €0.50, fixed test sensitivity = 90%, fixed test specificity = 90%.

angioedema in the first month of treatment (3.6/1000 vs 0.4/1000 after 24 weeks of follow-up) [18,30]. Observational studies by Toh *et al.* and Miller *et al.* reported that respectively 66 and 55% of events occurred in the first 90 days after ACEi initiation [16,17]. Based on these findings, we assume a 1-year time frame for the development of angioedema and all related healthcare utilization. Model parameters are shown in Table 2. Model parameter sensitivity was assessed by probabilistic and deterministic sensitivity analysis (DSA). In a deterministic sensitivity analyses the robustness of the model is tested for variations between the extremes of a plausible range of all parameters. In a probabilistic sensitivity analysis (PSA) uncertainty of the analysis is examined by first constructing distributions for all parameters in the model. Second, the model picks a random value for all parameters from these distributions and the results are recalculated. This is repeated 5000 times and the results are depicted in a scatterplot. We did not vary the cost components as these are based on reference prices.

Results

Base-case

The influence of sensitivity, specificity and test price on the ICER are shown in Figure 2A & B. Data points represent the test price at which the ICER exactly matches the WTP threshold. A red point reflects a negative test price and a green point reflects a positive test price.

With a willingness-to-pay (WTP) threshold of €20,000 and €80,000 per QALY, a 100% sensitive and 100% specific test has a maximum cost of €1.30 and €1.95, respectively. A free and 100% sensitive test must at least be 87 and 81% specific to be cost-effective at aforementioned WTP thresholds. The ICER of a free and 100% specific test is, only in this scenario, not influenced by sensitivity as it is free anyway and does, therefore, not generate false positives. At 90% specificity, a free test should be at least 79% and 52% sensitive for €20,000 and €80,000 WTP thresholds.

A change in specificity has a 3.5-fold higher impact on the ICER than a change in sensitivity. This is due to the additional cost of switching to another, more expensive, antihypertensive treatment in the case of false positives. False negatives do not cause additional costs; they only lower the maximum but ever positive price, indicated by a green dot at 100% specificity and lowest (50%) sensitivity.

Subgroups

Limiting genotyping to individuals at higher risk for ACEi-induced angioedema has a profound influence on test requirements. Figure 3A & B displays the relation between test parameters and the maximum price to meet WTP thresholds of €20,000 and €80,000, respectively. In this scenario, a perfect test meets the WTP thresholds at €5.03 and €7.55. The bandwidth

for a positive test price has increased dramatically, as well as the spread between the two WTP thresholds. The requirement of a high specificity is no longer present: For a 100% sensitive test costing €3.00, the minimum specificity is 81 and 56% for aforementioned thresholds. Besides, the influence of specificity versus sensitivity lowered from ±3.5:1 to 1:1.

Probabilistic sensitivity analysis

PSA was based on a 90% sensitive and 90% specific test costing €0.50. Results, shown in Figure 4, indicate 100% probability for both QALY gain and higher costs. Furthermore, there is a 10.6 and 55.3% probability of meeting €20,000 and €80,000 WTP thresholds, respectively. The base case ICER at specified parameters is €56,896. The PSA results are higher and lower than this base case in 57 and 43% of cases.

Deterministic sensitivity analysis

DSA, shown in Figure 5, was also performed with a 90% sensitive and 90% specific test costing €0.50. Incidence rate of angioedema resulted in the largest effect, followed by the additional cost of 'other antihypertensive'. ICU admission and mortality have a

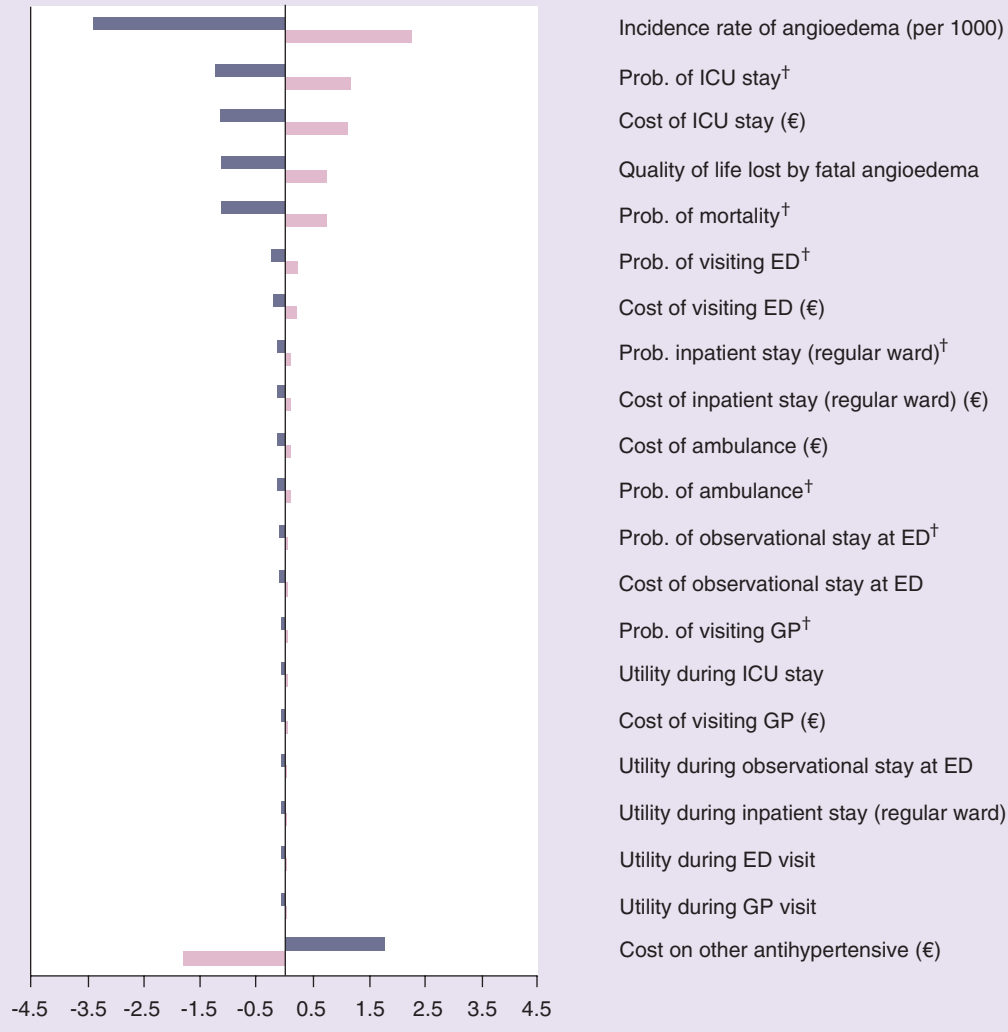

Figure 5. Deterministic sensitivity analysis. X-axis indicates the magnitude of the difference in ICER compared with a parameter. Pink indicates a negative parameter change, purple a positive change. Parameters used: fixed test price = €0.50, fixed test sensitivity = 90%, fixed test specificity = 90%. The x-axis indicates the factor of the response versus a change in a parameter.
†Probability is per angioedema event.
ED: Emergency department; GP: General practitioner; ICU: Intensive care unit.
For color figures please see http://www.futuremedicine.com/doi/full/10.2217/pgs-2017-0063

substantial effect on the ICER. The other parameters have a small or negligible influence.

Discussion

We evaluated the specifications of a pharmacogenomic test for preventing ACEi-induced angioedema in terms of the required specificity, sensitivity and price for achieving cost–effectiveness. Our findings indicate that testing all ACEi starters is unlikely to be cost-effective as >90% specificity, >93% sensitivity and a low (<€1.00) price would be required.

Our results highlight that a focused approach on testing high-risk populations can be a fruitful endeavor for increasing cost–effectiveness. This statement is further supported by the DSA demonstrating a major influence of angioedema incidence on the ICER. Miller *et al.* reported a relative risk of 3.88 and 1.45 for people of African–American ethnicity and for women, respectively. In our model this had a profound positive impact on parameter requirements. Further clarification of risk factors, for example women of African–American ethnicity, could prove to lower diagnostic accuracy and test price to more favorable ranges that could warrant actual development of a pharmacogenomic test for this specific indication.

Nevertheless, individual tests for rare ADRs may not be very efficient. Plumpton and colleagues have shown that single testing is not always cost-effective, even when a proper biomarker or SNP is present [1]. Their results indicate that mainly human leukocyte antigen polymorphisms are cost-effective single targets. These human leukocyte antigen polymorphisms predispose for hypersensitivity reactions, sometimes leading to very severe ADRs like Stevens–Johnson Syndrome and toxic epidermal necrolysis, induced by carbamazepine, abacavir and allopurinol. Not only are these ADRs more severe with mortality ranging from 10 to 40% for toxic epidermal necrolysis, incidence rates of up to 5% are much higher than incidence rates of ACEi-induced angioedema [1,31].

There could be a solution to biomarkers that do have value but are too costly to implement separately: combine many of these tests into a single package or perform them together with a test that will be performed in routine daily practice. This way, the fixed costs of sampling, transport to a lab and reporting the results are spread and incremental costs per test could decrease dramatically. We can extend the idea of combining tests to whole exome or whole genome sequencing. Currently, these sequencing techniques are considered to be too costly for implementation in routine practice but prices have been falling dramatically [32]. When efforts are focused toward making sequencing a routine part of daily clinical practice, all future genomic markers will deliver additional benefit to patients, regardless of the rarity of the predictor. Sadly, the full potential value that innovations may deliver in the future cannot be captured in traditional cost–effectiveness analysis.

The two most important limitations of our study need to be addressed. First, the DSA indicates a strong influence of the additional cost of antihypertensive treatment. This is the cost of a false positive case. In Dutch practice, switching to another antihypertensive is more expensive than ACEi treatment. This price difference is likely to be country specific. In other jurisdictions where ACEi treatment is more expensive than other antihypertensive treatment, the genotyping strategy would result in drug-cost savings in the event of a (false) positive diagnosis.

Second, model parameters were based on multiple studies with different study designs possibly leading to biased estimates. Especially our assessment of mortality risk was based on suboptimal evidence that required some assumptions. However, the DSA indicates a relatively low influence of mortality risk on model outcomes. Utility scores were assessed by estimating the answers to the EQ5D questionnaire which is clearly suboptimal. The DSA indicates that these parameters have a negligible effect on the results. Furthermore, cost parameters could be underestimated. Only ICU-related costs seem, as shown by the DSA, to have some impact on the ICER.

Conclusion

Our study indicates that testing all patients starting an ACEi for developing angioedema is unlikely to be cost-effective as the test should have a high diagnostic accuracy combined with a sub €2.00 cost. Selectively testing only populations that have an increased risk of developing ACEi-induced angioedema improves test characteristics needed and price for an ICER below €20,000 and €80,000. While separate testing for this variation for all ACEi starters or subgroups is not cost-effective, implementing whole exome or genome sequencing in routine clinical practice will result in economically attractive benefits of finding genetic variations like the one discussed here.

Financial & competing interests disclosure

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Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/pgs-2017-0063

Summary points

- Angiotensin-converting enzyme inhibitors (ACEi) are commonly used cardiovascular drugs. They can cause the severe and possibly lethal adverse drug reaction angioedema in a very small part (0.2%) of the patients. A pharmacogenomic test could be used to identify patients at risk for this severe adverse drug reaction and advise them to use another drug.
- With a willingness-to-pay threshold of €20,000 and €80,000 per quality adjusted life year, a 100% sensitive and specific test may have a maximum cost of €1.30 and €1.95, respectively.
- When only genotyping high-risk populations, the maximum test price would be €5.03 and €7.55, respectively.
- Testing all patients starting an ACEi for developing angioedema is unlikely to be cost–effective as the test should have a high diagnostic accuracy combined with a low price.
- Selectively testing only populations that have an increased risk of developing ACEi-induced angioedema improves test characteristics needed.
- While separate testing for this variation for all ACEi starters or subgroups is not cost-effective, implementing whole exome or genome sequencing in routine clinical practice will result in economically attractive benefits of finding genetic variations like the one discussed here.

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