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Published in:
Drug Development Research

DOI:
[10.1002/ddr.20424](https://doi.org/10.1002/ddr.20424)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Vegter, S., Jansen, E., Postma, M. J., & Boersma, C. (2010). Economic Evaluations of Pharmacogenetic and Genomic Screening Programs: Update of the Literature. *Drug Development Research*, 71(8), 492-501. <https://doi.org/10.1002/ddr.20424>

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Economic Evaluations of Pharmacogenetic and Genomic Screening Programs: Update of the Literature

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Strategy, Management and Health Policy				
Enabling Technology, Genomics, Proteomics	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT Pharmacogenetics and pharmacogenomics show great potential for developing individual treatment modalities to achieve optimal therapy effectiveness. Economic analyses are performed to determine whether pharmacogenetic screening strategies provide good value for money. The current review provides an update of published economic studies. Economic analyses of pharmacogenetic screening programs published between 2000 and July 2010 were included in the review. Information was extracted on research area, genetic information, type of economic analysis, key aspects of adherence to economic guidelines, costs and commercial availability of genetic tests, and the role of the funding party. A total of 42 economic studies on pharmacogenetic screening strategies were included. Over time, more cost-utility analyses were performed, longer time windows were employed, and more extensive sensitivity analyses were conducted. Considerable differences in costs of screening tests for the same polymorphism were found, which often, but not always, had a large influence on the costs of screening strategies. Most studies were conducted from an academic or hospital perspective without direct links to pharmaceutical or diagnostic manufacturers. The quality of economic analyses of pharmacogenetic screening programs has improved over time. However, input variables are not always clearly described. In particular, substantial variation exists in the reported costs of the pharmacogenetic tests. Often these test costs are considered a major cost driver and could therefore be of particular importance for the interpretation of cost-effectiveness results. Furthermore, the economic studies seem to be conducted to increase awareness of possibilities and perspectives of genetic testing rather than to influence policy decisions on reimbursement. *Drug Dev Res* 71:492–501, 2010. © 2010 Wiley-Liss, Inc.

Key words: economics; pharmacogenetics; pharmacogenomics; literature review

INTRODUCTION

Pharmacogenetics and pharmacogenomics are the disciplines that study the influence of genetic and genomic variations on patients' response to drug treatment. In particular, using pharmacogenetics and pharmacogenomics, individual treatment modalities can be developed to achieve optimal therapy effectiveness, in terms of both increased treatment efficacy and improved treatment persistence due to minimization of adverse events [Farrall and Morris, 2005; Swen et al., 2007]. The terms "pharmacogenetics" and "pharmacogenomics" are

Grant sponsor: European Commission; Grant numbers: FP7-223533 and FP6-037696.

Disclaimer: The content of this publication is the sole responsibility of the authors and can in no way be taken to reflect the views of the European Union. The authors have no conflicts of interest that are directly relevant to the content of this review.

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Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ddr.20424

often used interchangeably. Some prefer to distinguish them in that pharmacogenetics covers only single genes, whereas pharmacogenomics implies the study of several genes; others define pharmacogenomics to imply genetic studies also including transcriptomic (mRNA) or proteomic information [FDA, 2006; Goldstein et al., 2003]. Over the past few decades, experimental and epidemiological studies have investigated a multitude of pharmacogenetic and pharmacogenomic treatment strategies. Although the viability of some of these strategies is conditional on unknown factors [Costa-Scharplatz et al., 2007; Patrick et al., 2009] or even hypothetical [Vegter et al., 2009; Welton et al., 2008] in nature, a growing number of pharmacogenetic tests are indeed becoming commercially available and are used increasingly in clinical practice [Swen et al., 2007]. Generally speaking, these tests can be divided into two principally distinct areas: (1) pharmacodynamic based pharmacogenetics, which aim to target specific diseases or disease subtypes; and (2) pharmacokinetic based tests, commonly when referring to genes influencing drug metabolism [Hopkins et al., 2006]. Pharmacokinetic based testing before treatment initiation seems to be one of the most promising applications of pharmacogenetics. Pharmacogenetic testing prior to treatment initiation can be helpful to predict treatment response and assess the risks for adverse drug reactions.

Notwithstanding the clinical relevance of pharmacogenetics, economic analyses are being performed to determine whether individual pharmacogenetic tests provide good value for money. Different types of economic evaluations can be distinguished: (1) cost minimization analysis (CMA), in which only the costs of two or more treatment strategies are compared (and the health benefits are assumed to be identical); (2) cost effectiveness analysis (CEA), in which health benefits are also taken into account, measured in natural units (such as life years saved); and (3) cost utility analysis (CUA), which combines health outcomes from CEA with measurements of patient wellbeing (utility) such as quality-adjusted life-years (QALYs). In a CUA, outcomes can be compared across different disease fields, in contrast to CEA, which are often confined to their respective disease areas. A fourth type of economic analysis, the cost-benefit analysis (CBA), in which both benefits and costs are expressed in monetary terms, is seldom performed and is not recommended in guidelines for conducting economic analyses [International Society for Pharmacoeconomics and Outcomes, 2010; Walley and Haycox, 1997].

In 2008, we published a systematic review on economic evaluations of pharmacogenetic screening programs [Vegter et al., 2008]. Twenty economic analyses, published up until 2007, were included in this

previous review, focusing on the different disease fields and the level of adherence to international economic guidelines [International Society for Pharmacoeconomics and Outcomes, 2010]. Many economic evaluations reported an acceptable cost effectiveness or even dominating (cost savings as well as clinical benefits) outcome for pharmacogenetic screen-and-treat strategies. However, we expressed concerns regarding the consistency and overall quality of the selected economic analyses. Several other literature reviews on the economics of pharmacogenetic screening programs have previously been published. These studies give an overview of studies conducted and describe the role and interpretation of cost effectiveness in the field of pharmacogenetics and pharmacogenomics [Dervieux and Bala, 2006; Flowers and Veenstra, 2004; Phillips and Van Bebber, 2004].

The purpose of the current study was to perform an update of newly published economic studies to describe the status quo of cost-effectiveness analysis for pharmacogenetic and pharmacogenomic testing.

METHODS

Literature searches were performed using PubMed. Studies published between 2000 and July 2010 were collected. MESH terms used were “economics,” “pharmacogenetics,” “cost-effectiveness analysis,” “genotype,” and “economic outcomes,” in different combinations. Studies were included if they met the following requirements: (1) articles were peer-reviewed and available in full text; (2) an economic analysis was performed on a genetic screening method, screening either human or viral genome; and (3) the genetic or genomic variations were shown, or were at least assumed, to influence drug efficacy or drug safety. Editorials, reviews, and other nonoriginal research articles were excluded. All studies were searched by two reviewers (SV and EJ).

The following data were extracted from the included articles: area of disease or patient population; gene(s) analyzed by the pharmacogenetic test; pharmaceutical compound influenced by the genetic variation; type of economic analysis; several key aspects of adherence to economic guidelines (sensitivity analysis, time window and discounting [Vegter et al., 2008]; outcome measurements; and outcome. The costs and commercial status of the pharmacogenetic tests were extracted and compared. Furthermore, we screened all selected papers for the role of the funding party (e.g., academic, pharmaceutical industry, or other institutes involved with drug development or genetic tests) to value the authors' publishing aim. Overall, these aspects do not only cover basic information on the economic analyses but also on the level of adherence to economic guidelines [International Society for

Pharmacoeconomics and Outcomes, 2010] as well as practicalities and the scope or incentives for conducting these analyses.

RESULTS

Number and Type of Studies

A total of 42 economic studies on pharmacogenetic screen-and-treat strategies were included, more than twice the number of studies ($n = 20$) included in our previous review [Vegter et al., 2008]. The number of studies published in the second half of the decade ($n = 30$) was almost three times that of the first half of the decade ($n = 12$); only two studies were published in 2000, compared with nine studies in 2009. An overview of all the studies is shown in Table 1. There was a clear shift in the type of economic analysis performed over time. In particular, whereas a mix of CMA, CEA, and CUA studies were performed before 2008, most studies published after 2007 were CEA or CUA, reporting clinical outcomes in life-years gained and QALYs gained, respectively.

Topics

Cost-effectiveness analyses of thiopurine methyltransferase (TPMT) polymorphism screening was popular before 2008, being the topic of seven (27%) out of the 27 studies included in a previous systematic review [Vegter et al., 2008]. Interestingly, none of the economic studies published after 2007 examined pharmacogenetic testing of this gene. On the other hand, the number of studies examining CYP2C9 or VKORC1 testing in relation to warfarin treatment increased markedly from only 2 (8%) out of 27 studies published before 2008 [Vegter et al., 2008], to four (25%) out of 16 studies published after 2007. All economic studies on pharmacogenetic tests are summarized in Table 1.

Outcome

Most studies were not unambiguous in giving positive or negative conclusions on the cost effectiveness of the genetic screening program. In fact, two studies mainly focused on the circumstances required for a pharmacogenetic test to be cost effective with different levels of clinical effectiveness [Patrick et al., 2009; Vegter et al., 2009]. Other studies include the availability of resources and practical possibilities to calculate "conditional" cost-effectiveness outcomes. In an example on CYP2C9 and VKORC1 screening, the authors assumed that most institutions cannot perform genotype testing in their own laboratories, which results in a high cost effectiveness of US\$171,800 per QALY gained [Eckman et al., 2009]. However, with in-hospital genotyping, the cost effectiveness was much

more favorable at US\$51,000 per QALY gained [Eckman et al., 2009]. In general, the cost-effectiveness outcomes of CYP2C9 and VKORC1 genotyping are often high, whereas CYP2C19 and TPMT testing are often reported to result in cost-saving strategies.

Cost of Genetic Tests

The costs of genetic testing used in the economic analyses are also shown in Table 1. Considerable differences in screening tests for the same polymorphisms were found. These differences are expected to be caused by estimates including only material costs versus estimates with including personnel costs, such as in ACE (I/D) genotyping, which varied between €7 (Netherlands, 2002) [Maitland-van der Zee et al., 2004] and €50 (Netherlands, 2005/2008) [Costa-Scharplatz et al., 2007; Vegter et al., 2009]. Other differences might be caused by between country differences or costing year, such as in HER-2 testing, in which the assumed screening costs varied between €283 (France, 2002) [Morelle et al., 2006] and €548 (Sweden, 2005) [Lidgren et al., 2008a,b]. Commercial available tests are expected to have fixed prices rather than large variation in costs. Still, some differences in the base case estimate of screening costs were observed among studies that both were based on commercially available tests, were conducted from the same study perspective and in the same country and year, for example of CYP2C9 and VKORC1 testing, varying between US\$175 (USA, 2007) [Meckley et al., 2010] and US\$575 (USA, 2007) [Patrick et al., 2009]. The costs of genetic screening tests were often, but not always, explored in sensitivity analyses.

Sensitivity Analyses

Economic evaluations invariably have to deal with some degree of uncertainty in their analyses. This is especially true for pharmacogenetic screening programs, which are often not yet (commonly) implemented in clinical practice or might even be hypothetical in nature. Therefore, sensitivity analyses are invaluable to determine the influence of key parameters and the preconditions for cost effectiveness of the screening strategy. Furthermore, probabilistic sensitivity analyses are performed to determine the range of cost effectiveness and the probability of a screening strategy of being cost effective. All studies included in this review performed some form of sensitivity analysis. Before 2008, most of these were limited to deterministic sensitivity analyses (in which only one variable is varied at a time). In contrast to this, almost all (except one) studies that were published after 2007 performed probabilistic sensitivity analyses, a method that allows for assessing more of the inherent uncertainty associated

TABLE 1. Overview of Pharmacogenetic Studies

Study (year of publication)	Therapeutic/disease area	Gene/Test	Screening/test costs	Drug type	Evaluation type	Outcome measure	Base case economic outcome or ICER
You et al. [2004]	Thromboembolism	CYP2C9	US \$100	Coumarin	CEA	Bleeding events	US \$5,778 per bleeding event averted
Schalekamp et al. [2006]	Thromboembolism	CYP2C9	€55	Coumarin	CEA	Bleeding events	€4,233 (all patients) or €2,210 (INR > 2.5) per bleeding avoided
Eckman et al. [2009]	Nonvalvular atrial fibrillation	CYP2C9; VKORC1	US \$400	Warfarin	CUA	QALYs	US \$171,800 per QALY
You et al. [2009]	Thromboembolism	CYP2C9; VKORC1	US \$200	Warfarin	CUA	QALYs	US \$347,059 per QALY
Patrick et al. [2009]	Nonvalvular atrial fibrillation (70 y)	CYP2C9; VKORC1	US \$575	Warfarin	CUA	QALYs	US \$50,000 per QALY (if time spent in INR range increases by ≥9%)
Meckley et al. [2010]	Thromboembolism	CYP2C9; VKORC1	US \$175	Warfarin	CUA	QALYs	US \$60,725 per QALY
Desta et al. [2002]	<i>Helicobacter pylori</i> infection (Asian ethnicity)	CYP2C19	US \$30	PPI	CMA	Costs of eradication treatment	US \$500 per person
Lehmann et al. [2003]	<i>Helicobacter pylori</i> and duodenal ulcer	CYP2C19	Not known	PPI	CEA	Ulcer episodes	Dominant
Furuta et al. [2007]	<i>Helicobacter pylori</i> infection	CYP2C19	Not known	PPI	CEA	Ulcer episodes	Dominant
Chou et al. [2000]	Psychiatric in-patients	CYP2D6	US \$100	Antipsychotics	CMA	Total costs of treatment and adverse drug effects per year	Lower costs for efficient metabolizers
Tavadia et al. [2000]	Dermatology, in particular, bulbous pemphigoid	TPMT	US \$100	AZA	CMA	Total costs related to treatment	Cost-neutral for testing all patients for TPMT gene mutations and cost-beneficial if only those if patients heterogeneous for mutant TPMT alleles also experience myelosuppression
Marra et al. [2002]	Rheumatologic conditions	TPMT	CAN \$100	AZA	CEA	Adverse event avoided	Dominant
Oh et al. [2004]	Rheumatoid arthritis and systemic lupus erythematosus	TPMT	US \$50	AZA	CEA	Serious adverse events	Dominant
Winter et al. [2004]	IBD	TPMT	£30	AZA	CEA	LYs	£487 (30 yr old) or £951 (60 yr old) per LY
Dubinsky et al. [2005]	IBD	TPMT	US \$510	AZA	CEA	Time to response	Dominant
Priest et al. [2006]	IBD	TPMT	US \$210	AZA	CUA	QALYs	Dominant
van den Akker-van Marle et al. [2006]	Acute lymphoblastic leukemia	TPMT	€150	6-MP	CEA	LYs	€4,800 per LY

TABLE 1. Continued

Study (year of publication)	Therapeutic/disease area	Gene/Test	Screening/test costs	Drug type	Evaluation type	Outcome measure	Base case economic outcome or ICER
Maitland-van der Zee et al. [2004]	Hypercholesterolemia (male patients)	ACE I/D	€7	Statins	CUA	QALYs	Dominant
Costa-Scharplatz et al. [2007]	Nephropathy	ACE I/D	€49	ACE inhibitors	CEA	ESRD free years	Dominant
Vegter et al. [2009]	Chronic kidney disease	ACE I/D	€50	ACE inhibitors	CUA	QALYs	€20,000 per QALY (if effectiveness in delaying dialysis of alternative treatment increased by more than 9.1%) US \$47,705 per QALY
Perlis et al. [2005]	Schizophrenia	Several*	US \$500	Clozapine	CUA	QALYs	US \$1,944 per LY and Dominant (compared to tamoxifen alone); US \$3,385 per LY and US \$4,432 per QALY (compared to chemotherapy plus tamoxifen)
Costler and Lyman [2009]	Early-stage breast cancer	Several**	US \$3460	Adjuvant chemotherapy	CUA	LYs QALYs	Dominant to €22,811 per hypersensitivity reaction avoided (depending on chosen HAART therapy) US \$36,700 per QALY
Hughes et al. [2004]	HIV-1	HLA	€43	Abacavir	CEA	Hypersensitivity reaction avoided	Dominant
Schackman et al. [2008]	HIV	HLA-B*5701	US \$68	Abacavir	CUA	QALYs	Dominant
Kim et al. [2006]	Rheumatoid arthritis	MTHFR	US \$50	MTX	CEA	Drug discontinuation	Dominant
Meckley and Veenstra [2006]	Hypertension	α -Adducin	US \$250	Thiazide	CUA	QALYs	Dominant
Veenstra et al. [2007]	Cystic fibrosis	A155G	US \$345	Aminoglycosides	CUA	QALYs	US \$79,343 per QALY
Welton et al. [2008]	Smoking cessation	DRD2 Taq1A	£24	NRT, bupropion	CUA	QALYs	Unlikely to be cost-effective
Smith et al. [2008]	Thromboembolism in women starting oral contraceptives	Factor V	US \$50	Prophylactic anticoagulants	CUA	QALYs	Dominant (screening+counseling); US \$147 per QALY (screening+counseling+prophylaxis)
Gold et al. [2009]	Metastatic colorectal cancer	UGT1A1*28	US \$102	Irinotecan	CUA	QALYs	Dominant

Cosler and Lyman [2009]	Non-small-cell lung cancer	EGFR	US \$320	EGFR-tyrosine kinase inhibitor therapy	CUA	QALYs	US \$162,015 per QALY
Perlis et al. [2009]	Major depressive disorder	HTR2A	US \$500	SSRI	CUA	QALYs	US \$93,500 per QALY
Weinstein et al. [2001]	HIV	GART	US \$400	HAART	CUA	QALYs	US \$17,900 per QALY (secondary resistance testing) or US \$22,300 (primary resistance testing) per QALY
Sax et al. [2005]	HIV	GART	US \$400	HAART	CEA/CUA	QALYs	US \$23,900 per QALY
Sendi et al. [2007]	HIV	GART	US \$625 (Switzerland) US \$400-500 (USA)	HAART	CUA	QALYs	US \$35,000 (health-care perspective) per QALY or dominant (societal perspective)
Elkin et al. [2004]	Metastatic breast cancer	HER-2	US \$381	Trastuzumab	CUA	QALYs	US \$125,100 (IHC+confirmation FISH); US \$145,400 (FISH only) per QALY
Morelle et al. [2006]	Invasive breast carcinomas	HER-2	€283	Trastuzumab	CEA	Correctly managed case	€722 (IHC+confirmation FISH) or €6,127 (FISH only) per correctly managed case
Dendukuri et al. [2007]	HER-2-positive breast cancer	HER-2	US \$467	Trastuzumab	CEA	Accurately determined HER-2 status	\$6,175 (IHC+confirmation FISH) or \$8,401 (FISH only) per correctly diagnosed case
Lidgren et al. [2008a]	Early breast cancer patients	HER-2	€548	Trastuzumab	CUA	QALYs	€36,000 (IHC+confirmation FISH) or €41,500 (FISH only) per QALY
Lidgren et al. [2008b]	Metastatic HER-2-positive breast cancer	HER-2	SEK 5086	Trastuzumab	CUA	QALYs	SEK 485,039 (IHC+confirmation FISH) or SEK 561,207 (FISH only) per QALY
Blank et al. [2010]	HER-2-positive breast carcinomas	HER-2	€686	Trastuzumab	CUA	QALYs	Dominated (IHC+confirmation FISH) or €12,245 (FISH only) per QALY
Siebert et al. [2009]	Chronic hepatitis C	HCV viral genotype	Not known	Peg-interferon- α -2b+ribavirin	CUA	QALYs	€1,500 per QALY

*6 polymorphisms in neurotransmitter-receptor-related genes; **21 polymorphisms in cancer-related genes.
 ACE I/D, angiotensin-converting enzyme insertion/deletion; ACEi, ACE inhibitors; AZA, azathioprine; A1555G, mitochondrial 12S rRNA gene variation A1555G; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; CUA, cost-utility analysis; CYP, cytochrome P-450; DRD2, dopamine D2 receptor; EGFR, epidermal growth factor receptor; ESRD, end-stage renal disease; FISH, fluorescent in situ hybridization technique; GART, genotypic antiretroviral resistance testing; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HER-2, human epidermal growth factor receptor-2; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HTR, serotonin receptor; IBD, inflammatory bowel disease; ICER, incremental cost-effectiveness ratio; IHC, immunohistochemical technique; INR, international normalized ratio; LYS, life-years gained; LYS, life-years saved; 6-MP, 6-mercaptopurine; MTHFR, methylenetetrahydrofolate reductase; MTX, methotrexate; NRT, nicotine replacement therapy; PPI, proton pump inhibitor; QALY, quality-adjusted life-year; SSRi, selective serotonin reuptake inhibitor; TPMT, thiopurine S-methyltransferase; UGT, uridine diphosphate glycosyltransferase; VKORC, vitamin K epoxide reductase complex subunit 1.

with genetic screening programs. As discussed above, we identified large variation in the costs of the genetic screening test. In the case of HER-2 testing and CYP2C9 and VKORC1 testing, sensitivity analyses demonstrated that the uncertainty around the costs of the pharmacogenomic test showed high influence on the calculated cost effectiveness [Eckman et al., 2009; Meckley et al., 2010; Morelle et al., 2006; Patrick et al., 2009; You et al., 2009]. Therefore, economic outcomes for pharmacogenetic tests could be (highly) sensitive for these cost estimates. However, for ACE (I/D) genotyping and genotypic antiretroviral resistance testing (GART), the influence of screening costs was limited [Maitland-van der Zee et al., 2004; Sax et al., 2005; Vegter et al., 2009; Weinstein et al., 2001]. Here, the costs of the tests are not a direct total cost driver.

Time Window and Discounting

Guidelines state that the length of any economic evaluation should be long enough to capture all differential effects of compared interventions. Since genetic variations occur at birth and do not change during life, with the exception of cancer cells, evaluations of genetic screening programs can be expected to employ a lifelong time window or at least as long as treatment effects are expected to last. Most studies published before 2008 employed a time window of 12 months; only five of the 20 paper included in our previous review employed a life-time horizon [Vegter et al., 2008]. In contrast, most studies published after 2007 employed a lifetime horizon, although this might be as short as 24 months as in the case of metastatic colorectal cancer [Gold et al., 2009]. Time horizons other than 1 year can be appropriate if incidental effects occur that do not last for more than a certain specified time period. Discounting—the method to correct for time preferences that occur in relation to gains and losses—was applied in all studies [Drummond et al., 2005].

Role of Funding

Most studies included were not (directly) funded by pharmaceutical companies or pharmacogenetic test suppliers and were written from an academic or hospital perspective rather than a commercial perspective. Only two studies on trastuzumab treatment of HER-2-positive breast cancer [Lidgren et al., 2008a,b] were found to be directly funded by a pharmaceutical company. The company involved produces the drug and owns the company that supplies diagnostic instruments for HER-2 screening. As another example, in a study on CYP2D6 screening before antipsychotic therapy [Chou et al., 2000], 6 of the 11 authors were

employed at a company that supplies genetic analysis technologies.

DISCUSSION

The previously reported increase in good economic practice in the evaluation of pharmacogenetic and genomic screening programs [Vegter et al., 2008], further improved the last years. After 2007, almost all economic studies included in the current review were CEA and CUA studies, both recommended for economic analysis [International Society for Pharmacoeconomics and Outcomes, 2010]. Over the years, more elaborate and robust sensitivity analyses were performed, with probabilistic sensitivity analyses also becoming the standard in the field of pharmacogenetics. Applied time horizons of almost all studies were lifetime and future costs and health effects were discounted at appropriate rates.

In addition to an improvement in the quality of economic analysis, also a natural change in the topics of research was identified. In particular, no new analyses on TMPT testing for azathioprine therapy were published after 2008. This may be attributable to previously reported favorable health economic outcomes for such TPMT testing. Health economic analyses recently focused on different and more novel pharmacogenetic areas, such as CYP polymorphisms. Indeed, an increasing number of studies examined polymorphisms involved in the functioning of cytochrome P-450 enzymes, such as CYP2C9 tests for genetic-guided warfarin therapy. An explanation for this may be that in 2007, the US Food and Drug Administration (FDA) updated the warfarin label, mentioning use of genetic testing before starting warfarin therapy [FDA, 2007]. This may have prompted health economists to explore the value of genetic testing. Interestingly, economic studies in this field generally showed unfavorable value for money of CYP2C9 screening despite the FDA update. This underlines the importance of cost-effectiveness studies in pharmacogenetic screening programs, which should always be considered prior to clinical implementation in addition to clinical evidence.

We reported that the cost-effectiveness outcomes of CYP2C9 and VKORC1 genotyping are high whereas CYP2C19 and TPMT testing results in cost-saving strategies. The CYP2C9 and VKORC1 polymorphisms explain between 35% and 55% of variability in warfarin dose requirements [Meckley et al., 2008; Sconce et al., 2005]. Despite this, the clinical evidence that genetic dosing can reduce bleeding events and improve drug efficacy is limited and the projected benefits are small [Anderson et al., 2007]. Furthermore, reducing warfarin doses based on genetic information might also

have deleterious effects by increasing the risk of thromboembolic events [Meckley et al., 2010], which are more severe than bleeding events. This might explain the unfavorable cost effectiveness of this type of genetic dosing. In contrast, the clinical benefits of CYP2C19 screening, used for genetic dosing of *Helicobacter pylori* eradication treatment, are large, screening is inexpensive and there is no increased risk for adverse events with genetic dosing. Similarly, TPMT screening, used for genetic dosing of immunomodulating agents, is assumed to have large clinical benefits, even preventing cases of life-threatening leukopenia. These clinical benefits however were based on retrospective data or even expert opinion; the true cost effectiveness of TPMT screening should be evaluated based on more robust clinical and economic evidence [Payne et al., 2009].

Despite the increasing quality of economic analyses in this field, the practical implications of pharmacogenetic testing remain unclear in some studies included for this review. There are large variations in the estimated costs of (conducting) genetic screening tests, which can partly but not fully be explained by variations in the cost categories included, country of origin, and commercialization of the screening tests. An important additional factor is that screening costs often were based on catalogue prices, whereas negotiated prices might be substantially lower [Morelle et al., 2006], especially when modeling a large-scale implementation of a genetic screening program. These findings underline the importance of determining the correct price for genetic screening procedures. In some studies, the cost of the screening test was in fact a main determinant for valuing the intervention as cost effective or not. Therefore, it is important to state here that sensitivity analyses should be performed to determine the influence of all estimated and relevant input variables on the economic outcome.

Surprisingly, for most included economic studies on pharmacogenetic and pharmacogenomic screening programs, no direct link with commercial sponsors was identified. This is in contrast to economic analyses for other healthcare interventions [Bell et al., 2006]. Most studies were conducted from an academic or hospital perspective without direct links with pharmaceutical and/or diagnostic industries. This finding could indicate that cost-effectiveness studies in the field of pharmacogenetics and pharmacogenomics are, at least currently, more driven by academic interest rather than commercial interests. This could be attributable to the limited or less strict procedures for policy decisions (e.g., reimbursement) on such diagnostic tests compared with existing procedures for drugs.

In conclusion, the quality of economic analyses of pharmacogenetic and pharmacogenomic screening

programs improved over time. However, input variables are not always clearly described. In particular, substantial variation exists in the costs of the pharmacogenetic tests that are not always fixed or estimated consistently. Often these test costs are considered as the major cost driver and could therefore be of particular importance for the interpretation of cost-effectiveness results. Furthermore, the currently published economic studies seem to be conducted to increase awareness of possibilities and perspectives of genetic testing rather than to influence policy decisions on reimbursement. Because economic outcomes are of growing importance for implementation of health care programs, it is highly desirable to further explore ways to further improve the quality of cost-effectiveness analysis for genetic tests and to give guidance to health care decision makers.

ACKNOWLEDGMENTS

This work was supported by the Health Investments in Screening and Diagnosis (HIScreenDiag) project, funded by the European Commission under the 7th Framework Programme Theme: Health, FP7-Health-2007-B, 3.4.2 Effectiveness of Health Investments (project 223533), for the HIScreenDiag project. Parts of this work were supported by the applied GENomic strategies for Treatment and Prevention of Cardiovascular death in Uraemia and End stage RENal disease (GENECURE) project (www.genecure.eu), funded by the European Commission under the 6th Framework Programme as FP6-037696.

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