Cost-effectiveness of Molecular Profile Patient Selection for First-line Treatment of Recurrent/ Metastatic Head and Neck Cancer

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ABSTRACT

Purpose: Patients with recurrent and/or metastatic head and neck squamous cell cancer are offered platinum-based chemotherapy plus cetuximab; however, this strategy is not cost-effective. We evaluated the cost-effectiveness of a hypothetical predictive molecular test to identify and treat only patients potentially responsive to cetuximab (C) added to platinum-fluorouracil (PF) (PF + C POS) versus the administration of PF + C to all patients (PF + C ALL).

Methods: A Markov model has been developed to estimate health outcomes (quality-adjusted life years [QALYs]; life years [LYs]) and costs of the 2 strategies on a time horizon of 3 years from the Italian health care perspective. For the response to treatment, a definition, including partial or complete response, has been applied. In the base-case scenario, molecular test sensitivity, specificity, and cost have been assumed equal to 85%, 70%, and €4000, respectively.

Findings: The model estimated 0.5285 QALYs (0.9245 LYs) and 0.5666 QALYs (0.9949 LYs) for PF + C POS and PF + C ALL, respectively. The incremental cost-utility ratio of PF + C ALL versus PF + C POS was €112,462/QALY, suggesting the administration of PF + C only to patients who would be responsive to it.

Implications: The use of cetuximab with chemotherapy could be a cost-effective choice in first-line recurrent and/or metastatic head and neck squamous cell cancer if based on a molecular selection able to identify which patients will achieve partial or complete response to the treatment. The developed model may be usefully applied to new emerging treatments, such as immunotherapeutic agents in the same setting. (*Clin Ther*. 2019;41:2517–2528)

Keywords: cetuximab, chemotherapy, cost-effectiveness, head and neck cancer, predictive molecular test, recurrent/metastatic setting.

INTRODUCTION

Head and neck squamous cell cancer (HNSCC) accounts for ~3%–4% of all new cancers diagnosed every year, with most cases at locoregional advanced stages (stage III and IV).[1–3] Treatment of advanced HNSCC consists of variable combinations of surgery, radiotherapy, and systemic therapies and yields long-term results (in terms of 5-year overall survival [OS]) in 20%–80% of cases, depending on age, primary disease, stage, human papillomavirus (HPV) status, sex, and performance status.[2,4] Locoregional or distant relapses are usually detected in the first 2 years after treatment completion.[2]

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In the presence of recurrent and/or metastatic (RM) disease, not amenable for salvage surgery and/or irradiation, patients are offered a combination of platinum-based chemotherapy plus cetuximab, a monoclonal antibody directed toward the epidermal growth factor receptor (EGFR). Indeed, when used in combination with chemotherapy, cetuximab has been proved to yield significantly longer survival than with cisplatin-based chemotherapy alone.[5] However, according to 2 separate economic evaluations, the use of cetuximab with chemotherapy was not a cost-effective strategy.[6,7] The former study,[6] performed in the United Kingdom, found that the incremental cost-effectiveness ratio (ICER) for cetuximab + platinum-based chemotherapy compared with platinum-based chemotherapy of £166,307 (US $218,408/€186,532) per quality-adjusted life year (QALY) was considerably above the National Institute for Health and Care Excellence (NICE) threshold of £20,000 to £30,000 (US $26,266/€22,432 to US $39,398/€33,648); therefore, cetuximab in combination with platinum-based chemotherapy was not recommended for the treatment of patients with RM-HNSCC. The second study,[7] conducted in Canada, reported that cetuximab plus platinum-based chemotherapy compared with platinum-based chemotherapy alone led to an increase of 0.093 QALY and an increase in cost of CaD $36,000 (US $27,628/€23,590) per patient, resulting in an ICER of CaD $386,000 (US $296,230/€252,935) per QALY gained; thus, the addition of cetuximab to standard platinum-based chemotherapy in first-line treatment of patients with RM-HNSCC reported an ICER that exceeded CaD $100,000 (US $76,732/€65,527) per QALY gained. In this context, cetuximab may be attractive if its cost is significantly reduced or if future investigation may identify predictive markers to select patients most likely to benefit from the addition of cetuximab to chemotherapy.

Olsen and Jørgensen[8] suggest that predictive biomarkers and companion diagnostics offer the opportunity for a tailored approach, allowing to select patients for response to a targeted agent. Moreover, some regulatory authorities now show a clear interest in promoting the approval of drugs linked to selection of patients who are most likely to gain benefit.[9]

We have clinicoeconomic evidence that a biomarker-driven approach can reduce the ICER, in the context of colorectal cancer.[10] However, as far as RM-HNSCC is concerned, to date researchers have yet to identify a patient-selection testing strategy for the addition of cetuximab to platinum-based chemotherapy.[11,12]

A solution may lie with a molecular approach, judging from the encouraging results of the 2 predictive models developed to test cetuximab sensitivity in patients with HNSCC.[13,14] A serum proteomic profile and a genomic signature were shown to discriminate patients receiving the highest benefit by anti-EGFR treatment in the RM setting. Even with the limits of small, mainly retrospective series, these researches underscored the feasibility to investigate molecular determinants of therapeutic benefit induced by anti-EGFR (Epidermal Growth Factor Receptor) approaches. However, because these biomarkers have not been prospectively validated, at the moment they should be considered only as hypothesis generating.

Therefore, we decided to evaluate the cost-effectiveness of a hypothetical molecular test (HMT) as a possible strategy to profile patients with RM-HNSCC for positive treatment with cetuximab. As comparator, we considered the same treatment but without any patient selection.

METHODS

Assumptions

We summarize the following test modeling assumptions.

Accuracy

Ideally, the test should correctly identify all potentially treatment-responsive patients and all nonresponsive patients. However, the evaluation of any clinical test always must take into account its sensitivity and specificity. For example, the MammaPrint test for breast cancer reported a 5-year sensitivity and specificity for distant metastases ranging from 78% to 95% and from 73% to 92%, respectively.[15] Oncotype DX recurrence score for breast cancer found a sensitivity range of 31%−85% and specificity range of 55%−87%.[16] The prostate-specific antigen test results in a 33%−59% sensitivity and a 87%−95% specificity.[17] This background led us to assume basal values of sensitivity and specificity

equal to 85% and 70%, respectively, preferring in our case the minimization of false negatives. Moreover, given the high uncertainty of those values, the influence of their variation on the results was investigated through sensitivity analysis.

Costs

At present, the most expensive prognostic tests are Oncotype Dx[18] (€4000) and MammaPrint[19] (€2700). In our model, we used the higher value as the cost of the HMT.

Test target

We considered the ability of the HMT to identify responsive patients based on disease response, defined as partial or complete response according to RECIST (Response Evaluation Criteria in Solid Tumors).[20] The EXTREME (ErbituX in first-line Treatment of REcurrent or MEtastatic head and neck cancer) study reported disease response in 36% of patients.[5]

Decision Model Design

A decision tree combined with Markov models has been developed to estimate health outcomes (QALYs; life years [LYs]), and costs of the 2 treatment strategies.

As shown in Figure 1, the administration of platinum-fluorouracil chemotherapy plus cetuximab (PF + C) to all patients (strategy PF + C ALL) was compared with the same regimen (PF + C) administered only to patients who would be positive to a HMT able to identify patients' responsiveness to cetuximab (strategy PF + C POS), assuming that only responsive patients clinically benefit from the treatment.[21,22]

In the PF + C POS strategy, patients identified as responders (Test +) undergo PF + C and patients identified as nonresponders (Test –) undergo PF. To calculate the probability of response in positive and negative patients, we considered the probability of false-positive and false-negative results (see formulas in Figure 1).

The Markov process considers the following health states: disease control with no adverse events (AEs), disease control with mild AEs (grade 1/2), disease control with severe AEs (with different health states for the following grade 3/4 AEs: allergy/anaphylaxis, skin reactions, sepsis, hypomagnesemia, anorexia), disease progression, and death. Disease control health states are defined as complete response, partial response, or stable disease, as defined by Vermorken et al.[5] A cycle length of 1 month has been considered for the Markov process. The cycle represents the

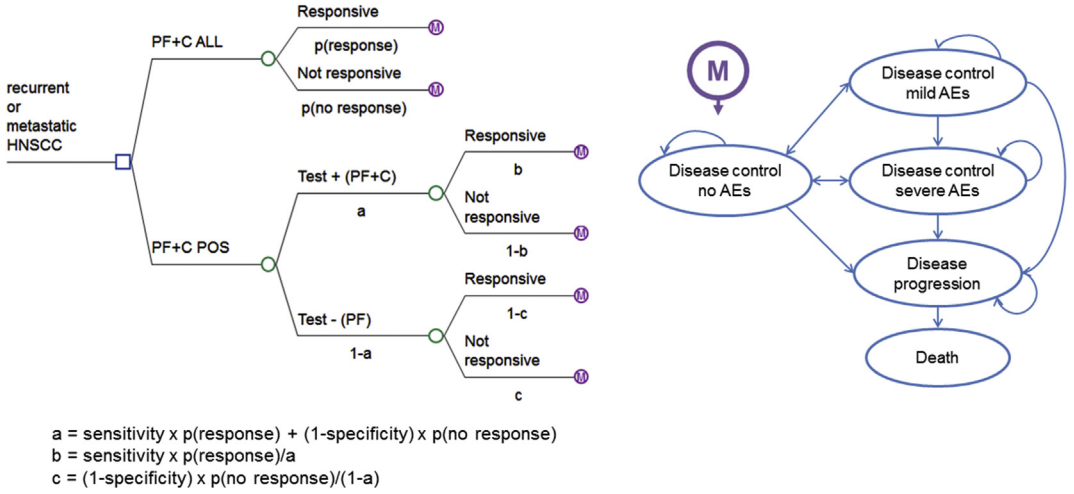

Figure 1. Simplified representation of the decision model and bubble diagram of the Markov state-transition model. A, b, and c probabilities in the tree are calculated according to the formulas for total probabilities and Bayes theorem. Purple arrow indicates the initial state of the process. AE = adverse event; ALL = all patients; C = cetuximab; HNSCC = head and neck squamous cell cancer; POS = patients with positive molecular test; PF = platinum-fluorouracil chemotherapy.

minimum amount of time that any individual will spend in a state before the possibility of transition to another state.[23] The choice of monthly cycle length has been performed to be consistent with a previous study in the same setting[7] and with the unit of measure of the clinical outcomes (OS and progression-free survival) reported by the reference study.[5]

Frequencies of AEs, response rates to systemic treatment, and rates of progression and survival were retrieved by Vermorken et al[5] (EXTREME trial). Only AEs affecting at least 0.5% have been considered in the model. Moreover, we only considered those affecting a number of patients significantly different between the 2 arms.

A hypothetical cohort of 56-year-old patients (90% men), representing the median age of the EXTREME trial population, entered the Markov process in the disease control, no AE state.

The model assumes that patients who have any persisting severe condition and those experiencing disease progression would stop receiving PF + C and be transitioned to second-line chemotherapy or best supportive care. AEs requiring treatment suspension are reported in ~20% of patients in both arms.[5] Time occurrence of AEs was modeled according to Hannouf et al.[7]

Our model considers 3 years as the time horizon for the analyses. The model was developed with TreeAge software.[24]

Valuing Probabilities, Health Care Resource Consumption, Costs, and Utility Weights

From the EXTREME trial data,[5] we estimated transition probabilities to generate median treatment durations of 4 cycles for the PF regimen and of 5 cycles for the PF + C regimen. In the trial 67% of patients underwent cisplatin chemotherapy in combination with cetuximab, although for the remaining patients, carboplatin was used. Because the choice was at the discretion of the investigator, we assumed that all patients underwent the combination with cisplatin. The impact on the results of the higher cost sustained for patients treated with cetuximab plus carboplatin was taken into account in sensitivity analyses.

For both regimens, we applied time-dependent transition probabilities from disease control to disease progression health states. Because Vermorken et al[5] did not report data stratification to calculate the difference in progression probability for responders and nonresponders, we assumed a hazard ratio (HR) for progression of 1.25 for nonresponders and therefore 0.8 (1/1.25) for responders compared with the whole cohort of patients. For sake of consistency, we applied this value to both regimens (PF + C and PF alone).

For both responders and nonresponders, the time-dependent transition probabilities from progression to death were calibrated according to the final OS curves as reported by Vermorken et al[5] (see Supplemental Figure 1 in the online version at https://doi.org/10.1016/j.clinthera.2019.09.015).

Mortality rates were further adjusted for age and sex, according to Italian national mortality data (ISTAT, http://demo.istat.it/).

Table Supplementary 1 (see in the online version at https://doi.org/10.1016/j.clinthera.2019.09.015) reports all the transition probabilities used in our decision model.

The distribution of health care resources utilization is reported in Table I, and health care costs are reported in Table II (along with model parameters). Costs were estimated from the Italian health care service perspective (€; 2017) (Table II). The HMT cost is applied only to patients belonging to the PF + C POS strategy of the model.

The costs for the management of AEs were estimated based on diagnosis-related groups.

As for quality of life, we assigned a utility coefficient to each health state (Table II). Because the only available utility coefficients found in the literature are related to "partial/complete response or stable disease" (u = 0.67) and "disease progression" (u = 0.52),[25] we used those values for the states of disease control without AEs and disease progression, respectively.

To account for worsening of quality of life due to severe AEs, we applied the disutility estimates used by Hannouf et al[7] (Table II). AEs occur with different probabilities in patients undergoing different treatments, and this allows to account for treatment-related changes in quality of life (eg, cetuximab is responsible for a higher disutility associated to skin reactions).

Analyses

ICER and incremental cost-utility ratio (ICUR) were calculated as dividing the difference of costs by the difference of health outcomes for the 2 strategies. LYs, QALYs, and costs have been discounted at 3.5% annually.[26] To evaluate the cost-effectiveness of PF + C ALL versus PF + C POS, the ICUR has been compared

Table I. Health care resource consumption.

Resource	Frequency	Reference
Cisplatin 100 mg/m^2 of body surface area or carboplatin AUC 5 mg/mL/min + fluorouracil 1000 mg/m^2 per day for 4 days*	Every 3 weeks	Vermorken et al[5]
Cetuximab 400 mg/m^2 of body surface area*	First week only	Vermorken et al[5]
Cetuximab 250 mg/m^2 of body surface area*	Weekly	Vermorken et al[5]
Specialist visit for mild AEs, %		Vermorken et al,[5] Hannouf et al[7]
PF + C	32	
PF	3	
Treatment for mild AEs: intravenous antihistamines, hydrocortisone, and clindamycin, %		Vermorken et al,[5] Hannouf et al[7]
PF + C	32	
PF	3	
Hospitalization, %		Vermorken et al[5]
Severe skin reactions (first month)		
PF + C	9	
PF	0.5	
Severe infusion-related reactions		
PF + C	2.7	
PF	0	
Severe anorexia		
PF + C	5	
PF	1.4	
Severe hypomagnesemia		
PF + C	5	
PF	1.4	
Severe sepsis		
PF + C	4.1	
PF	0.5	

AE = adverse event; AUC = area under the curve; C = cetuximab; PF = platinum-fluorouracil chemotherapy.
*For drugs, a body surface area of 1.8 m^2 was considered.

with a cost-effectiveness threshold. In particular, the World Health Organization (WHO) cost-effectiveness threshold was applied.[27] WHO considers the cost-effectiveness threshold of 3 times the gross domestic product per capita. For EURO-A zone, which includes Italy, this translates into €66,402.

One-way deterministic sensitivity analyses were performed on the main model parameters, although a

Table II. Base-case model parameters, costs, utility, and disutility values.

Variable	Base Case Value*	Distribution	Alpha	Beta or Lambda	Reference
Model parameters					
Test sensitivity, %	85 (20)	Beta	3.750	0.662	Assumption
Test specificity, %	70 (20)	Beta	7.500	3.214	Assumption
Percentage of PF + C responsive patients, %	36 (29–42)	Beta	78.527	139.603	Vermorken et al[5]
HR for PFS (chemotherapy vs cetuximab + chemotherapy)	1.852 (1.49–2.33)	Gamma	952.599	514.403	Vermorken et al[5]
HR for PFS (responders vs whole cohort)	0.8 (0.16)	Gamma	25	31.250	Assumption
Costs, €					
First cycle of cetuximab	1260 (±20%)	Gamma	25	0.020	Local tariff
Subsequent cycles of cetuximab	804 (±20%)	Gamma	25	0.031	Local tariff
Cycle of platinum + fluorouracil + cetuximab	852 (±20%)‡	Gamma	25	0.029	Local tariff
Platinum-based chemotherapy administration†	425 (±20%)	Gamma	25	0.059	Local tariff
Cetuximab administration	44.00 (±20%)	Gamma			Local tariff
Specialist visit	22.50 (±20%)	Gamma	25	1.111	Local tariff
Antihistamines or hydrocortisone administration	9.50 (±20%)	Gamma	25	2.632	Local tariff
Severe infusion-related reactions (mainly allergy or anaphylaxis)	1467 (±20%)	Gamma	25	0.017	DRG 447
Severe anorexia	2734 (±20%)	Gamma	25	0.009	DRG 296
Severe hypomagnesemia	1758 (±20%)	Gamma	25	0.014	DRG 297
Severe sepsis	4952 (±20%)	Gamma	25	0.005	DRG 576
Severe skin reactions	797 (±20%)	Gamma	25	0.031	DRG 284
Molecular test	4000 (±20%)	Gamma	25	0.006	Assumption
Utility values					
Disease control	0.67 (0.35–0.99)	Beta	5.787	2.850	ERG Report 2008[25]
Progression	0.52 (0.11–0.93)	Beta	3.088	2.851	ERG Report 2008[25]
Disutilities, %					
Severe allergy or anaphylaxis (1-month duration)	15 (20)	Beta	21.250	120.417	Hannouf et al[7]
Severe anorexia (20-month duration)	20 (20)	Beta	20	80	Hannouf et al[7]

Table II. (*Continued*)

Variable	Base Case Value*	Distribution	Alpha	Beta or Lambda	Reference
Severe hypomagnesemia (20-month duration)	24 (20)	Beta	19	60.167	Hannouf et al[7]
Severe sepsis (lifetime sequalae)	41 (20)	Beta	14.750	21.226	Hannouf et al[7]
Severe skin reactions (2-month duration)	65.70 (20)	Beta	8.575	4.477	Hannouf et al[7]

C = cetuximab; DRG = diagnosis-related group; HR = hazard ratio; PF = platinum-fluorouracil chemotherapy; PFS = progression-free survival.
*Values are expressed as mean (SD) or median (range).
†This reimbursement code is used for both carboplatin and cisplatin.
‡This range variation takes into account that all patients could be treated with carboplatin instead of cisplatin.

probabilistic sensitivity analysis was performed based on the distribution of all model parameters (Table II). In addition, we also performed a 3-way sensitivity analysis that focused on the characteristics of the HMT: cost, sensitivity, and specificity.

Considering that most people diagnosed with head and neck cancer are of working age, a scenario analysis has been included to evaluate the cost-effectiveness of PF + C ALL versus PF + C POS from the societal perspective, thus considering patients' productivity losses due to the time away from the workplace caused by cancer and by premature mortality. Yabroff et al[28] presented data on the patient working time lost in the initial and final phases of care for head and neck cancer, respectively, of 149 and 188.5 h. Considering that in Italy the mean annual wage of a 56-year-old patient is equal to €23,633[29] and considering 46 working weeks per year (36 h per week), patients' productivity losses were estimated at €177 and €224 monthly for disease control and progressive disease states, respectively. Moreover, a monthly productivity loss of €1969, derived by the above reported yearly wage, has been considered in case of premature death over the horizon of 3 years considered in the analysis, considering that patients are of working age during the process.

RESULTS

In the base-case scenario the ICUR for PF + C ALL versus PF + C POS was €112,462/QALY (Table III). As a matter of fact, the QALYs obtained with the strategy PF + C ALL are higher than in the case of administering cetuximab to HMT-positive patients only (0.5666 vs 0.5285), but these QALYs are obtained at a higher mean cost per patient (€19,269 vs €14,983). As reported in the Methods section, the ICUR derived from these figures has been compared with the WHO cost-effectiveness threshold for Italy, equal to €66,402. Because the ICUR was higher than €66,402, PF + C ALL was not cost-effective compared with PF + C POS, and the model suggestion (ie, the cost-effective choice) was to add cetuximab only to patients with a positive HMT (PF + C POS strategy).

Table III. Cost-effectiveness results.

Strategy	Cost, €	Life expectancy, y	QALYs	ICER, €/LY	ICUR, €/QALY
PF+C POS	14,983	0.9245	0.5285	60,873	112,462
PF+C ALL	19,269	0.9949	0.5666		

ALL = all patients; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LY = life year; PF+C ALL = platinum-fluorouracil chemotherapy plus cetuximab for all patients; PF+C POS = platinum-fluorouracil chemotherapy plus cetuximab for patients positive to a hypothetical molecular test; QALY = quality-adjusted life year.

Table Supplementary 2 (see in the online version https://doi.org/10.1016/j.clinthera.2019.09.015) reports for both strategies the cost details at different times for the main cost categories: treatment, management of AEs, and molecular test. The cost for treatment and for the management of AEs is higher for the PF + C ALL strategy, although a constant cost of €4000 was reported for patients undergoing the molecular test (PF + C POS strategy).

One-way sensitivity analyses found that variations of time horizon, patients' age, discount rate, HR for progression, test sensitivity and specificity (see Table Supplementary 3 in the online version at https://doi.org/10.1016/j.clinthera.2019.09.015) did not influence the outcomes.

Concerning the HMT, for a cost higher than €8,300, PF + C ALL would result as the dominant strategy; however, this figure is very high compared with the cost of current available molecular tests. Variation in the cost of HMT from €2000 (halved base value) to €8000 (doubled base value) generated an ICUR for PF + C ALL versus PF + C POS that ranged between €164,939/QALY and €7507/QALY. For a HMT cost lower than €5750, that is, the value reporting an ICUR equal to the cost-effectiveness threshold (€66,402), giving PF + C only to selected patients resulted in the most cost-effective choice (see Supplemental Table III in the online version).

In case the proportion of patients in partial/complete response exceeded 66.8%, the HMT use was no longer justified, so the cost-effective choice would be the administration of PF + C to all patients (ICUR for PF + C ALL vs PF + C POS lower than the threshold) (see Supplemental Table III in the online version).

The 3-way sensitivity analysis (Fig. 2) performed according to variations of HMT characteristics (specificity, sensitivity, and cost) found that in 65% of combinations of the 3 parameters PF + C POS resulted in the cost-effective option (in the remaining, PF + C ALL resulted in the cost-effective choice) (see Supplemental Figure 2 and Table Supplementary 4 for detailed results in the online version at https://doi.org/10.1016/j.clinthera.2019.09.015).

The acceptability curve for the ICUR is shown in Fig. 3. For a threshold value of €66,402/QALY, the administration of PF + C only to test-positive patients (green curve) was found to be a cost-effective choice with a probability of 79%. Lower threshold values found higher cost-effectiveness probabilities for the PF + C POS strategy.

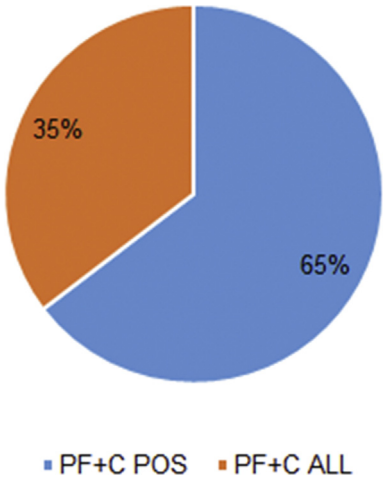

Figure 2. Percentage of combinations of test sensitivity, test sensibility, and test cost leading to cost-effectiveness for the two considered strategies, platinum-fluorouracil chemotherapy plus cetuximab for patients with positive molecular test (PF + C POS) and platinum-fluorouracil chemotherapy plus cetuximab for all patients (PF + C ALL).

In the scenario analysis performed to consider the societal perspective, the productivity losses over the horizon of 3 years resulted as €49,620 and €48,032 for PF + C POS and PF + C ALL, respectively, highlighting that the better clinical outcomes, achievable with the administration of PF + C to all patients compared with PF + C POS, led to lower working time lost. The total societal cost resulted in €64,603 and €67,301, respectively, for PF + C POS and PF + C ALL, yielding an ICER of €38,324 and an ICUR of €70,814. Although the ICER resulted lower than the considered cost-effectiveness threshold of €66,402, the ICUR resulted slightly superior. This means that broadening the perspective of analysis could lead to a better cost-effectiveness profile of the option to administer PF + C to all patients.

DISCUSSION

Cetuximab plus platinum-based chemotherapy until now is considered the most effective first-line systemic

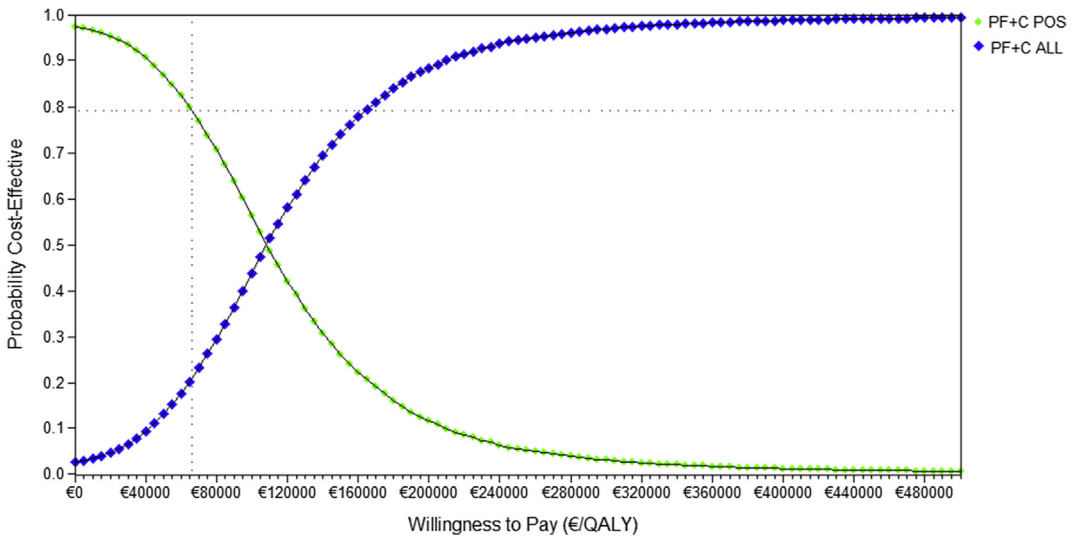

Figure 3. Acceptability curve for the incremental cost-utility ratio. QALY = quality-adjusted life year.

therapy for RM-HNSCC. However, it has been proved to not be cost-effective in the United Kingdom and in Canada, where the ICUR has been estimated equal to £166,307 (US $218,408/€186,532) and CaD $386,000 (US $296,230/€252,935) per QALY, respectively,[6,7] exceeding the thresholds of cost-effectiveness of £20,000 to £30,000 (US $26,266/€22,432 to US $39,398/€33,648) (United Kingdom) and CaD $100,000 (US $76,732/€65,527) (Canada).

In lack of tried and tested selection criteria, we hypothesized different decision scenarios deriving from a hypothetical molecular test, basing our cost-effectiveness analysis on unprecedented molecular predictive profiles that still need validation.[13,14]

Our HMT proved to be cost-effective if intended to identify patients with clinical/radiologic response to the drug combination. The addition of cetuximab to chemotherapy exerts its highest benefit in substantially increasing the treatment response rate (complete plus partial) from 20% to 36% of patients, although it causes a minimal improvement in the rate of disease stabilization from 40% to 45%. It is reasonable to try to predict response in patients with RM-HNSCC, because this population is often symptomatic, and symptom control may be better achieved with tumor shrinkage.[30] Moreover, it has been shown that patients who respond well to chemotherapy also benefit from longer survival.[22,30]

It should be highlighted that the cost-effectiveness of the HMT is maintained as long as the partial/complete response does not exceed 66.8%, which is almost the double of what was reported in clinical trials until now.[5]

The combination of targeted therapy plus polychemotherapy in the EXTREME regimen involved several toxicities,[5] with 82% of patients experiencing at least 1 AE of grade 3/4. In this scenario, our analysis suggests that an efficient patient selection saves unnecessary toxicities to patients and resources for the health care system, thus proving to be desirable both on clinical and economic grounds.

The quality of life of patients with RM-HNSCC is severely affected, and an improvement in some domains has been reported in less than half of the patients with the use of palliative chemotherapy.[31] So, the adoption of a HMT would enable the identification of those patients who may benefit from the combined treatment in terms of quality of life but also in terms of clinical benefit, a broader emerging concept that entails costs.[32]

Assuming a HMT with 85% sensitivity and 70% specificity and a cost <€5750, we found that administering PF + C only to patients with a positive test could be a cost-effective choice compared with the administration of PF + C to all patients with RM-HNSCC. From the clinical point of view, it is quite hard to accept PF + C POS as the best strategy because it brings to a reduction of survival (LY, QALY) in

comparison with PF + C ALL, although balanced from a cost reduction. However, this result may give insights to decision makers on how to distribute health care funds in resource-limited settings. However, it could be reasonable to offer alternative treatments to patients with a limited probability of responding to PF + C, for example, in the context of clinical trials that experiment with new drugs able to limit AEs for patients. Moreover, the present study found that broadening the perspective of analysis, moving from the National Healthcare Service to the societal perspective, including at least patients' productivity losses, a better cost-effectiveness profile of administering PF + C to all patients may result. In this context, it is likely that by extending the analysis, including also informal care and out-of-pocket costs, the cost-effectiveness of administering PF + C to all patients could be revealed.

Our study has some limitations, beginning with the assumptions about the modeling of disease progression in responding and nonresponding patients. In particular, we applied for both regimens a HR for progression of 0.8 for responders (1.25 for nonresponders) compared with the whole cohort of patients, leading to a HR of ~1.56 comparing nonresponders with responders. In the literature there is lack of studies that report such HR for PF and PF + C treatments. The only available evidence refers to settings quite different from ours; 1 study considers taxane-based induction chemotherapy for nonoperated locally advanced HNSCC,[33] whereas another study focuses on chemoradiotherapy in patients with advanced HNSCC.[34] Both studies are however concordant and report a HR for progression or loss of local control in the range of 3.2−3.4 for nonresponsive patients compared with responsive patients. Translated into our setting, this would mean applying a HR in the range of 0.54−0.56 for responders compared with the whole cohort of patients. The 1-way sensitivity analyses found for such HR range an ICUR of ~€100,000, thus confirming the cost-effectiveness of administering cetuximab only to patients with a positive HMT.

Although in a real-world setting a patient may experience different AEs at the same time, the implemented model considers AEs for mutually exclusive health states. Unfortunately, the reference trial that has been used for modeling reported data only on the number of patients who experienced the different AEs during the observation period and did not report the number of patients experiencing the different combinations of side effects.[5] Therefore, a more precise modeling of AEs was not possible.

Another limitation is that our model did not account for HPV status. However, although there are solid data on the role of HPV as prognostic biomarker in head and neck cancer, the benefit of adding cetuximab to chemotherapy in the EXTREME trial was irrespective of the disease HPV status.[35]

As for quality of life, we used utility coefficients related to disease control and progressive disease states measured during the EXTREME trial. The EXTREME study found that patients treated with cetuximab had improved quality of life; however, it did not distinguish between responders and nonresponders.[36] We thus made assumptions that may have underestimated quality-of-life scores.

Finally, the model has been developed from the Italian health care service perspective. However, we provided data about resource consumption to allow generalizability to other countries as suggested by EUnetHTA.[37]

CONCLUSIONS

Our analysis found the cost-effectiveness of a molecular selection before starting a treatment for RM-HNSCC that includes cetuximab. The developed model may be usefully applied to new emerging treatments, such as immunotherapeutic agents in the same setting. Recently, the NICE committee stated that in platinum-resistant RM-HNSCC the ICERs for PD-1 inhibitor nivolumab compared with the comparators were substantially above the range of £20,000 to £30,000 (US $26,266/€22,432 to US $39,398/€33,648) per QALY gained, usually considered for the cost-effectiveness of health care resources.[38] Even if they recognized there is a high unmet need for effective treatment options for people with RM-SCCHN and that nivolumab met all the criteria to be considered a life-extending end-of-life therapy, the treatment was not considered cost-effective. This underlines the importance of models that incorporate predictors of activity and efficacy in determining the future scenarios of drug approvals.

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Carla Rognoni, Silvana Quaglini, and Paolo Bossi were responsible for conceptualization; Carla Rognoni, Silvana Quaglini, Paolo Bossi, and Loris De Cecco were responsible for data curation; Carla Rognoni and Silvana Quaglini were responsible for formal analysis; Carla Rognoni, Silvana Quaglini, and Paolo Bossi were responsible for investigation; Carla Rognoni and Silvana Quaglini were responsible for methodology; Carla Rognoni was responsible for project administration; Carla Rognoni, Silvana Quaglini, Paolo Bossi, Loris De Cecco, and Lisa Licitra were responsible for resources; Carla Rognoni and Silvana Quaglini were responsible for software; Silvana Quaglini, Paolo Bossi, Lisa Licitra, and Jan Baptist Vermorken were responsible for supervision; Silvana Quaglini, Paolo Bossi, Lisa Licitra, and Jan Baptist Vermorken were responsible for validation; Carla Rognoni and Silvana Quaglini were responsible for visualization; Carla Rognoni, Silvana Quaglini, and Paolo Bossi wrote the original draft; and Carla Rognoni, Lisa Licitra, Loris De Cecco, and Jan Baptist Vermorken were responsible for review and editing.

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DISCLOSURES

Paolo Bossi reports personal fees outside the submitted work from Roche, Merck-Serono, AstraZeneca, Helsinn, Mundipharma, and Kyowa Kyrin. Lisa Licitra reports personal fees outside the submitted work from EISAI, BMS, MSD, Merck–Serono, Boehringer Ingelheim, DEBIOPHARM, SOBI, Novartis, AstraZeneca, Bayer, Roche, and AMGEN. Jan B. Vermorken reports personal fees outside the submitted work from Merck–Serono, AMGEN, Innate Pharma, PCI Biotech, Synthon Biopharmaceuticals, and Sanofi. The remaining authors declare that they have no conflict of interest. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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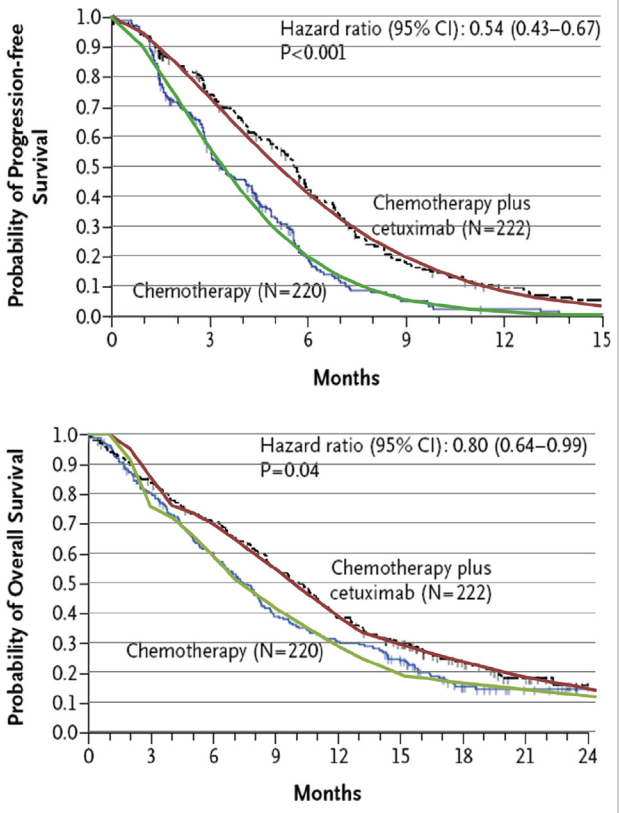
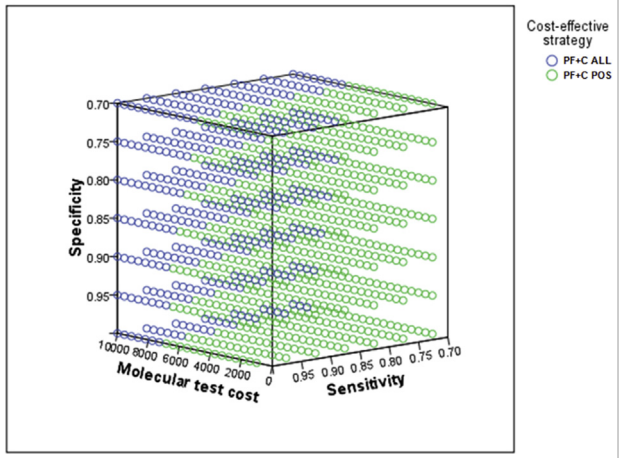
APPENDIX



Supplemental Figure 1. Model curves for progression-free survival (top) and overall survival (bottom). Black and blue curves represent the EXTREME trials' results for platinum-fluorouracil chemotherapy plus cetuximab (PF+C) and PF cohorts, respectively. Continuous lines represent the model result, that is, weighted mean curves based on the predicted responders and non-responders for the two treatments (pink for PF+C and green for PF alone).



Supplemental Figure 2. Three-dimensional scatterplot representing the cost-effective strategy for different combinations of model parameters. PF+C ALL = platinum-fluorouracil chemotherapy plus cetuximab to all patients; PF+C POS = platinum-fluorouracil chemotherapy plus cetuximab for patients with positive molecular test.

Supplementary Table 1. Main transition probabilities of the Markov Model

From	To	Chemotherapy + cetuximab	Chemotherapy alone	Responders/Non-responders	Time Horizon
Disease control no AEs	Disease control mild AEs	0.3200	0.0300		first month
Disease control no AEs	Allergy/ anaphylaxis	0.0270	—		first month
Disease control no AEs	Severe skin reactions	0.0900	0.0050		first month
Disease control no AEs	Severe anorexia	0.0100	0.0044		monthly
Disease control no AEs	Severe hypomagnesemia	0.0100	0.0044		monthly
Disease control no AEs	Severe sepsis	0.0078	0.0016		monthly
Disease control no AEs/mild or severe AEs	Progression	Time dependent according to Weibull function (lambda = 0.051; gamma = 1.5515)	HR = 1/0.54 = 1.85 applied to lambda parameter	Adjustment with HR = 0.8 for responders (and 1/HR for non-responders)	monthly
Progression	Death	Time dependent according to calibration	Time dependent according to calibration		monthly

Supplementary Table 2. Cost components (cumulative) (€) for the considered strategies at different times

Time (months)	PF + C POS				PF + C ALL			
	Molecular test	Treatments	Management of adverse events	Total cost	Molecular test	Treatments	Management of adverse events	Total cost
6	4000	8500	266	12,766	0	15,106	437	15,543
12	4000	10,311	312	14,623	0	18,237	509	18,747
18	4000	10,621	319	14,940	0	18,694	520	19,213
24	4000	10,659	319	14,979	0	18,743	521	19,264
30	4000	10,663	320	14,983	0	18,748	521	19,269
36	4000	10,663	320	14,983	0	18,748	521	19,269

Supplementary Table 3. One-way sensitivity analyses on the main model parameters

	ICUR (€/QALY)
Baseline	112,462
Time horizon (years)	
1	162,506
2	110,348
3	112,462
Patient's age	
40	112,364
70	112,819
Discount rate	
0%	111,191
1%	111,553
2%	111,917
3%	112,280
5%	113,008
10%	114,832
Proportion of patients in partial/complete response	
0.36	112,462
0.39	109,258
0.42	105,851
0.45	102,219
0.48	98,341
0.51	94,190
0.54	89,736
0.57	84,946
0.6	79,779
0.63	74,189
0.66 §	68,122
0.69 §	61,514

(*continued on next page*)

Supplementary Table 3. (*Continued*)

	ICUR (€/QALY)
0.72	54,290
0.75	46,359
0.78	37,612
0.81	27,916
Molecular test sensitivity	
0.7	124,772
0.75	120,997
0.8	116,907
0.85	112,462
0.9	107,613
0.95	102,303
1	96,463
Molecular test specificity	
0.7	112,462
0.75	118,585
0.8	124,030
0.85	128,906
0.9	133,297
0.95	137,271
1	140,885
Molecular test cost	
€ 2000	164,939
€ 3000	138,701
€ 4000	112,462
€ 5000*	86,223
€ 6000*	59,985
€ 7000	33,746
€ 8000	7507
€ 9000	PF + C ALL dominant
€ 10,000	PF + C ALL dominant
HR for responders (PFS)	
0.2	84,627
0.25	84,756
0.3	86,573
0.35	89,098
0.4	91,897
0.45	94,759
0.5	97,582
0.55	100,316
0.6	102,945
0.65	105,466
0.7	107,885
0.75	110,214
0.8	112,462

Supplementary Table 3. (*Continued*)

	ICUR (€/QALY)
0.85	114,641
0.9	116,761
0.95	118,831

§ 0.668 is the value between 0.66 and 0.69 reporting an ICUR equal to the cost-effectiveness threshold (66,402€).
* 5750 is the value between 5000€ and 6000€ reporting an ICUR equal to the cost-effectiveness threshold (66,402€).

Supplementary Table 4. Three-way sensitivity analyses

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.7	0.7	1000	195928	PF + C POS
0.7	0.7	1450	185462	PF + C POS
0.7	0.7	1900	174996	PF + C POS
0.7	0.7	2350	164529	PF + C POS
0.7	0.7	2800	154063	PF + C POS
0.7	0.7	3250	143597	PF + C POS
0.7	0.7	3700	133130	PF + C POS
0.7	0.7	4150	122664	PF + C POS
0.7	0.7	4600	112197	PF + C POS
0.7	0.7	5050	101731	PF + C POS
0.7	0.7	5500	91265	PF + C POS
0.7	0.7	5950	80798	PF + C POS
0.7	0.7	6400	70332	PF + C POS
0.7	0.7	6850	59865	PF + C ALL
0.7	0.7	7300	49399	PF + C ALL
0.7	0.7	7750	38933	PF + C ALL
0.7	0.7	8200	28466	PF + C ALL
0.7	0.7	8650	18000	PF + C ALL
0.7	0.7	9100	7534	PF + C ALL
0.7	0.7	9550	–2933	PF + C ALL
0.7	0.7	10000	–13399	PF + C ALL
0.7	0.75	1000	197111	PF + C POS
0.7	0.75	1450	187190	PF + C POS
0.7	0.75	1900	177269	PF + C POS
0.7	0.75	2350	167348	PF + C POS
0.7	0.75	2800	157427	PF + C POS
0.7	0.75	3250	147506	PF + C POS
0.7	0.75	3700	137585	PF + C POS
0.7	0.75	4150	127664	PF + C POS
0.7	0.75	4600	117743	PF + C POS

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.7	0.75	5050	107822	PF + C POS
0.7	0.75	5500	97901	PF + C POS
0.7	0.75	5950	87980	PF + C POS
0.7	0.75	6400	78059	PF + C POS
0.7	0.75	6850	68138	PF + C POS
0.7	0.75	7300	58217	PF + C ALL
0.7	0.75	7750	48296	PF + C ALL
0.7	0.75	8200	38375	PF + C ALL
0.7	0.75	8650	28454	PF + C ALL
0.7	0.75	9100	18533	PF + C ALL
0.7	0.75	9550	8612	PF + C ALL
0.7	0.75	10000	–1309	PF + C ALL
0.7	0.8	1000	198176	PF + C POS
0.7	0.8	1450	188746	PF + C POS
0.7	0.8	1900	179317	PF + C POS
0.7	0.8	2350	169887	PF + C POS
0.7	0.8	2800	160457	PF + C POS
0.7	0.8	3250	151028	PF + C POS
0.7	0.8	3700	141598	PF + C POS
0.7	0.8	4150	132169	PF + C POS
0.7	0.8	4600	122739	PF + C POS
0.7	0.8	5050	113309	PF + C POS
0.7	0.8	5500	103880	PF + C POS
0.7	0.8	5950	94450	PF + C POS
0.7	0.8	6400	85021	PF + C POS
0.7	0.8	6850	75591	PF + C POS
0.7	0.8	7300	66161	PF + C ALL
0.7	0.8	7750	56732	PF + C ALL
0.7	0.8	8200	47302	PF + C ALL
0.7	0.8	8650	37873	PF + C ALL
0.7	0.8	9100	28443	PF + C ALL
0.7	0.8	9550	19013	PF + C ALL
0.7	0.8	10000	9584	PF + C ALL
0.7	0.85	1000	199140	PF + C POS
0.7	0.85	1450	190156	PF + C POS
0.7	0.85	1900	181171	PF + C POS
0.7	0.85	2350	172187	PF + C POS
0.7	0.85	2800	163202	PF + C POS
0.7	0.85	3250	154217	PF + C POS
0.7	0.85	3700	145233	PF + C POS
0.7	0.85	4150	136248	PF + C POS
0.7	0.85	4600	127264	PF + C POS
0.7	0.85	5050	118279	PF + C POS
0.7	0.85	5500	109294	PF + C POS

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.7	0.85	5950	100310	PF + C POS
0.7	0.85	6400	91325	PF + C POS
0.7	0.85	6850	82341	PF + C POS
0.7	0.85	7300	73356	PF + C POS
0.7	0.85	7750	64371	PF + C ALL
0.7	0.85	8200	55387	PF + C ALL
0.7	0.85	8650	46402	PF + C ALL
0.7	0.85	9100	37418	PF + C ALL
0.7	0.85	9550	28433	PF + C ALL
0.7	0.85	10000	19448	PF + C ALL
0.7	0.9	1000	200018	PF + C POS
0.7	0.9	1450	191438	PF + C POS
0.7	0.9	1900	182859	PF + C POS
0.7	0.9	2350	174279	PF + C POS
0.7	0.9	2800	165699	PF + C POS
0.7	0.9	3250	157120	PF + C POS
0.7	0.9	3700	148540	PF + C POS
0.7	0.9	4150	139960	PF + C POS
0.7	0.9	4600	131380	PF + C POS
0.7	0.9	5050	122801	PF + C POS
0.7	0.9	5500	114221	PF + C POS
0.7	0.9	5950	105641	PF + C POS
0.7	0.9	6400	97062	PF + C POS
0.7	0.9	6850	88482	PF + C POS
0.7	0.9	7300	79902	PF + C POS
0.7	0.9	7750	71322	PF + C POS
0.7	0.9	8200	62743	PF + C ALL
0.7	0.9	8650	54163	PF + C ALL
0.7	0.9	9100	45583	PF + C ALL
0.7	0.9	9550	37004	PF + C ALL
0.7	0.9	10000	28424	PF + C ALL
0.7	0.95	1000	200820	PF + C POS
0.7	0.95	1450	192610	PF + C POS
0.7	0.95	1900	184401	PF + C POS
0.7	0.95	2350	176191	PF + C POS
0.7	0.95	2800	167981	PF + C POS
0.7	0.95	3250	159771	PF + C POS
0.7	0.95	3700	151562	PF + C POS
0.7	0.95	4150	143352	PF + C POS
0.7	0.95	4600	135142	PF + C POS
0.7	0.95	5050	126932	PF + C POS
0.7	0.95	5500	118723	PF + C POS
0.7	0.95	5950	110513	PF + C POS

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.7	0.95	6400	102303	PF + C POS
0.7	0.95	6850	94093	PF + C POS
0.7	0.95	7300	85884	PF + C POS
0.7	0.95	7750	77674	PF + C POS
0.7	0.95	8200	69464	PF + C POS
0.7	0.95	8650	61254	PF + C ALL
0.7	0.95	9100	53045	PF + C ALL
0.7	0.95	9550	44835	PF + C ALL
0.7	0.95	10000	36625	PF + C ALL
0.7	1	1000	201556	PF + C POS
0.7	1	1450	193685	PF + C POS
0.7	1	1900	185815	PF + C POS
0.7	1	2350	177945	PF + C POS
0.7	1	2800	170074	PF + C POS
0.7	1	3250	162204	PF + C POS
0.7	1	3700	154334	PF + C POS
0.7	1	4150	146463	PF + C POS
0.7	1	4600	138593	PF + C POS
0.7	1	5050	130723	PF + C POS
0.7	1	5500	122852	PF + C POS
0.7	1	5950	114982	PF + C POS
0.7	1	6400	107111	PF + C POS
0.7	1	6850	99241	PF + C POS
0.7	1	7300	91371	PF + C POS
0.7	1	7750	83500	PF + C POS
0.7	1	8200	75630	PF + C POS
0.7	1	8650	67760	PF + C POS
0.7	1	9100	59889	PF + C ALL
0.7	1	9550	52019	PF + C ALL
0.7	1	10000	44149	PF + C ALL
0.75	0.7	1000	194924	PF + C POS
0.75	0.7	1450	184039	PF + C POS
0.75	0.7	1900	173155	PF + C POS
0.75	0.7	2350	162271	PF + C POS
0.75	0.7	2800	151387	PF + C POS
0.75	0.7	3250	140502	PF + C POS
0.75	0.7	3700	129618	PF + C POS
0.75	0.7	4150	118734	PF + C POS
0.75	0.7	4600	107850	PF + C POS
0.75	0.7	5050	96965	PF + C POS
0.75	0.7	5500	86081	PF + C POS
0.75	0.7	5950	75197	PF + C POS
0.75	0.7	6400	64313	PF + C ALL
0.75	0.7	6850	53428	PF + C ALL

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.75	0.7	7300	42544	PF + C ALL
0.75	0.7	7750	31660	PF + C ALL
0.75	0.7	8200	20776	PF + C ALL
0.75	0.7	8650	9891	PF + C ALL
0.75	0.7	9100	–993	PF + C ALL
0.75	0.7	9550	–11877	PF + C ALL
0.75	0.7	10000	–22761	PF + C ALL
0.75	0.75	1000	196205	PF + C POS
0.75	0.75	1450	185909	PF + C POS
0.75	0.75	1900	175614	PF + C POS
0.75	0.75	2350	165318	PF + C POS
0.75	0.75	2800	155022	PF + C POS
0.75	0.75	3250	144727	PF + C POS
0.75	0.75	3700	134431	PF + C POS
0.75	0.75	4150	124135	PF + C POS
0.75	0.75	4600	113840	PF + C POS
0.75	0.75	5050	103544	PF + C POS
0.75	0.75	5500	93248	PF + C POS
0.75	0.75	5950	82953	PF + C POS
0.75	0.75	6400	72657	PF + C POS
0.75	0.75	6850	62361	PF + C ALL
0.75	0.75	7300	52066	PF + C ALL
0.75	0.75	7750	41770	PF + C ALL
0.75	0.75	8200	31474	PF + C ALL
0.75	0.75	8650	21179	PF + C ALL
0.75	0.75	9100	10883	PF + C ALL
0.75	0.75	9550	587	PF + C ALL
0.75	0.75	10000	–9708	PF + C ALL
0.75	0.8	1000	197355	PF + C POS
0.75	0.8	1450	187587	PF + C POS
0.75	0.8	1900	177820	PF + C POS
0.75	0.8	2350	168052	PF + C POS
0.75	0.8	2800	158285	PF + C POS
0.75	0.8	3250	148517	PF + C POS
0.75	0.8	3700	138750	PF + C POS
0.75	0.8	4150	128983	PF + C POS
0.75	0.8	4600	119215	PF + C POS
0.75	0.8	5050	109448	PF + C POS
0.75	0.8	5500	99680	PF + C POS
0.75	0.8	5950	89913	PF + C POS
0.75	0.8	6400	80145	PF + C POS
0.75	0.8	6850	70378	PF + C POS
0.75	0.8	7300	60610	PF + C ALL

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.75	0.8	7750	50843	PF + C ALL
0.75	0.8	8200	41075	PF + C ALL
0.75	0.8	8650	31308	PF + C ALL
0.75	0.8	9100	21541	PF + C ALL
0.75	0.8	9550	11773	PF + C ALL
0.75	0.8	10000	2006	PF + C ALL
0.75	0.85	1000	198392	PF + C POS
0.75	0.85	1450	189101	PF + C POS
0.75	0.85	1900	179811	PF + C POS
0.75	0.85	2350	170520	PF + C POS
0.75	0.85	2800	161229	PF + C POS
0.75	0.85	3250	151938	PF + C POS
0.75	0.85	3700	142647	PF + C POS
0.75	0.85	4150	133357	PF + C POS
0.75	0.85	4600	124066	PF + C POS
0.75	0.85	5050	114775	PF + C POS
0.75	0.85	5500	105484	PF + C POS
0.75	0.85	5950	96193	PF + C POS
0.75	0.85	6400	86903	PF + C POS
0.75	0.85	6850	77612	PF + C POS
0.75	0.85	7300	68321	PF + C POS
0.75	0.85	7750	59030	PF + C ALL
0.75	0.85	8200	49739	PF + C ALL
0.75	0.85	8650	40449	PF + C ALL
0.75	0.85	9100	31158	PF + C ALL
0.75	0.85	9550	21867	PF + C ALL
0.75	0.85	10000	12576	PF + C ALL
0.75	0.9	1000	199333	PF + C POS
0.75	0.9	1450	190475	PF + C POS
0.75	0.9	1900	181616	PF + C POS
0.75	0.9	2350	172758	PF + C POS
0.75	0.9	2800	163899	PF + C POS
0.75	0.9	3250	155041	PF + C POS
0.75	0.9	3700	146182	PF + C POS
0.75	0.9	4150	137324	PF + C POS
0.75	0.9	4600	128465	PF + C POS
0.75	0.9	5050	119607	PF + C POS
0.75	0.9	5500	110748	PF + C POS
0.75	0.9	5950	101890	PF + C POS
0.75	0.9	6400	93031	PF + C POS
0.75	0.9	6850	84173	PF + C POS
0.75	0.9	7300	75314	PF + C POS
0.75	0.9	7750	66456	PF + C POS
0.75	0.9	8200	57597	PF + C ALL

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.75	0.9	8650	48739	PF + C ALL
0.75	0.9	9100	39880	PF + C ALL
0.75	0.9	9550	31022	PF + C ALL
0.75	0.9	10000	22163	PF + C ALL
0.75	0.95	1000	200191	PF + C POS
0.75	0.95	1450	191726	PF + C POS
0.75	0.95	1900	183261	PF + C POS
0.75	0.95	2350	174797	PF + C POS
0.75	0.95	2800	166332	PF + C POS
0.75	0.95	3250	157867	PF + C POS
0.75	0.95	3700	149403	PF + C POS
0.75	0.95	4150	140938	PF + C POS
0.75	0.95	4600	132473	PF + C POS
0.75	0.95	5050	124009	PF + C POS
0.75	0.95	5500	115544	PF + C POS
0.75	0.95	5950	107079	PF + C POS
0.75	0.95	6400	98615	PF + C POS
0.75	0.95	6850	90150	PF + C POS
0.75	0.95	7300	81685	PF + C POS
0.75	0.95	7750	73221	PF + C POS
0.75	0.95	8200	64756	PF + C ALL
0.75	0.95	8650	56291	PF + C ALL
0.75	0.95	9100	47827	PF + C ALL
0.75	0.95	9550	39362	PF + C ALL
0.75	0.95	10000	30897	PF + C ALL
0.75	1	1000	200975	PF + C POS
0.75	1	1450	192871	PF + C POS
0.75	1	1900	184766	PF + C POS
0.75	1	2350	176662	PF + C POS
0.75	1	2800	168558	PF + C POS
0.75	1	3250	160453	PF + C POS
0.75	1	3700	152349	PF + C POS
0.75	1	4150	144245	PF + C POS
0.75	1	4600	136140	PF + C POS
0.75	1	5050	128036	PF + C POS
0.75	1	5500	119932	PF + C POS
0.75	1	5950	111827	PF + C POS
0.75	1	6400	103723	PF + C POS
0.75	1	6850	95619	PF + C POS
0.75	1	7300	87514	PF + C POS
0.75	1	7750	79410	PF + C POS
0.75	1	8200	71306	PF + C POS
0.75	1	8650	63201	PF + C ALL

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.75	1	9100	55097	PF + C ALL
0.75	1	9550	46993	PF + C ALL
0.75	1	10000	38888	PF + C ALL
0.8	0.7	1000	193835	PF + C POS
0.8	0.7	1450	182498	PF + C POS
0.8	0.7	1900	171162	PF + C POS
0.8	0.7	2350	159825	PF + C POS
0.8	0.7	2800	148488	PF + C POS
0.8	0.7	3250	137151	PF + C POS
0.8	0.7	3700	125814	PF + C POS
0.8	0.7	4150	114477	PF + C POS
0.8	0.7	4600	103140	PF + C POS
0.8	0.7	5050	91803	PF + C POS
0.8	0.7	5500	80467	PF + C POS
0.8	0.7	5950	69130	PF + C POS
0.8	0.7	6400	57793	PF + C ALL
0.8	0.7	6850	46456	PF + C ALL
0.8	0.7	7300	35119	PF + C ALL
0.8	0.7	7750	23782	PF + C ALL
0.8	0.7	8200	12445	PF + C ALL
0.8	0.7	8650	1108	PF + C ALL
0.8	0.7	9100	–10229	PF + C ALL
0.8	0.7	9550	–21565	PF + C ALL
0.8	0.7	10000	–32902	PF + C ALL
0.8	0.75	1000	195228	PF + C POS
0.8	0.75	1450	184528	PF + C POS
0.8	0.75	1900	173829	PF + C POS
0.8	0.75	2350	163129	PF + C POS
0.8	0.75	2800	152429	PF + C POS
0.8	0.75	3250	141729	PF + C POS
0.8	0.75	3700	131030	PF + C POS
0.8	0.75	4150	120330	PF + C POS
0.8	0.75	4600	109630	PF + C POS
0.8	0.75	5050	98930	PF + C POS
0.8	0.75	5500	88231	PF + C POS
0.8	0.75	5950	77531	PF + C POS
0.8	0.75	6400	66831	PF + C POS
0.8	0.75	6850	56131	PF + C ALL
0.8	0.75	7300	45432	PF + C ALL
0.8	0.75	7750	34732	PF + C ALL
0.8	0.75	8200	24032	PF + C ALL
0.8	0.75	8650	13332	PF + C ALL
0.8	0.75	9100	2633	PF + C ALL
0.8	0.75	9550	–8067	PF + C ALL

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.8	0.75	10000	−18767	PF + C ALL
0.8	0.8	1000	196473	PF + C POS
0.8	0.8	1450	186342	PF + C POS
0.8	0.8	1900	176212	PF + C POS
0.8	0.8	2350	166081	PF + C POS
0.8	0.8	2800	155951	PF + C POS
0.8	0.8	3250	145820	PF + C POS
0.8	0.8	3700	135690	PF + C POS
0.8	0.8	4150	125560	PF + C POS
0.8	0.8	4600	115429	PF + C POS
0.8	0.8	5050	105299	PF + C POS
0.8	0.8	5500	95168	PF + C POS
0.8	0.8	5950	85038	PF + C POS
0.8	0.8	6400	74908	PF + C POS
0.8	0.8	6850	64777	PF + C ALL
0.8	0.8	7300	54647	PF + C ALL
0.8	0.8	7750	44516	PF + C ALL
0.8	0.8	8200	34386	PF + C ALL
0.8	0.8	8650	24255	PF + C ALL
0.8	0.8	9100	14125	PF + C ALL
0.8	0.8	9550	3995	PF + C ALL
0.8	0.8	10000	−6136	PF + C ALL
0.8	0.85	1000	197591	PF + C POS
0.8	0.85	1450	187973	PF + C POS
0.8	0.85	1900	178354	PF + C POS
0.8	0.85	2350	168735	PF + C POS
0.8	0.85	2800	159117	PF + C POS
0.8	0.85	3250	149498	PF + C POS
0.8	0.85	3700	139880	PF + C POS
0.8	0.85	4150	130261	PF + C POS
0.8	0.85	4600	120642	PF + C POS
0.8	0.85	5050	111024	PF + C POS
0.8	0.85	5500	101405	PF + C POS
0.8	0.85	5950	91787	PF + C POS
0.8	0.85	6400	82168	PF + C POS
0.8	0.85	6850	72549	PF + C POS
0.8	0.85	7300	62931	PF + C ALL
0.8	0.85	7750	53312	PF + C ALL
0.8	0.85	8200	43694	PF + C ALL
0.8	0.85	8650	34075	PF + C ALL
0.8	0.85	9100	24456	PF + C ALL
0.8	0.85	9550	14838	PF + C ALL
0.8	0.85	10000	5219	PF + C ALL

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.8	0.9	1000	198602	PF + C POS
0.8	0.9	1450	189446	PF + C POS
0.8	0.9	1900	180290	PF + C POS
0.8	0.9	2350	171134	PF + C POS
0.8	0.9	2800	161978	PF + C POS
0.8	0.9	3250	152822	PF + C POS
0.8	0.9	3700	143666	PF + C POS
0.8	0.9	4150	134510	PF + C POS
0.8	0.9	4600	125354	PF + C POS
0.8	0.9	5050	116198	PF + C POS
0.8	0.9	5500	107042	PF + C POS
0.8	0.9	5950	97886	PF + C POS
0.8	0.9	6400	88730	PF + C POS
0.8	0.9	6850	79574	PF + C POS
0.8	0.9	7300	70418	PF + C POS
0.8	0.9	7750	61262	PF + C ALL
0.8	0.9	8200	52106	PF + C ALL
0.8	0.9	8650	42950	PF + C ALL
0.8	0.9	9100	33794	PF + C ALL
0.8	0.9	9550	24638	PF + C ALL
0.8	0.9	10000	15482	PF + C ALL
0.8	0.95	1000	199521	PF + C POS
0.8	0.95	1450	190785	PF + C POS
0.8	0.95	1900	182049	PF + C POS
0.8	0.95	2350	173313	PF + C POS
0.8	0.95	2800	164577	PF + C POS
0.8	0.95	3250	155841	PF + C POS
0.8	0.95	3700	147105	PF + C POS
0.8	0.95	4150	138369	PF + C POS
0.8	0.95	4600	129634	PF + C POS
0.8	0.95	5050	120898	PF + C POS
0.8	0.95	5500	112162	PF + C POS
0.8	0.95	5950	103426	PF + C POS
0.8	0.95	6400	94690	PF + C POS
0.8	0.95	6850	85954	PF + C POS
0.8	0.95	7300	77218	PF + C POS
0.8	0.95	7750	68482	PF + C POS
0.8	0.95	8200	59746	PF + C ALL
0.8	0.95	8650	51010	PF + C ALL
0.8	0.95	9100	42274	PF + C ALL
0.8	0.95	9550	33539	PF + C ALL
0.8	0.95	10000	24803	PF + C ALL
0.8	1	1000	200359	PF + C POS
0.8	1	1450	192006	PF + C POS

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.8	1	1900	183653	PF + C POS
0.8	1	2350	175301	PF + C POS
0.8	1	2800	166948	PF + C POS
0.8	1	3250	158595	PF + C POS
0.8	1	3700	150243	PF + C POS
0.8	1	4150	141890	PF + C POS
0.8	1	4600	133537	PF + C POS
0.8	1	5050	125185	PF + C POS
0.8	1	5500	116832	PF + C POS
0.8	1	5950	108479	PF + C POS
0.8	1	6400	100127	PF + C POS
0.8	1	6850	91774	PF + C POS
0.8	1	7300	83422	PF + C POS
0.8	1	7750	75069	PF + C POS
0.8	1	8200	66716	PF + C POS
0.8	1	8650	58364	PF + C ALL
0.8	1	9100	50011	PF + C ALL
0.8	1	9550	41658	PF + C ALL
0.8	1	10000	33306	PF + C ALL
0.85	0.7	1000	192653	PF + C POS
0.85	0.7	1450	180824	PF + C POS
0.85	0.7	1900	168995	PF + C POS
0.85	0.7	2350	157166	PF + C POS
0.85	0.7	2800	145337	PF + C POS
0.85	0.7	3250	133509	PF + C POS
0.85	0.7	3700	121680	PF + C POS
0.85	0.7	4150	109851	PF + C POS
0.85	0.7	4600	98022	PF + C POS
0.85	0.7	5050	86193	PF + C POS
0.85	0.7	5500	74365	PF + C POS
0.85	0.7	5950	62536	PF + C ALL
0.85	0.7	6400	50707	PF + C ALL
0.85	0.7	6850	38878	PF + C ALL
0.85	0.7	7300	27049	PF + C ALL
0.85	0.7	7750	15221	PF + C ALL
0.85	0.7	8200	3392	PF + C ALL
0.85	0.7	8650	−8437	PF + C ALL
0.85	0.7	9100	−20266	PF + C ALL
0.85	0.7	9550	−32095	PF + C ALL
0.85	0.7	10000	−43923	PF + C ALL
0.85	0.75	1000	194171	PF + C POS
0.85	0.75	1450	183035	PF + C POS
0.85	0.75	1900	171898	PF + C POS

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.85	0.75	2350	160761	PF + C POS
0.85	0.75	2800	149624	PF + C POS
0.85	0.75	3250	138487	PF + C POS
0.85	0.75	3700	127350	PF + C POS
0.85	0.75	4150	116213	PF + C POS
0.85	0.75	4600	105077	PF + C POS
0.85	0.75	5050	93940	PF + C POS
0.85	0.75	5500	82803	PF + C POS
0.85	0.75	5950	71666	PF + C POS
0.85	0.75	6400	60529	PF + C ALL
0.85	0.75	6850	49392	PF + C ALL
0.85	0.75	7300	38255	PF + C ALL
0.85	0.75	7750	27119	PF + C ALL
0.85	0.75	8200	15982	PF + C ALL
0.85	0.75	8650	4845	PF + C ALL
0.85	0.75	9100	−6292	PF + C ALL
0.85	0.75	9550	−17429	PF + C ALL
0.85	0.75	10000	−28566	PF + C ALL
0.85	0.8	1000	195522	PF + C POS
0.85	0.8	1450	185001	PF + C POS
0.85	0.8	1900	174479	PF + C POS
0.85	0.8	2350	163958	PF + C POS
0.85	0.8	2800	153437	PF + C POS
0.85	0.8	3250	142915	PF + C POS
0.85	0.8	3700	132394	PF + C POS
0.85	0.8	4150	121873	PF + C POS
0.85	0.8	4600	111351	PF + C POS
0.85	0.8	5050	100830	PF + C POS
0.85	0.8	5500	90308	PF + C POS
0.85	0.8	5950	79787	PF + C POS
0.85	0.8	6400	69266	PF + C POS
0.85	0.8	6850	58744	PF + C ALL
0.85	0.8	7300	48223	PF + C ALL
0.85	0.8	7750	37701	PF + C ALL
0.85	0.8	8200	27180	PF + C ALL
0.85	0.8	8650	16659	PF + C ALL
0.85	0.8	9100	6137	PF + C ALL
0.85	0.8	9550	−4384	PF + C ALL
0.85	0.8	10000	−14906	PF + C ALL
0.85	0.85	1000	196732	PF + C POS
0.85	0.85	1450	186761	PF + C POS
0.85	0.85	1900	176791	PF + C POS
0.85	0.85	2350	166821	PF + C POS
0.85	0.85	2800	156850	PF + C POS

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.85	0.85	3250	146880	PF + C POS
0.85	0.85	3700	136909	PF + C POS
0.85	0.85	4150	126939	PF + C POS
0.85	0.85	4600	116969	PF + C POS
0.85	0.85	5050	106998	PF + C POS
0.85	0.85	5500	97028	PF + C POS
0.85	0.85	5950	87057	PF + C POS
0.85	0.85	6400	77087	PF + C POS
0.85	0.85	6850	67117	PF + C POS
0.85	0.85	7300	57146	PF + C ALL
0.85	0.85	7750	47176	PF + C ALL
0.85	0.85	8200	37205	PF + C ALL
0.85	0.85	8650	27235	PF + C ALL
0.85	0.85	9100	17265	PF + C ALL
0.85	0.85	9550	7294	PF + C ALL
0.85	0.85	10000	−2676	PF + C ALL
0.85	0.9	1000	197821	PF + C POS
0.85	0.9	1450	188347	PF + C POS
0.85	0.9	1900	178872	PF + C POS
0.85	0.9	2350	169398	PF + C POS
0.85	0.9	2800	159924	PF + C POS
0.85	0.9	3250	150450	PF + C POS
0.85	0.9	3700	140975	PF + C POS
0.85	0.9	4150	131501	PF + C POS
0.85	0.9	4600	122027	PF + C POS
0.85	0.9	5050	112553	PF + C POS
0.85	0.9	5500	103078	PF + C POS
0.85	0.9	5950	93604	PF + C POS
0.85	0.9	6400	84130	PF + C POS
0.85	0.9	6850	74656	PF + C POS
0.85	0.9	7300	65181	PF + C ALL
0.85	0.9	7750	55707	PF + C ALL
0.85	0.9	8200	46233	PF + C ALL
0.85	0.9	8650	36759	PF + C ALL
0.85	0.9	9100	27285	PF + C ALL
0.85	0.9	9550	17810	PF + C ALL
0.85	0.9	10000	8336	PF + C ALL
0.85	0.95	1000	198807	PF + C POS
0.85	0.95	1450	189781	PF + C POS
0.85	0.95	1900	180756	PF + C POS
0.85	0.95	2350	171731	PF + C POS
0.85	0.95	2800	162706	PF + C POS
0.85	0.95	3250	153681	PF + C POS

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.85	0.95	3700	144656	PF + C POS
0.85	0.95	4150	135631	PF + C POS
0.85	0.95	4600	126606	PF + C POS
0.85	0.95	5050	117581	PF + C POS
0.85	0.95	5500	108555	PF + C POS
0.85	0.95	5950	99530	PF + C POS
0.85	0.95	6400	90505	PF + C POS
0.85	0.95	6850	81480	PF + C POS
0.85	0.95	7300	72455	PF + C POS
0.85	0.95	7750	63430	PF + C ALL
0.85	0.95	8200	54405	PF + C ALL
0.85	0.95	8650	45380	PF + C ALL
0.85	0.95	9100	36354	PF + C ALL
0.85	0.95	9550	27329	PF + C ALL
0.85	0.95	10000	18304	PF + C ALL
0.85	1	1000	199703	PF + C POS
0.85	1	1450	191086	PF + C POS
0.85	1	1900	182470	PF + C POS
0.85	1	2350	173853	PF + C POS
0.85	1	2800	165237	PF + C POS
0.85	1	3250	156620	PF + C POS
0.85	1	3700	148003	PF + C POS
0.85	1	4150	139387	PF + C POS
0.85	1	4600	130770	PF + C POS
0.85	1	5050	122153	PF + C POS
0.85	1	5500	113537	PF + C POS
0.85	1	5950	104920	PF + C POS
0.85	1	6400	96303	PF + C POS
0.85	1	6850	87687	PF + C POS
0.85	1	7300	79070	PF + C POS
0.85	1	7750	70453	PF + C POS
0.85	1	8200	61837	PF + C ALL
0.85	1	8650	53220	PF + C ALL
0.85	1	9100	44603	PF + C ALL
0.85	1	9550	35987	PF + C ALL
0.85	1	10000	27370	PF + C ALL
0.9	0.7	1000	191363	PF + C POS
0.9	0.7	1450	178997	PF + C POS
0.9	0.7	1900	166632	PF + C POS
0.9	0.7	2350	154267	PF + C POS
0.9	0.7	2800	141901	PF + C POS
0.9	0.7	3250	129536	PF + C POS
0.9	0.7	3700	117171	PF + C POS
0.9	0.7	4150	104805	PF + C POS

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.9	0.7	4600	92440	PF + C POS
0.9	0.7	5050	80075	PF + C POS
0.9	0.7	5500	67709	PF + C POS
0.9	0.7	5950	55344	PF + C ALL
0.9	0.7	6400	42979	PF + C ALL
0.9	0.7	6850	30613	PF + C ALL
0.9	0.7	7300	18248	PF + C ALL
0.9	0.7	7750	5883	PF + C ALL
0.9	0.7	8200	–6483	PF + C ALL
0.9	0.7	8650	–18848	PF + C ALL
0.9	0.7	9100	–31213	PF + C ALL
0.9	0.7	9550	–43579	PF + C ALL
0.9	0.7	10000	–55944	PF + C ALL
0.9	0.75	1000	193025	PF + C POS
0.9	0.75	1450	181413	PF + C POS
0.9	0.75	1900	169802	PF + C POS
0.9	0.75	2350	158191	PF + C POS
0.9	0.75	2800	146580	PF + C POS
0.9	0.75	3250	134969	PF + C POS
0.9	0.75	3700	123357	PF + C POS
0.9	0.75	4150	111746	PF + C POS
0.9	0.75	4600	100135	PF + C POS
0.9	0.75	5050	88524	PF + C POS
0.9	0.75	5500	76913	PF + C POS
0.9	0.75	5950	65302	PF + C ALL
0.9	0.75	6400	53690	PF + C ALL
0.9	0.75	6850	42079	PF + C ALL
0.9	0.75	7300	30468	PF + C ALL
0.9	0.75	7750	18857	PF + C ALL
0.9	0.75	8200	7246	PF + C ALL
0.9	0.75	8650	–4366	PF + C ALL
0.9	0.75	9100	–15977	PF + C ALL
0.9	0.75	9550	–27588	PF + C ALL
0.9	0.75	10000	–39199	PF + C ALL
0.9	0.8	1000	194496	PF + C POS
0.9	0.8	1450	183552	PF + C POS
0.9	0.8	1900	172608	PF + C POS
0.9	0.8	2350	161664	PF + C POS
0.9	0.8	2800	150721	PF + C POS
0.9	0.8	3250	139777	PF + C POS
0.9	0.8	3700	128833	PF + C POS
0.9	0.8	4150	117889	PF + C POS
0.9	0.8	4600	106946	PF + C POS

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.9	0.8	5050	96002	PF + C POS
0.9	0.8	5500	85058	PF + C POS
0.9	0.8	5950	74114	PF + C POS
0.9	0.8	6400	63171	PF + C ALL
0.9	0.8	6850	52227	PF + C ALL
0.9	0.8	7300	41283	PF + C ALL
0.9	0.8	7750	30339	PF + C ALL
0.9	0.8	8200	19396	PF + C ALL
0.9	0.8	8650	8452	PF + C ALL
0.9	0.8	9100	–2492	PF + C ALL
0.9	0.8	9550	–13436	PF + C ALL
0.9	0.8	10000	–24379	PF + C ALL
0.9	0.85	1000	195807	PF + C POS
0.9	0.85	1450	185458	PF + C POS
0.9	0.85	1900	175109	PF + C POS
0.9	0.85	2350	164760	PF + C POS
0.9	0.85	2800	154411	PF + C POS
0.9	0.85	3250	144062	PF + C POS
0.9	0.85	3700	133714	PF + C POS
0.9	0.85	4150	123365	PF + C POS
0.9	0.85	4600	113016	PF + C POS
0.9	0.85	5050	102667	PF + C POS
0.9	0.85	5500	92318	PF + C POS
0.9	0.85	5950	81969	PF + C POS
0.9	0.85	6400	71620	PF + C POS
0.9	0.85	6850	61271	PF + C ALL
0.9	0.85	7300	50922	PF + C ALL
0.9	0.85	7750	40574	PF + C ALL
0.9	0.85	8200	30225	PF + C ALL
0.9	0.85	8650	19876	PF + C ALL
0.9	0.85	9100	9527	PF + C ALL
0.9	0.85	9550	–822	PF + C ALL
0.9	0.85	10000	–11171	PF + C ALL
0.9	0.9	1000	196983	PF + C POS
0.9	0.9	1450	187167	PF + C POS
0.9	0.9	1900	177352	PF + C POS
0.9	0.9	2350	167537	PF + C POS
0.9	0.9	2800	157721	PF + C POS
0.9	0.9	3250	147906	PF + C POS
0.9	0.9	3700	138091	PF + C POS
0.9	0.9	4150	128275	PF + C POS
0.9	0.9	4600	118460	PF + C POS
0.9	0.9	5050	108645	PF + C POS
0.9	0.9	5500	98829	PF + C POS

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.9	0.9	5950	89014	PF + C POS
0.9	0.9	6400	79199	PF + C POS
0.9	0.9	6850	69383	PF + C POS
0.9	0.9	7300	59568	PF + C ALL
0.9	0.9	7750	49753	PF + C ALL
0.9	0.9	8200	39937	PF + C ALL
0.9	0.9	8650	30122	PF + C ALL
0.9	0.9	9100	20307	PF + C ALL
0.9	0.9	9550	10491	PF + C ALL
0.9	0.9	10000	676	PF + C ALL
0.9	0.95	1000	198043	PF + C POS
0.9	0.95	1450	188709	PF + C POS
0.9	0.95	1900	179375	PF + C POS
0.9	0.95	2350	170041	PF + C POS
0.9	0.95	2800	160707	PF + C POS
0.9	0.95	3250	151373	PF + C POS
0.9	0.95	3700	142039	PF + C POS
0.9	0.95	4150	132705	PF + C POS
0.9	0.95	4600	123370	PF + C POS
0.9	0.95	5050	114036	PF + C POS
0.9	0.95	5500	104702	PF + C POS
0.9	0.95	5950	95368	PF + C POS
0.9	0.95	6400	86034	PF + C POS
0.9	0.95	6850	76700	PF + C POS
0.9	0.95	7300	67366	PF + C POS
0.9	0.95	7750	58032	PF + C ALL
0.9	0.95	8200	48697	PF + C ALL
0.9	0.95	8650	39363	PF + C ALL
0.9	0.95	9100	30029	PF + C ALL
0.9	0.95	9550	20695	PF + C ALL
0.9	0.95	10000	11361	PF + C ALL
0.9	1	1000	199005	PF + C POS
0.9	1	1450	190107	PF + C POS
0.9	1	1900	181209	PF + C POS
0.9	1	2350	172311	PF + C POS
0.9	1	2800	163413	PF + C POS
0.9	1	3250	154515	PF + C POS
0.9	1	3700	145618	PF + C POS
0.9	1	4150	136720	PF + C POS
0.9	1	4600	127822	PF + C POS
0.9	1	5050	118924	PF + C POS
0.9	1	5500	110026	PF + C POS
0.9	1	5950	101128	PF + C POS

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.9	1	6400	92230	PF + C POS
0.9	1	6850	83332	PF + C POS
0.9	1	7300	74435	PF + C POS
0.9	1	7750	65537	PF + C ALL
0.9	1	8200	56639	PF + C ALL
0.9	1	8650	47741	PF + C ALL
0.9	1	9100	38843	PF + C ALL
0.9	1	9550	29945	PF + C ALL
0.9	1	10000	21047	PF + C ALL
0.95	0.7	1000	189950	PF + C POS
0.95	0.7	1450	176997	PF + C POS
0.95	0.7	1900	164044	PF + C POS
0.95	0.7	2350	151091	PF + C POS
0.95	0.7	2800	138138	PF + C POS
0.95	0.7	3250	125186	PF + C POS
0.95	0.7	3700	112233	PF + C POS
0.95	0.7	4150	99280	PF + C POS
0.95	0.7	4600	86327	PF + C POS
0.95	0.7	5050	73374	PF + C POS
0.95	0.7	5500	60421	PF + C ALL
0.95	0.7	5950	47469	PF + C ALL
0.95	0.7	6400	34516	PF + C ALL
0.95	0.7	6850	21563	PF + C ALL
0.95	0.7	7300	8610	PF + C ALL
0.95	0.7	7750	–4343	PF + C ALL
0.95	0.7	8200	–17296	PF + C ALL
0.95	0.7	8650	–30249	PF + C ALL
0.95	0.7	9100	–43201	PF + C ALL
0.95	0.7	9550	–56154	PF + C ALL
0.95	0.7	10000	–69107	PF + C ALL
0.95	0.75	1000	191776	PF + C POS
0.95	0.75	1450	179648	PF + C POS
0.95	0.75	1900	167520	PF + C POS
0.95	0.75	2350	155393	PF + C POS
0.95	0.75	2800	143265	PF + C POS
0.95	0.75	3250	131137	PF + C POS
0.95	0.75	3700	119009	PF + C POS
0.95	0.75	4150	106882	PF + C POS
0.95	0.75	4600	94754	PF + C POS
0.95	0.75	5050	82626	PF + C POS
0.95	0.75	5500	70499	PF + C POS
0.95	0.75	5950	58371	PF + C ALL
0.95	0.75	6400	46243	PF + C ALL
0.95	0.75	6850	34115	PF + C ALL

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.95	0.75	7300	21988	PF + C ALL
0.95	0.75	7750	9860	PF + C ALL
0.95	0.75	8200	−2268	PF + C ALL
0.95	0.75	8650	−14396	PF + C ALL
0.95	0.75	9100	−26523	PF + C ALL
0.95	0.75	9550	−38651	PF + C ALL
0.95	0.75	10000	−50779	PF + C ALL
0.95	0.8	1000	193383	PF + C POS
0.95	0.8	1450	181982	PF + C POS
0.95	0.8	1900	170580	PF + C POS
0.95	0.8	2350	159179	PF + C POS
0.95	0.8	2800	147777	PF + C POS
0.95	0.8	3250	136376	PF + C POS
0.95	0.8	3700	124975	PF + C POS
0.95	0.8	4150	113573	PF + C POS
0.95	0.8	4600	102172	PF + C POS
0.95	0.8	5050	90770	PF + C POS
0.95	0.8	5500	79369	PF + C POS
0.95	0.8	5950	67967	PF + C POS
0.95	0.8	6400	56566	PF + C ALL
0.95	0.8	6850	45164	PF + C ALL
0.95	0.8	7300	33763	PF + C ALL
0.95	0.8	7750	22361	PF + C ALL
0.95	0.8	8200	10960	PF + C ALL
0.95	0.8	8650	−441	PF + C ALL
0.95	0.8	9100	−11843	PF + C ALL
0.95	0.8	9550	−23244	PF + C ALL
0.95	0.8	10000	−34646	PF + C ALL
0.95	0.85	1000	194809	PF + C POS
0.95	0.85	1450	184052	PF + C POS
0.95	0.85	1900	173295	PF + C POS
0.95	0.85	2350	162537	PF + C POS
0.95	0.85	2800	151780	PF + C POS
0.95	0.85	3250	141023	PF + C POS
0.95	0.85	3700	130266	PF + C POS
0.95	0.85	4150	119508	PF + C POS
0.95	0.85	4600	108751	PF + C POS
0.95	0.85	5050	97994	PF + C POS
0.95	0.85	5500	87237	PF + C POS
0.95	0.85	5950	76479	PF + C POS
0.95	0.85	6400	65722	PF + C ALL
0.95	0.85	6850	54965	PF + C ALL
0.95	0.85	7300	44208	PF + C ALL

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.95	0.85	7750	33450	PF + C ALL
0.95	0.85	8200	22693	PF + C ALL
0.95	0.85	8650	11936	PF + C ALL
0.95	0.85	9100	1179	PF + C ALL
0.95	0.85	9550	–9579	PF + C ALL
0.95	0.85	10000	–20336	PF + C ALL
0.95	0.9	1000	196082	PF + C POS
0.95	0.9	1450	185900	PF + C POS
0.95	0.9	1900	175718	PF + C POS
0.95	0.9	2350	165536	PF + C POS
0.95	0.9	2800	155354	PF + C POS
0.95	0.9	3250	145173	PF + C POS
0.95	0.9	3700	134991	PF + C POS
0.95	0.9	4150	124809	PF + C POS
0.95	0.9	4600	114627	PF + C POS
0.95	0.9	5050	104445	PF + C POS
0.95	0.9	5500	94263	PF + C POS
0.95	0.9	5950	84081	PF + C POS
0.95	0.9	6400	73899	PF + C POS
0.95	0.9	6850	63717	PF + C ALL
0.95	0.9	7300	53535	PF + C ALL
0.95	0.9	7750	43353	PF + C ALL
0.95	0.9	8200	33171	PF + C ALL
0.95	0.9	8650	22989	PF + C ALL
0.95	0.9	9100	12807	PF + C ALL
0.95	0.9	9550	2625	PF + C ALL
0.95	0.9	10000	–7557	PF + C ALL
0.95	0.95	1000	197226	PF + C POS
0.95	0.95	1450	187561	PF + C POS
0.95	0.95	1900	177896	PF + C POS
0.95	0.95	2350	168231	PF + C POS
0.95	0.95	2800	158566	PF + C POS
0.95	0.95	3250	148901	PF + C POS
0.95	0.95	3700	139236	PF + C POS
0.95	0.95	4150	129571	PF + C POS
0.95	0.95	4600	119906	PF + C POS
0.95	0.95	5050	110241	PF + C POS
0.95	0.95	5500	100576	PF + C POS
0.95	0.95	5950	90911	PF + C POS
0.95	0.95	6400	81246	PF + C POS
0.95	0.95	6850	71581	PF + C POS
0.95	0.95	7300	61915	PF + C ALL
0.95	0.95	7750	52250	PF + C ALL
0.95	0.95	8200	42585	PF + C ALL

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
0.95	0.95	8650	32920	PF + C ALL
0.95	0.95	9100	23255	PF + C ALL
0.95	0.95	9550	13590	PF + C ALL
0.95	0.95	10000	3925	PF + C ALL
0.95	1	1000	198260	PF + C POS
0.95	1	1450	189062	PF + C POS
0.95	1	1900	179863	PF + C POS
0.95	1	2350	170665	PF + C POS
0.95	1	2800	161467	PF + C POS
0.95	1	3250	152269	PF + C POS
0.95	1	3700	143071	PF + C POS
0.95	1	4150	133873	PF + C POS
0.95	1	4600	124675	PF + C POS
0.95	1	5050	115477	PF + C POS
0.95	1	5500	106279	PF + C POS
0.95	1	5950	97080	PF + C POS
0.95	1	6400	87882	PF + C POS
0.95	1	6850	78684	PF + C POS
0.95	1	7300	69486	PF + C POS
0.95	1	7750	60288	PF + C ALL
0.95	1	8200	51090	PF + C ALL
0.95	1	8650	41892	PF + C ALL
0.95	1	9100	32694	PF + C ALL
0.95	1	9550	23496	PF + C ALL
0.95	1	10000	14298	PF + C ALL
1	0.7	1000	188396	PF + C POS
1	0.7	1450	174797	PF + C POS
1	0.7	1900	161198	PF + C POS
1	0.7	2350	147599	PF + C POS
1	0.7	2800	134000	PF + C POS
1	0.7	3250	120401	PF + C POS
1	0.7	3700	106802	PF + C POS
1	0.7	4150	93203	PF + C POS
1	0.7	4600	79604	PF + C POS
1	0.7	5050	66005	PF + C ALL
1	0.7	5500	52406	PF + C ALL
1	0.7	5950	38807	PF + C ALL
1	0.7	6400	25208	PF + C ALL
1	0.7	6850	11609	PF + C ALL
1	0.7	7300	−1989	PF + C ALL
1	0.7	7750	−15588	PF + C ALL
1	0.7	8200	−29187	PF + C ALL
1	0.7	8650	−42786	PF + C ALL

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
1	0.7	9100	−56385	PF + C ALL
1	0.7	9550	−69984	PF + C ALL
1	0.7	10000	−83583	PF + C ALL
1	0.75	1000	190411	PF + C POS
1	0.75	1450	177719	PF + C POS
1	0.75	1900	165026	PF + C POS
1	0.75	2350	152334	PF + C POS
1	0.75	2800	139641	PF + C POS
1	0.75	3250	126949	PF + C POS
1	0.75	3700	114257	PF + C POS
1	0.75	4150	101564	PF + C POS
1	0.75	4600	88872	PF + C POS
1	0.75	5050	76179	PF + C POS
1	0.75	5500	63487	PF + C ALL
1	0.75	5950	50795	PF + C ALL
1	0.75	6400	38102	PF + C ALL
1	0.75	6850	25410	PF + C ALL
1	0.75	7300	12718	PF + C ALL
1	0.75	7750	25	PF + C ALL
1	0.75	8200	−12667	PF + C ALL
1	0.75	8650	−25360	PF + C ALL
1	0.75	9100	−38052	PF + C ALL
1	0.75	9550	−50744	PF + C ALL
1	0.75	10000	−63437	PF + C ALL
1	0.8	1000	192174	PF + C POS
1	0.8	1450	180275	PF + C POS
1	0.8	1900	168376	PF + C POS
1	0.8	2350	156476	PF + C POS
1	0.8	2800	144577	PF + C POS
1	0.8	3250	132678	PF + C POS
1	0.8	3700	120779	PF + C POS
1	0.8	4150	108880	PF + C POS
1	0.8	4600	96981	PF + C POS
1	0.8	5050	85082	PF + C POS
1	0.8	5500	73183	PF + C POS
1	0.8	5950	61284	PF + C ALL
1	0.8	6400	49384	PF + C ALL
1	0.8	6850	37485	PF + C ALL
1	0.8	7300	25586	PF + C ALL
1	0.8	7750	13687	PF + C ALL
1	0.8	8200	1788	PF + C ALL
1	0.8	8650	−10111	PF + C ALL
1	0.8	9100	−22010	PF + C ALL
1	0.8	9550	−33909	PF + C ALL

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
1	0.8	10000	−45808	PF + C ALL
1	0.85	1000	193729	PF + C POS
1	0.85	1450	182530	PF + C POS
1	0.85	1900	171331	PF + C POS
1	0.85	2350	160132	PF + C POS
1	0.85	2800	148933	PF + C POS
1	0.85	3250	137733	PF + C POS
1	0.85	3700	126534	PF + C POS
1	0.85	4150	115335	PF + C POS
1	0.85	4600	104136	PF + C POS
1	0.85	5050	92937	PF + C POS
1	0.85	5500	81738	PF + C POS
1	0.85	5950	70538	PF + C POS
1	0.85	6400	59339	PF + C ALL
1	0.85	6850	48140	PF + C ALL
1	0.85	7300	36941	PF + C ALL
1	0.85	7750	25742	PF + C ALL
1	0.85	8200	14543	PF + C ALL
1	0.85	8650	3343	PF + C ALL
1	0.85	9100	−7856	PF + C ALL
1	0.85	9550	−19055	PF + C ALL
1	0.85	10000	−30254	PF + C ALL
1	0.9	1000	195112	PF + C POS
1	0.9	1450	184535	PF + C POS
1	0.9	1900	173958	PF + C POS
1	0.9	2350	163381	PF + C POS
1	0.9	2800	152804	PF + C POS
1	0.9	3250	142227	PF + C POS
1	0.9	3700	131650	PF + C POS
1	0.9	4150	121073	PF + C POS
1	0.9	4600	110496	PF + C POS
1	0.9	5050	99919	PF + C POS
1	0.9	5500	89342	PF + C POS
1	0.9	5950	78765	PF + C POS
1	0.9	6400	68188	PF + C POS
1	0.9	6850	57611	PF + C ALL
1	0.9	7300	47034	PF + C ALL
1	0.9	7750	36457	PF + C ALL
1	0.9	8200	25880	PF + C ALL
1	0.9	8650	15303	PF + C ALL
1	0.9	9100	4726	PF + C ALL
1	0.9	9550	−5851	PF + C ALL
1	0.9	10000	−16428	PF + C ALL

(*continued on next page*)

Supplementary Table 4. (*Continued*)

Test sensitivity	Test specificity	Test cost (€)	ICUR (€/QALY)	Cost-effective strategy
1	0.95	1000	196349	PF + C POS
1	0.95	1450	186329	PF + C POS
1	0.95	1900	176308	PF + C POS
1	0.95	2350	166288	PF + C POS
1	0.95	2800	156268	PF + C POS
1	0.95	3250	146247	PF + C POS
1	0.95	3700	136227	PF + C POS
1	0.95	4150	126207	PF + C POS
1	0.95	4600	116186	PF + C POS
1	0.95	5050	106166	PF + C POS
1	0.95	5500	96146	PF + C POS
1	0.95	5950	86126	PF + C POS
1	0.95	6400	76105	PF + C POS
1	0.95	6850	66085	PF + C ALL
1	0.95	7300	56065	PF + C ALL
1	0.95	7750	46044	PF + C ALL
1	0.95	8200	36024	PF + C ALL
1	0.95	8650	26004	PF + C ALL
1	0.95	9100	15983	PF + C ALL
1	0.95	9550	5963	PF + C ALL
1	0.95	10000	–4057	PF + C ALL
1	1	1000	197462	PF + C POS
1	1	1450	187943	PF + C POS
1	1	1900	178424	PF + C POS
1	1	2350	168904	PF + C POS
1	1	2800	159385	PF + C POS
1	1	3250	149866	PF + C POS
1	1	3700	140347	PF + C POS
1	1	4150	130827	PF + C POS
1	1	4600	121308	PF + C POS
1	1	5050	111789	PF + C POS
1	1	5500	102269	PF + C POS
1	1	5950	92750	PF + C POS
1	1	6400	83231	PF + C POS
1	1	6850	73712	PF + C POS
1	1	7300	64192	PF + C ALL
1	1	7750	54673	PF + C ALL
1	1	8200	45154	PF + C ALL
1	1	8650	35634	PF + C ALL
1	1	9100	26115	PF + C ALL
1	1	9550	16596	PF + C ALL
1	1	10000	7077	PF + C ALL