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ORIGINAL ARTICLE

The cost-effectiveness of UGT1A1 genotyping before colorectal cancer treatment with irinotecan from the perspective of the German statutory health insurance

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ABSTRACT

Background. The evidence concerning the cost-effectiveness of UGT1A1*28 genotyping is ambiguous and does not allow drawing valid conclusions for Germany. This study evaluates the cost-effectiveness of UGT1A1 genotyping in patients with metastatic colorectal cancer undergoing irinotecan-based chemotherapy compared to no testing from the perspective of the German statutory health insurance.

Material and methods. A decision-analytic Markov model with a life time horizon was developed. No testing was compared to two genotype-dependent therapy strategies: 1) dose reduction by 25%; and 2) administration of a prophylactic G-CSF growth factor analog for homozygous and heterozygous patients. Probability, quality of life and cost parameters used in this study were based on published literature. Deterministic and probabilistic sensitivity analyses were performed to account for parameter uncertainties.

Results. Strategy 1 dominated all remaining strategies. Compared to no testing, it resulted in only marginal QALY increases (0.0002) but a cost reduction of €580 per patient. Strategy 2 resulted in the same health gains but increased costs by €10 773. In the probabilistic analysis, genotyping and dose reduction was the optimal strategy in approximately 100% of simulations at a threshold of €50 000 per QALY. Deterministic sensitivity analysis shows that uncertainty for this strategy originated primarily from costs for irinotecan-based chemotherapy, from the prevalence of neutropenia among heterozygous patients, and from whether dose reduction is applied to both homozygotes and heterozygotes or only to the former.

Conclusion. This model-based synthesis of the most recent evidence suggests that pharmacogenetic UGT1A1 testing prior to irinotecan-based chemotherapy dominates non-personalized colon cancer care in Germany. However, as structural uncertainty remains high, these results require validation in clinical practice, e.g. based on a managed-entry agreement.

Personalized medicine is considered promising because more precise diagnosis and risk assessment can increase treatment effectiveness and prevent side effects [1]. Also, it has the potential to increase the cost-effectiveness of healthcare [2]. However, the cost-effectiveness of personalized medicine strongly depends on how molecular markers are used for stratification so that specific personalization strategies need to be assessed economically [3]. In oncology, personalized medicine plays a special role in the form of pharmacogenetic approaches [4]. One example is the genetic test for the common *28 allele of

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the UDP-glucuronosyltransferase 1A1 (UGT1A1) gene in patients with metastatic colorectal cancer (mCRC) undergoing irinotecan-based chemotherapy [5]. In Germany, colorectal cancer is the second most common type of cancer and cause of cancer death for both women and men [6]. The Centre for Cancer Registry Data in the Robert Koch Institute predicted a number of new cases of colorectal cancer of about 69 000 for 2012 [7]. Approximately half of the patients develop metastatic disease which involves high mortality [8]. The treatment options for mCRC have significantly improved over the recent years due to the introduction of new chemotherapeutic agents, such as irinotecan [9]. Among the adverse side effects of this drug, however, are neutropenia, a decrease in the number of neutrophil granulocytes, and diarrhea which both can be life threatening [5].

In the human body, irinotecan is converted into its active metabolite SN-38 which causes cell death. Excretion takes place via UGT1A1-catalyzed conversion to the inactive metabolite SN-38G [10]. A recent meta-analysis based on 16 individual studies concludes that both the heterozygous *1/*28 and the homozygous *28/*28 genotypes are associated with increased side effects of irinotecan, particularly neutropenia and diarrhea [11]. It is believed that the reduced activity of the enzyme UGT1A1 in these genotypes and the thus increased concentration of the toxic SN-38 in the human body is responsible for this effect [12]. Accordingly, it is already recommended in the prescribing information of irinotecan, to reduce the starting dose by at least one level in 'patients known to be homozygous for the UGT1A1*28 allele' [13].

To our knowledge, three cost-effectiveness analyses of UGT1A1 genotyping in irinotecan chemotherapy have been published to date. None of these studies considers the increased risk for diarrhea in UGT1A1 mutation carriers. In 2008, Obradovic et al. [14] compared standard therapy with the strategy of dose reduction and another strategy for the prevention of neutropenia, the administration of a G-CSF analog growth factor (pegfilgrastim). They reported the number of prevented cases of neutropenia and life years gained, as well as the costs from the perspective of a health care payer in the US. Genotyping in combination with dose reduction in homozygotes was cost saving in the study, when combined with the administration of growth factors it led to costs of approximately $3.8 million per life-year gained. Gold et al. [15] evaluated the costs per quality-adjusted life year (QALY) gained of dose reduction from the perspective of Medicare in the US. They also came to the conclusion that genotyping in combination with dose reduction leads to lower costs and improved health outcomes when compared with standard therapy. Furthermore, the most recent study evaluated genotyping in combination with the administration of growth factors from a hospital-perspective in France by Pichereau et al. in 2010 [16]. As a measure of effect, the number of prevented cases of neutropenia was reported and an incremental cost-effectiveness ratio (ICER) of about €1000 per avoided neutropenia was calculated.

If they were explicitly calculated, the study results agree regarding the assessment of the cost-effectiveness of genotyping in combination with dose reduction. Despite these promising results, UGT1A1 genotyping is not applied on a regular basis in Germany. This may be due to the fact that none of the existing evaluations described the German situation, which may differ greatly from that in other health care contexts [17]. Moreover, the results were heterogeneous regarding the cost-effectiveness of genotyping in combination with the prophylactic use of growth factors. Also, more evidence of costs and effect parameters may have been published in the meantime which can have a significant impact on the cost-effectiveness of genetic testing [18]. The cost-effectiveness of UGT1A1 genotyping in Germany is therefore unclear. Hence, the aim of the present study was to review the most recent evidence and assess the costs per QALY gained on an adapted decision-analytic model.

Materials and methods

Model structure

A decision-analytic model was developed from the perspective of the German statutory health insurance using Tree Age Pro 2011. The patient population of interest was mCRC patients who received an irinotecan combination therapy (FOLFIRI scheme existing of folinic acid, fluorouracil and irinotecan) as first-line therapy for mCRC.

Included strategies

In Germany, there is a lack of information on the optimal modified care pathways after UGT1A1 genotyping. Therefore, this study assesses the costs and QALYs of the two main strategies described in the literature [5] as well as the no testing strategy. Genotyping identifies not only the homozygous (i.e. *28/*28) but also the heterozygous (mainly *1/*28) mutation carriers. As a recently published meta-analysis reported a significantly increased risk of neutropenia and diarrhea for homozygous (i.e. *28/*28) as well as heterozygous (mainly *1/*28) mutation carriers [11] the adapted treatment pathways were assumed to be applied to both types of patients. The following strategies were included:

1. Strategy 1: dose reduction (wildtypes receive standard dose of irinotecan, hetero- and homozygotes receive a dose reduction of irinotecan by 25%);
2. Strategy 2: prophylactic administration of bone marrow protective G-CSF growth factor analogs (all patients receive standard dose of irinotecan, hetero- and homozygotes additionally receive the growth factor 'pegfilgrastim');
3. Strategy 3: no genetic test (all patients receive standard dose of irinotecan).

Markov model

Lifetime Markov models with a cycle length of two weeks were used to estimate cancer related mortality and treatment costs of the included strategies. The Markov process continued until approximately 99% of modeled cohort had died (which was after 113 Markov cycles).

Figure 1 gives an overview of the model structure and (Supplementary Appendix 1 available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2015.1053983) lists all main assumptions the Markov structure is based on. All patients start in the Markov state 'initial cancer care' and can then incur an episode of severe neutropenia, severe diarrhea, stay without neutropenia and diarrhea or die from colorectal cancer. Adverse events are incorporated within the overall Markov model by bridge models. The bridge models characterize the adverse events and their immediate consequences by integrating probabilities for different care pathways (inpatient or outpatient care), QALY-decrements during this time, and probabilities of death from the adverse event within one period. Persons who survive adverse events leave the bridge model and enter the overall Markov state 'post-neutropenia care'. Here, they are assumed to receive a subsequent chemotherapy regimen which prevents further cases of neutropenia and diarrhea. The subsequent regimen was also administered to those patients that had completed the first-line FOLFIRI treatment for a maximum of 26 weeks (13 Markov cycles). This corresponds with the medium treatment duration of the FOLFIRI regime observed in the multicenter CRYSTAL trial [19]. The duration of the subsequent therapy line was limited to a maximum of 24 weeks based on a Delphi panel reported in a German study [20]. The subsequent line of therapy is only assumed to influence costs but it does not affect overall survival and quality of life.

Input parameters

We obtained input parameters from the published literature using PubMed searches and reference tracking. Due to the study perspective, if available, data referring to German populations were used to parameterize this model. (Supplementary Appendix 2 available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2015.1053983) provides additional information about the literature

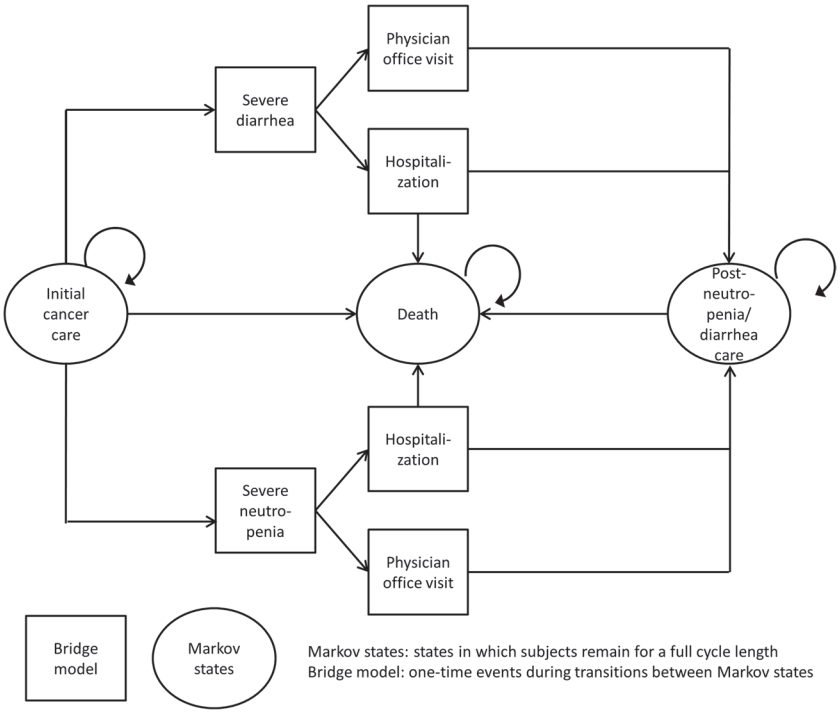

Figure 1. Model structure.

search and (Supplementary Appendix 3 available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2015.1053983) lists all model parameters.

Survival

Transition probabilities for overall survival form CRC patients treated with first-line FOLFIRI were based on the CRYSTAL study [19]. We digitized the published Kaplan-Meier curve reported in this study using the Digitizeit software. The digitized product was then used to construct curve fits using methods developed by Guyot and colleagues [21]. Parametric fits were obtained for exponential, lognormal, Weibull, loglogistic and Gompertz distributions using R software. The Weilbull distribution was selected as the best-fitted curve according to visual assessment and the Bayesian information criterion.

Probabilities

The population prevalence of the different UGT1A1 genotypes was derived from a study among 105 Caucasian patients [22]. The analytic sensitivity and specificity of UGT1A1 genotyping was assumed to be 100% which is supported by an EGAPP review [23].

Incidences of severe (defined as grade 3 and 4) neutropenia for the respective genotypes were taken from a French clinical trial [24], which assumes an incidence of 14% for wildtype patients, 23% for heterozygous patients and 50% for homozygous patients. Incidence of severe diarrhea was taken from a Spanish study which reports an incidence of severe diarrhea of 23% for wildtype patients, 30% for heterozygous patients and 60% for homozygous patients [25]. For both side effects conversion to rate was used to convert incidences into two-week probabilities assuming that reported rates are constant over time [26].

Dose reduction and administration of growth factors were both assumed to decrease the risk of toxicity in heterozygous and homozygous patients without affecting the therapeutic effect of irinotecan. This was based on the assumption that the mutation leads to increased concentration of active molecules and that dose reduction reduces these to approximately the same level as the initial dose in non-mutated individuals. Furthermore, it is assumed that that increasing the dose of active molecules above this level does not impact treatment effect. Limitations of these assumptions are addressed in the discussion section.

Concerning the dose reduction strategy, the associated risk ratio was deduced from a clinical trial where incidences of severe neutropenia and diarrhea were compared between the first cycle and the entire course of chemotherapy [27]. The proxy was based on the assumption that irinotecan doses were lowered for patients encountering an episode of severe neutropenia in the first cycle. The resulting risk ratios of 33% for severe diarrhea and 30% for severe neutropenia were applied to both heterozygous and homozygous patients.

Concerning the growth factors strategy, we could not find any evidence from the clinical setting that the administration of growth factors does impact the risk for diarrhea. Therefore the study assumes that the risk for diarrhea does not change when growth factors are added to the FOLFIRI regime. However, there is published evidence that the administration of growth factors has an impact on the risk of neutropenia. The risk ratio for severe neutropenia was assumed 31% as reported in a randomized clinical trial conducted with the growth factor pegfilgrastim [28]. Like in the dose reduction strategy, the risk ratio for the growth factor was applied to both heterozygous and homozygous mutation carriers.

No study could be identified which reported hospitalization rates due to severe neutropenia and diarrhea among mCRC patients with irinotecan treatment. Assuming that all cases of febrile neutropenia must be treated in hospital, the rate of febrile neutropenia among severe neutropenia served as a proxy for the hospitalization rate and was drawn from a clinical trial [29]. Hospitalization rate due to diarrhea was assumed to be 25% based on expert judgment. The remainder of patients with severe neutropenia and diarrhea was assumed to be treated on an outpatient basis.

Evidence for mortality due to febrile neutropenia or diarrhea is limited. Except for the study by Aranda et al. [30] which reports on one death due to febrile neutropenia among 173 patients treated with the FOLFIRI regime, identified clinical trials do not report on any treatment related death due to neutropenia or diarrhea [31,32]. To provide a conservative estimate of effectiveness, the base case analysis of this study therefore assumes a zero risk of death due to neutropenia and diarrhea. As this assumption is subject to uncertainty, deterministic and probabilistic sensitivity analysis accounts for increased risk of treatment-related death due to neutropenia and diarrhea.

Health-related quality of life

Health-related quality of life for patients with mCRC was derived from a study based on evaluation with the EQ-5D HIS in mCRC patients treated with FOLFIRI in a second-line trial [33].

Quality of life associated with adverse events was modeled using quality of life decrements which were multiplied with the duration of the adverse event to estimate the corresponding QALY losses. The Diagnostic Assessment report by the National Institute for Health and Care Excellence (NICE) summarizes

the evidence on quality of life decrements for chemotherapy related adverse events [34]. In line with this report we assume quality of life decrements of 0.074 for diarrhea, of 0.073 for neutropenia and of 0.112 for febrile neutropenia.

Costs

Costs were calculated in 2013 euros (€) and both costs and effects were discounted at a rate of 3% per annum. Adopting the perspective of the German statutory health insurance, the health resource consumption was evaluated with the current reimbursement rates.

Costs of pegfilgrastim growth factors were estimated from Germans official pharmacists' price schedule (Lauer-Taxe) [35]. Calculation of costs for FOLFIRI treatment was also based on the Lauer-Taxe multiplying the drug unit costs with the required numbers of units (assuming wastage). Standard dose of irinotecan was calculated for a female patient with a body surface of 1.5 m^2 and for a male patient with 2 m^2. (Supplementary Appendix 4 available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2015.1053983) provides calculation details. Average cost for chemotherapy was calculated with a share of 55% of men and 45% of women [7]. Reduced dose of FOLFIRI treatment were calculated likewise and then expressed as a fraction of the full dose.

To provide a conservative assessment, costs of subsequent chemotherapy were assumed lower than the initial FOLFIRI therapy. Precisely, costs of subsequent chemotherapy were taken from Asseburg et al. [20] who provide a weighted cost average for second-line chemotherapies according to the frequency of use in patients with metastatic colorectal cancer in Germany. As Asseburg et al. report costs in 2010 euros, costs of second-line treatment were transferred to 2013 values based on the consumer price index provided by the German Federal Statistical Office [36].

Cost for UGT1A1 genotyping was calculated from the German ambulatory fee schedule, based on fixed points per type of service multiplied by a baseline point value [37]. Costs for hospitalization due to neutropenia and diarrhea were calculated using Diagnosis Related Groups (DRG) multiplied with the current German DRG value [38].

Deterministic sensitivity analysis

Univariate sensitivity analyses were performed on all input parameters for the two genetic testing strategies compared to no genetic testing. Upper and lower limits of the 95% confidence intervals were used for building the value ranges. Concerning the variable 'death from hospitalized neutropenia' and 'death from hospitalized diarrhea' the values for the upper limits of the confidence intervals were chosen from literature [39,40]. The conjoint probabilities of the Dirichlet distributions were varied by choosing the probability for one category and by holding the proportions of the remaining probabilities constant. The 10 variables with the highest impact on model uncertainty are presented in a tornado diagram, expressed in terms of net monetary benefit. Net monetary benefit is calculated by taking the difference in effectiveness between two strategies and multiplying by society's willingness-to-pay, less the difference in costs. Given that there exists no explicit cost-effectiveness threshold for Germany, net benefits were calculated with the frequently quoted willingness to pay threshold of €50 000 for illustration [41].

As the amount of dose-reduction might considerably impact the calculated costs, we also performed structural sensitivity analysis, assuming different degrees of dose-reduction in heterozygotes.

Probabilistic sensitivity analysis

To assess for overall parameter uncertainty, a probabilistic sensitivity analysis based on 100 000 Monte Carlo simulations was performed. As proposed by Briggs et al. [42] Dirichlet distribution was used to model the prevalence of the UGT1A1 genotypes [wildtype (*1/*1), heterozygous (*1/*28), homozygous (*28/*28) mutation carriers]. Beta distributions were assigned to probabilities and quality of life weights and gamma distributions to costs. The distribution parameters for quality of life weights and costs were approximated based on their mean values and standard errors. If no standard error was available, an estimate was derived. Normal distributions were adopted for log risk ratios.

Decision uncertainty is presented by means of cost-effectiveness acceptability curves. Furthermore, the potential value of collecting further evidence on uncertain parameter was quantified using expected value of perfect information (EVPI) analysis. Population EVPI was based on the assumption that around 80% of the approximate 30 000 patients diagnosed with mCRC each year in Germany (primary findings or in the course of disease) [43] received an irinotecan-based chemotherapy regimen. Given the high technology dynamic in personalized cancer care, population EVPI was calculated with a discount rate of 3% for a time horizon of five years as well as for an infinite time horizon.

Results

Effectiveness

According to our model results, approximately 45% of the homozygotes, 22% of the heterozygotes and 13% of the wildtype patients suffer from severe neutropenia if no genetic testing is performed. Moreover,

approximately 19% of the homozygotes, 10% of the heterozygotes and 8% of the wildtype patients develop severe diarrhea. Due to genetic testing and dose reduction cases of neutropenia can be reduced to 18% among homozygous and 7% among heterozygous patients and severe diarrhea can be reduced to 9% and 4%, respectively. In the case of genetic testing and administration of growth factors, approximately 17% of the homozygotes and 7% of the heterozygotes develop severe neutropenia and severe diarrhea occurs in 24% and 10%, respectively.

Cost-effectiveness

The strategy 'genetic test and dose reduction' is the cheapest strategy and is associated with costs of €23 414 and effects of approximately 1.1292 QALYs. The two other strategies are absolutely dominated. The strategy 'no genetic test' resulted in costs of €23 995 and 1.1290 QALYs. The strategy 'genetic test and growth factors' is most expensive with costs of €34 187 and effects of 1.1292 QALYs. These results are illustrated in Figure 2. The QALY differences between the three strategies are small (range 1.1290–1.1292) which can be explained by the assumption that febrile neutropenia and diarrhea does not increase mortality and quality of life increments occur for only one week. However, compared to the no testing strategy, 'genetic test and dose reduction' shows a cost-saving potential of about €600 per patient. This reduction in costs is primarily driven by reduced costs for the FOLFIRI chemotherapy. The strategy of growth factors yields approximately the same QALY gains as dose reduction. Due to its high costs, this strategy results in an ICER of about €65 million per QALY gained compared to the no testing strategy.

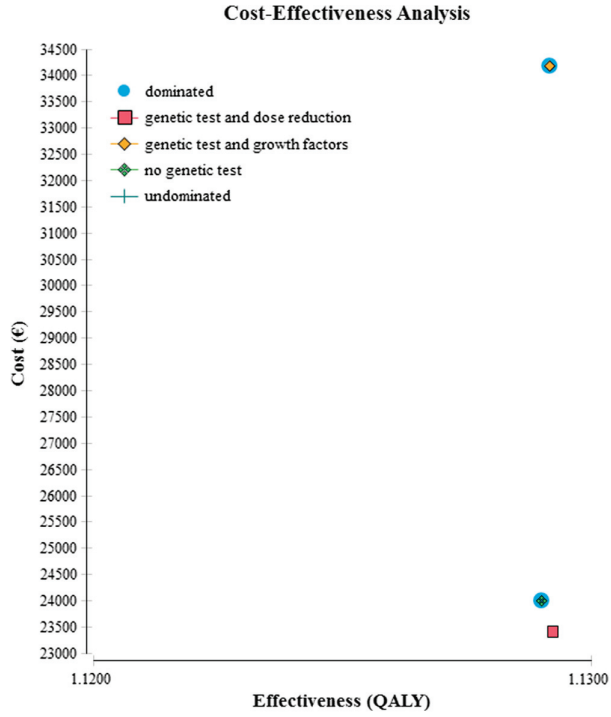

Figure 2. Cost-effectiveness.

Deterministic sensitivity analysis

Figures 3 and 4 show the impact of varying input parameters across wider intervals on net benefits of the dose reduction and the growth factors strategies. Concerning the dose reduction strategy, especially the costs for the FOLFIRI chemotherapy and the probability of severe neutropenia in heterozygous patients appear to be critical drivers of the net benefits. The costs of growth factors had a considerable effect on the net benefit of 'genetic test and growth factor' versus 'no genetic test' (Figure 4). To a lesser extent, the net benefit was influenced by the probability of having a heterozygous genotype.

The study assumed that homozygotes and heterozygotes were treated equally which may overestimate the cost savings if a dose reduction of 25% for heterozygotes was not considered acceptable. Given the importance of chemotherapy costs, a scenario analysis was conducted where dose reduction and associated costs and effects were restricted to homozygotes. In this scenario, the strategy increases costs compared to no testing by about €99 and results in a QALY gain about 0.0001. Compared to the no testing strategy this scenario would result in an ICER of €17 040 017 per QALY gained. We also investigated an intermediate scenario in which homozygous patients receive a full dose reduction of 25% and heterozygous patients receive a smaller dose reduction of only 15%, assuming that this has the same effects on the prevention of side effects as the full dose reduction. In this scenario, the strategy increases costs compared to no testing about €740 and would result in a QALY gain of about 0.0002. The calculated ICER of this scenario compared to 'no testing' is €3 285 545 per QALY gained.

Probabilistic sensitivity analysis

The impact of willingness-to-pay (WTP) on strategy selection was negligible in the examined range of €0–100 000 per QALY (Figure 5). As the strategy of dose reduction dominates the other strategies, cost-effectiveness is less relevant at this point. Moreover, the WTP range does not cover the relevant values because significant changes to the cost-effectiveness of the different strategies only occur at WTP values of approximately €1 500 000 and more per QALY. Based on a threshold value of, e.g. €50 000 per QALY, the strategy 'genetic test and dose reduction' was optimal in 100% of simulations. Mean QALYs and costs

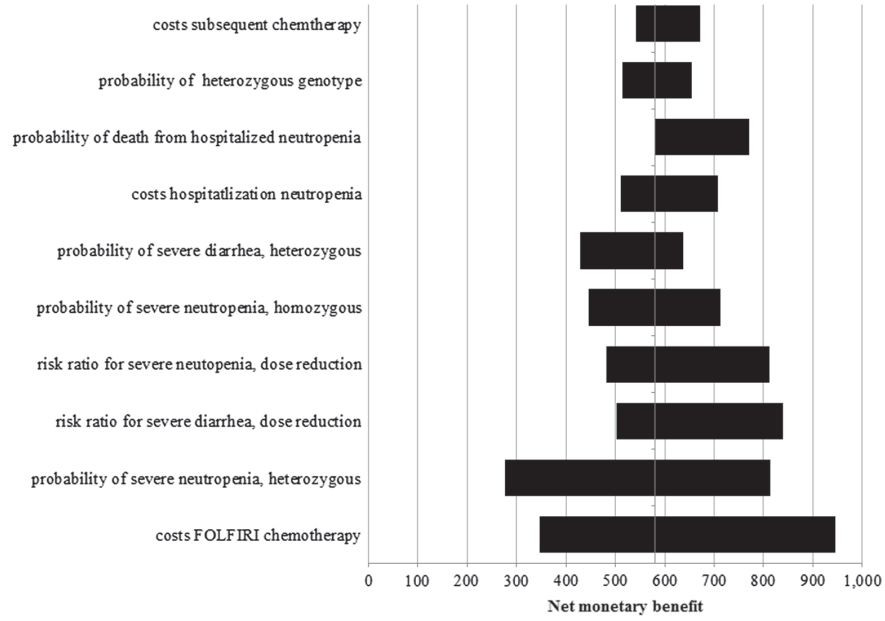

Figure 3. Impact of parameter variations on strategy 'dose reduction' versus strategy 'no genetic test'.

(standard deviation of mean QALY and costs) were 1.1270 QALYs (0.3231 QALYs) and €23 980 (€6152) for the no testing strategy, 1.1272 QALYs (0.3231 QALYs) and €23 374 (€6006) for the strategy with dose reduction, and 1.1272 QALYs (0.3231 QALYs) and €34 068 (€7339) for the strategy of growth factors, respectively.

The high probability that genetic test and dose reduction is optimal corresponds with a low EVPI: At a threshold of €50 000, the EVPI amounts to €0.6 and at a threshold of €0 it accounts to €0.7 per patient. With a time horizon of five years and a WTP of €50 000/QALY, the Population EVPI amounts to €67 926 (€480 000 for an infinite time horizon).

Discussion

To our knowledge, this is the first study which assesses the health and financial impact of UGT1A1 genotyping on the statutory health insurance in Germany. Also, it is the first study which considers diarrhea as possible side effect of irinotecan treatment. This study illustrated the results of a recent review that the cost-effectiveness of personalized medicine strongly depends on which personalization

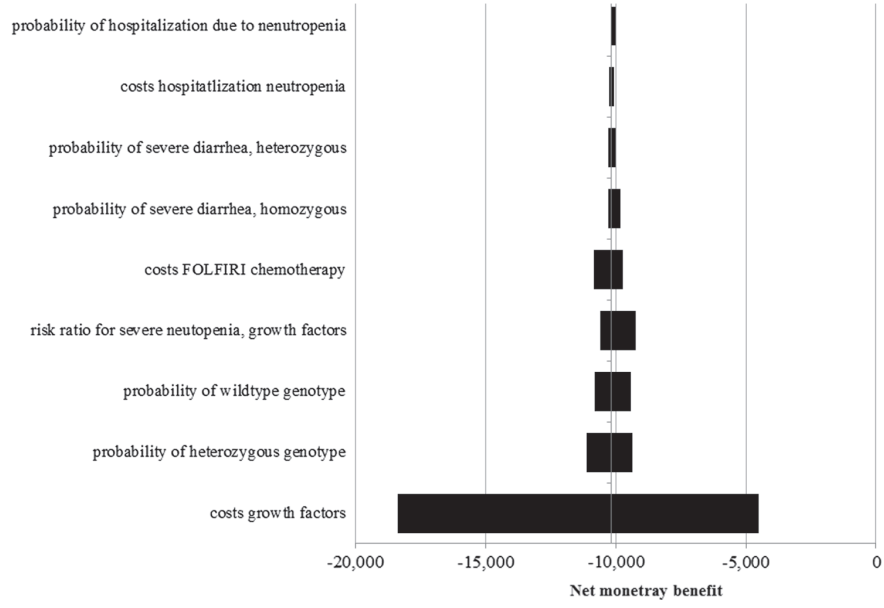

Figure 4. Impact of parameter variations on strategy 'growth factors' versus strategy 'no genetic test'.

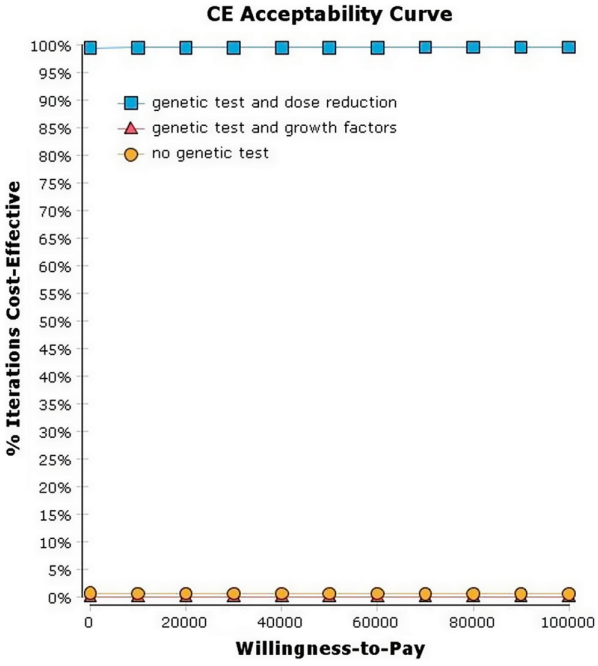

Figure 5. Cost-effectiveness acceptability curve.

strategy is chosen [3]. While the most expensive strategy is associated with about €65 million per QALY gained, the strategy 'genetic test and dose reduction' achieves marginally better results in terms of QALYs and saves about €600 per patient tested compared to the no testing strategy.

The findings of this study support results of previous studies from other health care system contexts which also indicate that UGT1A1 genotyping in combination with dose reduction is beneficial for patients and cost saving from a health care system perspective. If around 80% of the approximate 30 000 patients diagnosed with mCRC each year in Germany (primary findings or in the course of disease) [43] received an irinotecan-based chemotherapy regimen, the estimated annual savings yielded by using the genetic test could amount to around €14 000 000. For a large German health insurance company with five million insures this would imply savings of €900 000 per year of UGT1A1 testing alongside with health benefits for patients.

Limitations

This analysis is subject to several limitations which relate both to model parameters and structure. Regarding the parameters within the chosen model structure, there remains a lack of published evidence. In particular, the variables concerning hospitalization due to severe side effects had to be based on assumptions of a clinical expert (FO) and proxies. If rates of hospitalizations were higher as assumed in this study, the costs of treating side effects would be underestimated.

Moreover, the variables concerning death from hospitalized neutropenia and diarrhea were assumed to be zero in the base case. This was because we intended to provide a conservative estimate of effectiveness for the new intervention. The identified clinical trials among colorectal cancer patients did not report any death due to severe diarrhea and only one study reported one patient who died due to severe neutropenia [30]. These findings are in line with observations of zero or very low mortality from diarrhea or febrile neutropenia also in other cancers like advanced non-small cell lung cancer [44], pancreatic cancer [45] or advanced gastric cancer [46]. If, nevertheless, the probability of death from severe neutropenia and diarrhea in clinical practice is higher than assumed in the current study, QALY gains through genetic testing prior irinotecan-based chemotherapy would be higher and thus cost-effectiveness more favorable.

Moreover, discount agreements between manufacturers and health insurance companies as well as possible copayments by insures have not been taken into account. To obtain the best possible cost estimates, the cost values were chosen in collaboration with experts and conservative estimates were preferred.

Also, quality of life decrements used in this study stemmed from the diagnostic assessment report by the National Institute for Health and Care Excellence (NICE) which summarizes the international evidence on quality of life impacts of chemotherapy-related adverse events [34]. However, values reported in this study might not necessarily reflect the values of the German population. This was necessary because no German QALY weights could be identified.

Regarding the model structure, we had to make a number of simplifying assumptions. In the Markov stage 'post-neutropenia care', patients receive a subsequent chemotherapy regimen that completely prevents further cases of neutropenia. Also, the base case calculation assumes that when identified, heterozygous and homozygous mutation carriers are treated identically, which may not meet the requirements of the two different patient groups.

Furthermore, the impact of testing on the effectiveness of irinotecan was neglected. There is the possibility that a reduced dose in hetero- and homozygotes will lead to a decreased tumor response to chemotherapy, and thus reduced survival. However, the results of a recent meta-analysis concerned with this issue suggest, that this is not the case [47]. Also, Innocenti et al. [48] argue that it is too premature to conclude that lower dosage in UGT1A1 patient might result in lower efficacy of treatment. However, wildtypes might be able to cope with higher FOLFIRI dose than they usually receive [49]. If these patients are identified by the genetic test and their

treatment is adjusted, better efficacy of chemotherapy might be achieved. Further clinical research is necessary to provide a better basis for more detailed economic analysis.

The homozygous *28/*28 genotype is the genetic basis of Gilbert Meulengracht Hyperbilirubinemia syndrome. So besides genetic UGT1A1 testing also phenotypic testing of serum bilirubin has the potential to predict irinotecan toxicity [50]. How a genetic and a phenotypic test do compare in terms of cost, accuracy and efficiency was not part of this investigation as the genetic test has been more commonly used and will have to be investigated in future studies. Also, it is acknowledged that the DPYD*2A mutation is a predictive marker of severe toxicity to 5-FU based treatment and some severe toxicity in the UGT1A1*28 wildtype patients might be related to this polymorphism. How this polymorphism would impact on the development of further personalization strategies is an area of further research.

UGT1A1 genotyping may need to be seen in the context of other stratification approaches which may be applied in treatment practice but could not be assessed within this model. For example, the guidelines of the Association of the Scientific Medical Societies in Germany (AWMF) recommends an alignment of treatment on the specific side effects of chemotherapeutic agents, comorbidities, or the personal and professional situation of the patient [9]. Moreover, the European Organization for Research and Treatment of Cancer (EORTC) recommends the consideration of prophylactic administration of growth factors for chemotherapy regimens with moderate risk of neutropenia (10–20%) as FOLFIRI, dependent on individual risk factors, such as age or comorbidities [51].

Implications for further research

Uncertainty about costs and effects is a typical feature of personalized interventions [1]. Given that in this case, one strategy is expected to be cost saving with a very high probability, the population EVPI associated with the decision is comparatively low and that improved parameter estimates are unlikely to change the overall conclusion from the model. However, substantial structural uncertainty remains: the sensitivity analysis has shown that the degree of dose-reduction in heterozygotes patients has a high impact on cost-effectiveness. Also, the cost-effectiveness of UGT1A1 testing strongly depends on whether in clinical practice, physicians indeed chose dose reduction in both heterozygote and homozygote patients which is difficult to predict in the face of complex pathways of cancer care. This structural uncertainty is not accounted for in the EVPI estimates. Given the potentially high cost savings associated with UGT1A1 testing, therefore, collecting further evidence still appears worthwhile.

It has been proposed that managed entry agreements (MEAs) are promising arrangements to resolve uncertainty surrounding early value-estimates from decision-analytic modeling [52]. The term MEA stands for a variety of innovative reimbursement mechanisms addressing value uncertainties in coverage decisions [53]. For example, additional reimbursement for UGT1A1 testing could be offered to selected health care providers within 'coverage with evidence development' (CED) scheme where the reported results are verified in the real-world environment during a randomized controlled trial. Sickness fund routine data may provide a valuable data source for such type of evidence generation [54]. The results of the present model, in particular the reported differences in costs between the strategies and the corresponding standard errors, can provide indications for the sample size calculation in such a trial. Further work is needed to address the statistical issues and practical aspects concerning the study design such as how to (cluster-) randomize the recipients of the additional funding got UGT1A1 testing or how to assess the cost and effectiveness appropriately in sickness fund routine data.

Conclusion

This study assessed the cost-effectiveness of UGT1A1 genotyping prior to irinotecan-based chemotherapy in metastatic colorectal cancer patients. To our knowledge, it is the first study which also includes diarrhea as potential side effect of the FOLFIRI regime. The results confirm previous results that UGT1A1 testing and dose reduction is likely to be more effective and cost saving compared with the current standard of no testing. For a large sickness fund with five million insures this would imply savings of €900 000 per year of UGT1A1 testing. However, if physicians administer a prophylactic G-CSF growth factor analog instead, small QALY gains are associated with costs of about €65 million per QALY gained.

The results are subject to substantial structural uncertainty. Collecting further evidence within managed entry agreements for UGT1A1 genotyping thus appears to be a valuable investment not only from a scientific and medical perspective but also from the perspective of health care payers with a concern for cost containment.

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Supplementary material available online

Supplementary Appendix 1-4 available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2015.1053983.