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Journal Watch

Contents

Pharmaceutical medicine is an evolving discipline and research and development activity within the field is high. This section of the journal is intended to help you keep up to date with the latest advances worldwide in various aspects of pharmaceutical medicine. Each issue includes a selection of articles published in recent issues of other Adis publications. Full text versions of these papers are available at http://adisonline.com.

1. Do Biological Medicinal Products Pose a Risk to the Environment? A Current View on Ecopharmacovigilance

The occurrence of active pharmaceutical substances in the environment is of growing concern. The vast majority of the compounds in question are of low molecular weight, intended for oral use and designed to tolerate, for example, the digestive enzymes in the upper alimentary tract, the harsh milieus found in the acidic stomach, or the microbe rich intestine. Accordingly, these xenobiotic compounds may, due to their inherent biological activity, constitute a risk to the environment.

Biological medicinal products, for example recombinant human insulin or monoclonal antibodies, however, are different. They are primarily made up of oligomers or polymers of amino acids, sugars or nucleotides and are thus readily metabolized. They are therefore generally not considered to pose any risk to the environment.

Certain classes of biological medicinal products, however, are associated with specific safety issues. Genetically modified organisms as vectors in vaccines or in gene therapy products have attracted much attention in this regard. Issues include the degree of attenuation of the live recombinant vaccine, replication restrictions of the vaccine vector, alteration of the host and tissue tropism of the vector, the possibility of reversion to virulence, and risk to the ecosystem.

In this review we discuss the fate and the potential environmental impact of biological medicinal products following clinical use from an ecopharmacovigilance point of view, and review relevant policy documents and regulatory statements.

Kühler TC, Andersson M, Carlin G, et al. Do biological medicinal products pose a risk to the environment? A current view on ecopharmacovigilance. Drug Saf 2009; 32 (11): 995-1000

2. The Role of the Systemic Inflammatory Response as a Biomarker in Immunotherapy for Renal Cell Cancer

Treatment of metastatic renal cell cancer (RCC) has entered a new paradigm since the development of tyrosine kinase inhibitors such as sorafenib (Nexavar®) and sunitinib (Sutent®). Despite these advances, immunotherapy, the traditional mainstay of treatment, is not yet obsolete. Immunotherapy offers the possibility of a complete response for a small number of patients with favorable disease factors. However, immunotherapy is a toxic treatment, with a significant impact on quality of life in comparison with a relatively modest survival advantage for most. As such, the search for a biomarker to select patients for immunotherapy and to monitor their progress still remains a clinical and research goal for those involved in treating patients with metastatic renal cancer.

At present, performance status and a number of prognostic scores incorporating performance status and laboratory variables are the most widely used indicators of suitability for immunotherapy. More recently, the histological expression of carbonic anhydrase IX has been reported as a biomarker of response to interleukin (IL)-2 immunotherapy.

C-reactive protein (CRP) is an acute-phase protein synthesized as part of the systemic inflammatory response. It is readily measured by standardized assays and is reliable, without variability for age, sex, or bodyweight. The presence of an elevated CRP is a prognostic indicator in a number of solid tumors, both in localized and metastatic disease. In advanced renal cancer, the Glasgow Prognostic Score, which is based on elevated CRP and low albumin, has shown prognostic value. CRP is also superior to the widely used performance status in predicting survival for patients treated with either interferon (IFN)-α or IL-2. As such, CRP is an increasingly exciting biomarker for predicting outcomes in immunotherapy. Currently, no other biomarker has been applicable for use in both IFNα and IL-2 immunotherapy. More recently, changes in CRP kinetics have shown promise as a predictive tool, although more research is required. Use of CRP as a biomarker can improve stratification of patients with metastatic renal cancer, allowing the patients less likely to benefit from immunotherapy to avoid a potentially toxic treatment. The ongoing selection of patients based on biomarkers should enable continued research on the optimum dose and timing of immunotherapy while managing toxicity and optimizing outcomes.

Ramsey S. The role of the systemic inflammatory response as a biomarker in immunotherapy for renal cell cancer. Mol Diag Ther 2009; 13 (5): 277-81

3. Economic Evaluation and Cost-Effectiveness Thresholds: Signals to Firms and Implications for R&D Investment and Innovation

In this article we describe how reimbursement cost-effectiveness thresholds, per unit of health benefit, whether set explicitly or observed implicitly via historical reimbursement decisions, serve as a signal to firms about the commercial viability of their R&D projects (including candidate products for in-licensing). Traditional finance methods for R&D project valuations, such as net present value analyses (NPV), incorporate information from these payer reimbursement signals to help determine which R&D projects should be continued and which should be terminated (in the case of the latter because they yield an NPV < 0). Because the influence these signals have for firm R&D investment decisions is so significant, we argue that it is important for reimbursement thresholds to reflect the economic value of the unit of health benefit being considered for reimbursement.

Thresholds set too low (below the economic value of the health benefit) will result in R&D investment levels that are too low relative to the economic value of R&D (on the margin). Similarly, thresholds set too high (above the economic value of the health benefit) will result in inefficiently high levels of R&D spending. The US in particular, which represents approximately half of the global pharmaceutical market (based on sales), and which seems poised to begin undertaking cost effectiveness in a systematic way, needs to exert caution in setting policies that explicitly or implicitly establish cost-effectiveness reimbursement thresholds for healthcare products and technologies, such as pharmaceuticals.

Vernon JA, Goldberg R, Golec J. Economic evaluation and cost-effectiveness thresholds: signals to firms and implications for R&D investment and innovation. Pharmacoeconomics 2009; 27 (10): 797-806

4. Melanoma Biomarkers: Current Status and Utility in Diagnosis, Prognosis, and Response to Therapy

Melanoma is the most devastating form of skin cancer and represents a leading cause of cancer death, particularly in young adults. As even relatively small melanomas can readily metastasize, accurate staging of progression is critical. Diagnosis is typically made on the basis of histopathologic criteria; with tumor thickness (Breslow), invasion level (Clark), ulceration, and the extent of lymph node involvement being important prognostic indicators. However, histologic criteria alone cannot diagnose all melanomas and there are often problems in distinguishing subsets of benign nevi from melanoma. There also exists a group of patients with thin primary melanomas for whom surgery should be curative but who ultimately go on to develop metastases. Therefore, there is an urgent need to develop molecular biomarkers that identify melanoma patients with high-risk primary lesions to facilitate greater surveillance and possible adjuvant therapy.

The advent of large-scale genomic profiling of melanoma is revealing considerable heterogeneity, suggesting that melanomas could be subgrouped according to their patterns of oncogenic mutation and gene expression. It is hoped that this subgrouping will allow for the personalization of melanoma therapy using novel molecularly targeted agents. Much effort is now geared toward defining the genetic markers that may predict response to targeted therapy agents as well as identifying pharmacodynamic markers of therapy response. In this review, we discuss the utility of melanoma biomarkers for diagnosis and prognosis and suggest how novel molecular signatures can help guide both melanoma diagnosis and therapy selection.

Haass NK, Smalley KS. Melanoma biomarkers: current status and utility in diagnosis, prognosis, and response to therapy. Mol Diag Ther 2009; 13 (5): 283-96

5. The Role of Patient Preferences in Cost-Effectiveness Analysis: A Conflict of Values?

This paper reviews the role of patient preferences within the framework of cost-effectiveness analysis (CEA). CEA typically adopts a system-wide perspective by focusing upon efficiency across groups in the allocation of scarce healthcare resources, whereas treatment decisions are made over individuals. However, patient preferences have been shown to have a direct impact on the outcome of an intervention via psychological factors or indirectly via patient adherence/compliance rates. Patient values may also be in conflict with the results of CEA through the valuation of benefits. CEA relies heavily on the QALY model to reflect individual preferences, although the healthy year equivalent offers an alternative measure that may be better at taking individual preferences into account. However, both measures typically use mean general population or mean patient values and therefore create conflict with individual-level preferences.

For CEA to reflect practice, it must take into account the impact of individual patient preferences even where general population preferences are used to value the benefits of interventions. Patient preferences have implications for cost effectiveness through costs and outcomes, and it is important that cost-effectiveness models incorporate these through its structure (e.g. allowing for differing compliance rates) and parameter values, including clinical effectiveness. It will also be necessary to try to predict patient preferences in order to estimate any impact on cost effectiveness through analyses of revealed and stated preference

data. It is recognized that policy makers are concerned with making interventions available to patients and not forcing them to consume healthcare. One way of moving towards this would be to adopt a two-part decision process: the identification of the most cost-effective therapy using mean general population values (i.e. the current rule), then also making available those treatments that are cheaper than the most cost-effective therapy.

Brazier JE, Dixon S, Ratcliffe J. The role of patient preferences in cost-effectiveness analysis: a conflict of values? Pharmacoeconomics 2009; 27 (9): 705-12

6. Clinical Application of Proteomics in Ovarian Cancer Prevention and Treatment

As recent scientific findings using whole-genome mutational scanning technologies have concluded, cancer is a protein pathway disease, which is often diagnosed too late, when the success of therapeutic modalities is very limited. Proteomics has been proposed as the field that can help overcome this limitation and usher in a new era of molecular investigation for early diagnosis and classification of tumors. Proteomics applications in cancer research encompass two general aspects: (i) the study and characterization of protein production; and (ii) the definition of protein function. The first aims to identify qualitative or quantitative differences in the proteome that can help differentiate between healthy and diseased states or achieve a better clinical classification of diseases. The second studies the complexity of protein interactions and their activation states, mapping the network of signaling pathways within and outside the cells. The challenges in translating the findings of proteomics research into clinical practice are numerous. Lack of reproducibility, variable availability of samples and the bias associated with their selection and handling, the need for large, prospective validation trials, and finally the strict requirement for a very high level of clinical sensitivity and specificity are some of the hurdles that need to be overcome to achieve early detection and treatment. Nevertheless, proteomics is a field in rapid progression that has already developed beyond initial criticism and is making its way toward important applications and discoveries. Specifically, there has been an increasing number of reports on the potential clinical application of proteomics for early detection as well as risk assessment and management of ovarian cancer. This disease is the leading cause of death from gynecologic malignancies in the US, with poor prognosis resulting from the lack of reliable, sensitive screening tests and the limited understanding of the mechanisms of chemoresistance and relapse. In the future, serum proteomics applications in the gynecologic oncology field could identify blood-based biomarkers that are predictors of disease presence or progression, and tissue proteomics could help define the optimal targeted agent and effective dose for each patient's disease. These advances will allow improved monitoring of therapy response and disease relapse, and aid in the engineering of new drugs and strategies to circumvent resistance mechanisms while avoiding the adverse effects of traditional chemotherapy.

Meani F, Pecorelli S, Liotta L, et al. Clinical application of proteomics in ovarian cancer prevention and treatment. Mol Diag Ther 2009; 13 (5): 297-311

7. Implementing Differential Pricing for Essential Medicines via Country-Specific Bilateral Negotiated Discounts

It is widely acknowledged that limited access to essential medicines undermines efforts at improving the health and economic well-being of low-income populations. This has spurred on a number of solutions, including differential pricing based on the economics of price discrimination. A desirable feature of differential pricing is its potential ability to reconcile static and dynamic efficiency concerns. There are, however, various shades of differential pricing and this paper aims to evaluate their consistency with economic theory. Starting with the report of the workshop on 'Differential Pricing and Financing of Essential Drugs' held by secretariats of the World Trade Organization and WHO in Hosbjor, Norway, in 2001, this paper takes issue with how differential pricing has been defined as a tool for improving access to essential drug benefits.

The paper notes that inadequate attention has been given to policies and institutional arrangements for creating, expressing and maintaining 'truly' price-elastic demands in low-income nations and for segmenting markets. In addition, considerations of equity and solidarity have distracted policy advocates from balancing conflicting, yet well intended, views and general rules. The paper argues why differential pricing should be implemented via country-specific bilateral negotiated discounts. It maintains that it is feasible to muster an environment conducive to profitable differential pricing whilst satisfying general rules and concerns about self-reliance, transparency, accountability, equity and solidarity.

Tetteh EK. Implementing differential pricing for essential medicines via country-specific bilateral negotiated discounts. Appl Health Econ Health Pol 2009; 7 (2): 71-89

8. *In Vitro* Testing for the Diagnosis of Anticonvulsant Hypersensitivity Syndrome: A Systematic Review

Anticonvulsant hypersensitivity syndrome (AHS) is a rare and potentially fatal reaction that develops in susceptible

patients following exposure to certain drugs, including aromatic anticonvulsants. Because of its ill-defined clinical picture and resemblance to other diseases, the diagnosis of AHS is often difficult and requires a safe and reliable diagnostic test. Other than systemic rechallenge, which is not always ethically permissible and has its own limitations, no reliable diagnostic test is available for this type of disorder. This systematic review attempts to evaluate the usefulness of the available *in vitro* tests in the diagnosis of AHS – namely, the lymphocyte transformation test (LTT) and the lymphocyte toxicity assay (LTA) – and to examine the different technical aspects of these tests that may contribute to their performance. We included studies in which aromatic anticonvulsant drugs were the likely causes of the hypersensitivity reaction and either the LTT or the LTA was used to aid the diagnosis of AHS. Analysis of original publications from 1950 to the last week of March 2009 and cited in PubMed, MEDLINE and EMBASE has revealed that there are numerous factors affecting the final result of the test, including the following: the timing of the test after exposure; the clinical manifestation of the reactions; the specific drug; and the test procedure and read-out system. *In vitro* diagnostic tests have the advantage over *in vivo* tests of being safe to use; however, *in vitro* tests for the diagnosis of AHS are not well standardized and their sensitivity and specificity are not yet determined. From the reviewed literature, the sensitivity of the LTT and the LTA seem to be around 70% and 90%, respectively, and the positive and negative predictive values of the tests in highly imputable cases are quite high. However, the lack of a gold-standard diagnostic test to prove drug culpability, along with the paucity of large-scale studies, precludes accurate determination of the epidemiological characteristics of these tests. It appears that without further understanding of the mechanisms underlying the pathophysiology of AHS, and how specific drugs and metabolites differentially affect these mechanisms, the development of more reliable tools for AHS diagnosis will be compromised. Consequently, in the absence of further research, the predictability of these tests will remain questionable and they are unlikely to be utilized on a large scale.

Elzagallaai AA, Knowles SR, Rieder MJ, et al. In vitro testing for the diagnosis of anticonvulsant hypersensitivity syndrome: a systematic review. Mol Diag Ther 2009; 13 (5): 313-30

9. Circulating Tumor Cells as Markers for Cancer Risk Assessment and Treatment Monitoring

Carcinomas of epithelial origin represent the majority of malignancies in Europe. A substantial number of patients develop recurrent carcinoma, which is explained by tumor-cell dissemination into distant organs, preferentially bone marrow, which often occurs prior to surgery. In contrast to disseminated tumor cells in bone marrow, for which the prognostic value has been demonstrated, the role of circulating tumor cells (CTCs) in blood is not yet completely understood. Since bone marrow aspiration is less accepted by patients than blood withdrawal, it would be highly desirable to replace bone marrow aspiration by blood analysis. Presently, a variety of seemingly promising methods for the detection and characterization of CTCs are under evaluation, including immunocytologic and molecular approaches. However, these methods still need to be proven useful in clinical studies. The majority of studies published on CTCs to date have been related to primary and metastatic breast cancer; therefore, this article mainly addresses the role of CTCs in breast cancer.

Kasimir-Bauer S. Circulating tumor cells as markers for cancer risk assessment and treatment monitoring. Mol Diag Ther 2009; 13 (4): 209-15

10. Predicting the Clinical Relevance of Drug Interactions From Pre-Approval Studies

Drug interactions (DIs) may result in adverse drug events that could be prevented, but in many cases the available information on potential DIs is not easily transferable to clinical practice. The majority of studies date from preclinical or premarketing phases, using animals or human-derived sources that may not accurately reflect the growing clinical complexity of high-risk populations, such as the elderly, women, children, patients with chronic disease, polytherapy and impaired organ functions. Thus, at the time of approval of a new drug the information in the summary of product characteristics refers to potential DIs, but lacks specific management recommendations and is of limited clinical utility.

Therefore, we set out to review *in vitro* and *in vivo* methods to predict and quantify potential DIs, to see whether these studies could help the physician tackle daily problems of the assessment and choice of combined drug therapies, and to propose, from a clinical point of view, how premarketing studies could be improved so as to help the physician at the patient's bedside.

Preclinical and premarketing study design needs to be improved to make information easily accessible and clinically transferable. Studies should also take into account appropriate sample size, duration, co-morbidity, number of coadministered drugs, within- and between-subject variability, specific at-risk populations and/or drugs with a relatively narrow therapeutic window, and clinical endpoints. After premarketing development in situations where there is potential high risk of serious

adverse events, specific phase IV studies (and/or active pharmacovigilance studies) should be required to monitor and quantitatively assess their clinical impact.

Caccia S, Garattini S, Pasina L, et al. Predicting the clinical relevance of drug interactions from pre-approval studies. Drug Saf 2009; 32 (11): 1017-39

11. Progress towards Therapeutic Application of RNA Interference for HIV Infection

HIV-1 infection is the cause of acquired immune deficiency syndrome (AIDS). Highly active antiretroviral therapy (HAART) has been successful in reducing the rate of progression to AIDS, but a cure has not yet been achieved. New tools are required to delay progression of infection or to block the replication cycle of HIV. RNA interference (RNAi) has the potential to work as a powerful tool against HIV infection. The mode of action of small interfering RNAs (siRNAs) against their target genes is through sequence complementarity, which in turn results in target degradation. siRNAs are showing enormous potential to be used as a therapeutic tool in various diseases; however, this technology still requires refinement before its full potential can be utilized for the development of HIV therapies.

Singh SK, Gaur RK. Progress towards therapeutic application of RNA interference for HIV infection. Biodrugs 2009; 23 (5): 269-76

12. Therapeutic Breast Cancer Vaccines: A New Strategy for Early-Stage Disease

Treatment of breast cancer in the adjuvant setting has changed rapidly over the last few years. In addition to improvements in chemotherapy, radiation, hormone manipulation, and surgery, immunotherapy has emerged as an effective adjunct for the treatment of breast cancer. Passive immunotherapeutic agents such as trastuzumab have been widely adopted as the standard of care for HER-2/neu overexpressing breast cancer. Vaccine therapy in the metastatic setting has yet to demonstrate clinical significance in a phase III testing. This may be due to the enhanced immunosuppressive effects demonstrated in the tumor microenvironment. Lack of co-stimulatory molecules, activation of the cytotoxic T-lymphocyte antigen-4 (CTLA-4), increased T regulatory cells as well as soluble immunosuppressive factors produced by the tumor contribute to the ineffectiveness of vaccine therapy. Based on these observations, there has been a shift towards treating patients with minimal residual disease and a high risk of relapse. In this adjuvant setting, immune mechanisms of tumor evasion are less formidable, and the use of vaccine therapy in these patients may offer a higher chance of clinical benefit. There are several different vaccine approaches, including the use of cell-based vaccines (autologous, allogeneic, or dendritic cell-based), tumor-associated peptide or protein vaccines, DNA vaccines, heat shock proteins, and recombinant technology using viral or bacterial vectors to enhance immunogenicity of vaccine preparations. This review summarizes principles involving vaccine formulation and antigen selection, followed by a brief synopsis of therapeutic vaccines given in the metastatic setting and possible reasons for their lack of efficacy. The current literature regarding vaccine development for the treatment of breast cancer in the adjuvant setting is also reviewed.

Shumway NM, Ibrahim N, Ponniah S, et al. Therapeutic breast cancer vaccines: a new strategy for early-stage disease. Biodrugs 2009; 23 (5): 277-87

13. Monoclonal Antibodies Targeting Vascular Endothelial Growth Factor: Current Status and Future Challenges in Cancer Therapy

The use of monoclonal antibodies targeting the vascular endothelial growth factor (VEGF) pathway has been a significant addition to cancer therapy. One of the VEGF family members, VEGF-A (commonly referred to as VEGF), has been demonstrated to be important in angiogenesis. Although the mechanism of action of these antibodies is still under study, the anti-VEGF antibody bevacizumab has been approved for treatment of various solid cancers including colorectal, lung, and breast cancers as well as glioblastoma and renal cell carcinoma. Addition of bevacizumab to chemotherapy as adjuvant therapy in colorectal cancer did not improve disease-free survival. Bevacizumab is being tested in other clinical settings such as adjuvant therapy, maintenance therapy, and in combination with both chemotherapy and other targeted agents such as the epidermal growth factor receptor kinase inhibitor erlotinib. In addition to bevacizumab, other antibody-based therapies targeting the VEGF pathway are being tested. Ramucirumab and IMC-18F1 are monoclonal antibodies that target the VEGF receptors VEGFR-2 and VEGFR-1, respectively. Aflibercept (VEGF-Trap), a peptide-antibody fusion targeting VEGF ligand, is being tested in clinical trials. Much research is focused on identifying biomarkers to predict which patients will benefit from anti-VEGF therapy. Recent results suggest that VEGF single nucleotide polymorphisms may be predictive of patient response to bevacizumab. Improved imaging modalities such as dynamic contrast-enhanced MRI (DCE-MRI) can better characterize the efficacy of anti-angiogenic agents. As anti-VEGF treatments such as bevacizumab have

been integrated into the treatment of many different types of cancers, the development of bevacizumab-resistant tumors has become more common. Recent studies show that targeting other angiogenesis signaling pathways such as platelet-derived growth factor-C (PDGF-C), Bombina variagata peptide 8 (Bv8, also known as prokineticin-2), and VEGFR-3 may lead to enhanced response in anti-VEGF resistant tumors. In the future, tailored treatments consisting of combinations of chemotherapy, other targeted therapies, and anti-angiogenesis agents will hopefully result in better patient outcomes.

Hsu JY, Wakelee HA. Monoclonal antibodies targeting vascular endothelial growth factor: current status and future challenges in cancer therapy. Biodrugs 2009; 23 (5): 289-304

14. RNA Interference Technologies and Therapeutics: From Basic Research to Products

RNA interference (RNAi) is a natural cellular process that regulates gene expression by a highly precise mechanism of sequence-directed gene silencing at the stage of translation by degrading specific messenger RNAs or blocking translation. In recent years, the use of RNAi for therapeutic applications has gained considerable momentum. It has been suggested that most of the novel disease-associated targets that have been identified are not 'druggable' with conventional approaches. However, any disease-causing gene and any cell type or tissue can potentially be targeted with RNAi.

This review focuses on the current knowledge of RNAi mechanisms and the safety issues associated with its potential use in a therapeutic setting. Some of the most important aspects to consider when working towards the application of RNAi-based products in a clinical setting have been related to achieving high efficacies and enhanced stability profiles through a careful design of the nucleic acid sequence and the introduction of chemical modifications, but most of all, to developing improved delivery systems, both viral and non-viral. These new delivery systems allow for these products to reach the desired target cells, tissues or organs in a highly specific manner and after administration of the lowest possible doses. Various routes of application and target locations are currently being addressed in order to develop effective delivery systems for different targets and pathologies, including infectious pathologies, genetic pathologies and diseases associated with dysregulation of endogenous microRNAs. As with any new technology, several challenges and important aspects to be considered have risen on the road to clinical intervention, e.g. correct design of preclinical toxicology studies, regulatory concerns, and intellectual property protection. The main advantages related to the use of RNAi-based products in a clinical setting, and the latest clinical and preclinical studies using these compounds, are reviewed.

López-Fraga M, Martínez T, Jiménez A. RNA interference technologies and therapeutics: from basic research to products. Biodrugs 2009; 23 (5): 305-32

15. Polymorphism of Human Cytochrome P450 2D6 and Its Clinical Significance: Part I

Cytochrome P450 (CYP) 2D6 is one of the most investigated CYPs in relation to genetic polymorphism, but accounts for only a small percentage of all hepatic CYPs (~2–4%). There is a large interindividual variation in the enzyme activity of CYP2D6. The enzyme is largely non-inducible and metabolizes ~25% of current drugs. Typical substrates for CYP2D6 are largely lipophilic bases and include some antidepressants, antipsychotics, antiarrhythmics, antiemetics, β-adrenoceptor antagonists (β-blockers) and opioids. The CYP2D6 activity ranges considerably within a population and includes ultrarapid metabolizers (UMs), extensive metabolizers (EMs), intermediate metabolizers (IMs) and poor metabolizers (PMs). There is a considerable variability in the *CYP2D6* allele distribution among different ethnic groups, resulting in variable percentages of PMs, IMs, EMs and UMs in a given population.

To date, 74 allelic variants and a series of subvariants of the *CYP2D6* gene have been reported and the number of alleles is still growing. Among these are fully functional alleles, alleles with reduced function and null (non-functional) alleles, which convey a wide range of enzyme activity, from no activity to ultrarapid metabolism of substrates. As a consequence, drug adverse effects or lack of drug effect may occur if standard doses are applied. The alleles *10, *17, *36 and *41 give rise to substrate-dependent decreased activity. Null alleles of *CYP2D6* do not encode a functional protein and there is no detectable residual enzymatic activity. It is clear that alleles *3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *18, *19, *20, *21, *38, *40, *42, *44, *56 and *62 have no enzyme activity. They are responsible for the PM phenotype when present in homozygous or compound heterozygous constellations. These alleles are of clinical significance as they often cause altered drug clearance and drug response. Among the most important variants are *CYP2D6**2, *3, *4, *5, *10, *17 and *41. On the other hand, the *CYP2D6* gene is subject to copy number variations that are often associated with the UM phenotype. Marked decreases in drug concentrations have been observed in UMs with tramadol, venlafaxine, morphine, mirtazapine and metoprolol. The functional impact of *CYP2D6* alleles may be substrate-dependent. For example, *CYP2D6**17 is generally considered

as an allele with reduced function, but it displays remarkable variability in its activity towards substrates such as dextromethorphan, risperidone, codeine and haloperidol.

The clinical consequence of the CYP2D6 polymorphism can be either occurrence of adverse drug reactions or altered drug response. Drugs that are most affected by *CYP2D6* polymorphisms are commonly those in which CYP2D6 represents a substantial metabolic pathway either in the activation to form active metabolites or clearance of the agent. For example, encainide metabolites are more potent than the parent drug and thus QRS prolongation is more apparent in EMs than in PMs. In contrast, propafenone is a more potent β-blocker than its metabolites and the β-blocking activity during propafenone therapy is more prominent in PMs than EMs, as the parent drug accumulates in PMs. Since flecainide is mainly eliminated through renal excretion, and both *R*- and *S*-flecainide possess equivalent potency for sodium channel inhibition, the CYP2D6 phenotype has a minor impact on the response to flecainide. Since the contribution of CYP2D6 is greater for metoprolol than for carvedilol, propranolol and timolol, a stronger gene-dose effect is seen with this β-blocker, while such an effect is lesser or marginal in other β-blockers.

Concordant genotype-phenotype correlation provides a basis for predicting the phenotype based on genetic testing, which has the potential to achieve optimal pharmacotherapy. However, genotype testing for *CYP2D6* is not routinely performed in clinical practice and there is uncertainty regarding genotype-phenotype, gene-concentration and gene-dose relationships. Further prospective studies on the clinical impact of CYP2D6-dependent metabolism of drugs are warranted in large cohorts of subjects.

Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part I. Clin Pharmacoket 2009; 48 (11): 689-723

16. Evaluation of Bioequivalence for Highly Variable Drugs with Scaled Average Bioequivalence

Bioequivalence studies are performed to demonstrate *in vivo* that two pharmaceutically equivalent products (in the US) or alternative pharmaceutical products (in the EU) are comparable in their rate and extent of absorption. By definition, for highly variable drugs (HVDs), the estimated within-subject variability is >30%. HVDs often fail to meet current regulatory acceptance criteria for average bioequivalence (ABE). The determination of the bioequivalence of HVDs has been a vexing problem since the inception of the current regulations. It is of concern not only to the generic industry but also to the innovator industry. This article reviews the definition of HVDs, the present regulatory recommendations and the approaches proposed in the literature to deal with the bioequivalence problems of HVDs. The approach of scaled ABE (SABE) is proposed as the most adequate procedure to solve the problem. It is demonstrated that SABE has firm theoretical foundations. In fact, statistical tests similar to SABE are used in various fields, such as psychology and quality control. Algorithms and numerical examples are presented to calculate SABE from the data in conventional two-period and replicate-design studies. The most important feature of SABE is that a fixed sample size is adequate to demonstrate bioequivalence regardless of within-subject variability. The conditions for reaching consistent regulatory decisions with SABE are discussed. The required sample size, for a given statistical power, depends on the regulatory criteria. Sample sizes with different criteria are demonstrated and compared with those arising from a recent informal US FDA proposal.

Pragmatic considerations lead to modifications of the theoretical concept of SABE. Several modifications are proposed, including reference scaling, restriction on the estimated geometric mean ratios and possibly limiting SABE to only secondary bioequivalence metrics such as the maximum concentration. Each proposal has its own merit but is also a source of new controversy. Overall, the statistical evaluation of SABE is more complex than that of ABE, which means higher regulatory burden. Standardized open software could be very useful in this regard. A small program script is presented to calculate SABE confidence limits.

Tothfalusi L, Endrenyi L, Arieta AG. Evaluation of bioequivalence for highly variable drugs with scaled average bioequivalence. Clin Pharmacoket 2009; 48 (11): 725-43

17. Budget-Impact Analyses: A Critical Review of Published Studies

This article reviews budget-impact analyses (BIAs) published to date in peer-reviewed bio-medical journals with reference to current best practice, and discusses where future research needs to be directed.

Published BIAs were identified by conducting a computerized search on PubMed using the search term 'budget impact analysis'. The years covered by the search included January 2000 through November 2008. Only studies (i) named by authors as BIAs and (ii) predicting financial consequences of adoption and diffusion of a new health intervention(s) within a specific healthcare setting were included. Relevant studies were evaluated according to the checklist that focuses on issues unique to BIA, highlighting areas of agreement or dissent between published studies and methodological guidelines.

A total of 34 studies met the inclusion criteria, the majority published in 2007–8. Of these, 41% were from the US, 54% were prepared for pharmaceuticals and 65% had BIA as their main aim. The published BIAs were heterogeneous in respect of methods for deriving budget-impact estimates, time horizon and population. There is fairly good agreement between published studies and methodological guidelines within the scope of perspective, comparator, cost included and data sources. Specific issues that need to be addressed and/or improved are reporting format, sensitivity analysis and discounting.

The results indicate that, recently, BIAs have appeared more frequently in peer-reviewed journals, providing stimulus to development, validation and dissemination of methods. Many published studies fail to reach the desired quality, but this situation should change with good research practice principles that will help codify and clarify important issues and promote standardization and transparency. Future research needs to be directed to quality assurance of published BIAs and investment in data collection for parameters specific to BIAs.

Orlewska E, Gulácsi L. Budget-impact analyses: a critical review of published studies. Pharmacoeconomics 2009; 27 (10): 807-27

18. Strategies for Targeting Tetraspanin Proteins: Potential Therapeutic Applications in Microbial Infections

The identification of novel targets and strategies for therapy of microbial infections is an area of intensive research due to the failure of conventional vaccines or antibiotics to combat both newly emerging diseases (e.g. viruses such as severe acute respiratory syndrome [SARS] and new influenza strains, and antibiotic-resistant bacteria) and entrenched, pandemic diseases exemplified by HIV. One clear approach to this problem is to target processes of the host organism rather than the microbe. Recent data have indicated that members of the tetraspanin superfamily, proteins with a widespread distribution in eukaryotic organisms and 33 members in humans, may provide such an approach.

Tetraspanins traverse the membrane four times, but are distinguished from other four-pass membrane proteins by the presence of conserved charged residues in the transmembrane domains and a defining 'signature' motif in the larger of the two extracellular domains (the EC2). They characteristically form promiscuous associations with one another and with other membrane proteins and lipids to generate a specialized type of microdomain: the tetraspanin-enriched microdomain (TEM). TEMs are integral to the main role of tetraspanins as 'molecular organizers' involved in functions such as membrane trafficking, cell-cell fusion, motility, and signaling. Increasing evidence demonstrates that tetraspanins are used by intracellular pathogens as a means of entering and replicating within human cells. Although previous investigations focused mainly on viruses such as hepatitis C and HIV, it is now becoming clear that other microbes associate with tetraspanins, using TEMs as a 'gateway' to infection.

In this article we review the properties and functions of tetraspanins/TEMs that are relevant to infective processes and discuss the accumulating evidence that shows how different pathogens exploit these properties in infection and in the pathogenesis of disease. We then investigate the novel and exciting possibilities of targeting tetraspanins for the treatment of infectious disease, using specific antibodies, recombinant EC2 domains, small-molecule mimetics, and small interfering RNA. Such therapies, directed at host-cell molecules, may provide alternative options for combating fast-mutating or newly emerging pathogens, where conventional approaches face difficulties.

Hassuna N, Monk PN, Moseley GW, et al. Strategies for targeting tetraspanin proteins: potential therapeutic applications in microbial infections. Biodrugs 2009; 23 (6): 341-59

19. Methods for Measuring Temporary Health States for Cost-Utility Analyses

A variety of methods are available to measure preferences for temporary health states for cost-utility analyses. The objectives of this review were to summarize the available temporary health-state valuation methods, identify advantages and disadvantages of each, and identify areas for future research. We describe the key aspects of each method and summarize advantages and disadvantages of each method in terms of consistency with QALY theory, relevance to temporary health-state-specific domains, ease of use, time preference, and performance in validation studies. Two broad categories of methods were identified: traditional and adapted.

Traditional methods were health status instruments, time trade-off (TTO), and the standard gamble (SG). Methods adapted specifically for temporary health-state valuation were TTO with specified duration of the health state, TTO with a lifespan modification, waiting trade-off, chained approaches for TTO and SG, and sleep trade-off.

Advantages and disadvantages vary by method and no 'gold standard' method emerged. Selection of a method to value temporary health states will depend on the relative importance of the following considerations: ability to accurately capture

the unique characteristics of the temporary health state, level of respondent burden and cognition, theoretical consistency of elicited preference values with the overall purpose of the study, and resources available for study development and data collection. Further research should focus on evaluating validity, reliability and feasibility of temporary health-state valuation methods.

Wright DR, Wittenberg E, Swan JS, et al. Methods for measuring temporary health states for cost-utility analyses. Pharmacoeconomics 2009; 27 (9): 713-23

20. The Future of Molecular Approaches to Inflammatory Bowel Disease

Technological advances in genomics and transcriptomics have resulted in the introduction of molecular tests into the clinical arena. Despite established uses of such tests in the oncology field, their integration into the management of complex diseases has not been widely evaluated. Progress in the field of inflammatory bowel disease (IBD) genetics has been rapid in recent years, and these advances have provided more urgent impetus to investigating the role of molecular tests in IBD. This article summarizes the current state of molecular testing available for IBD, and the potential utility of such tests as research in the area widens.

Kabakchiev B, Halder S, Silverberg MS. The future of molecular approaches to inflammatory bowel disease. Mol Diag Ther 2009; 13 (4): 217-23

21. Disease Biomarkers in Multiple Sclerosis: Potential for Use in Therapeutic Decision Making

Multiple sclerosis (MS) is an autoimmune disorder of the brain and spinal cord that predominantly affects white matter. MS has a variable clinical presentation and has no 'diagnostic' laboratory test; this often results in delays to definite diagnosis. In confronting the disease, early diagnosis and appropriate, timely therapeutic intervention are critical factors in ensuring favorable long-term outcomes.

The availability of reliable biomarkers could radically alter our management of MS at critical phases of the disease spectrum. Identification of markers that could predict the development of MS in high-risk populations would allow for intervention strategies that may prevent evolution to definite disease. Work with anti-myelin antibodies and the ongoing analysis of microarray gene expression have thus far not yielded biomarkers that predict future disease development. Similarly, extensive studies with serum and cerebrospinal fluid (CSF) have not yielded a disease-specific and sensitive diagnostic biomarker for MS. Establishment of disease diagnosis always leads to questions about long-term prognosis because in an individual patient the natural history of the disease is clinically unpredictable. Biomarkers that correlate with myelin loss, spinal cord disease, grey matter and subcortical demyelination need to be developed in order to accurately predict the disease course. The bulk of effort in biomarker development in MS has been concentrated in the area of monitoring disease activity. At present, a disease 'activation' panel of CSF biomarkers would include the following: interleukin-6 or its soluble receptor, nitric oxide and nitric oxide synthase, osteopontin, and fetuin-A. Although disease activity in MS is predominantly inflammatory, disease progression is likely to be the result of neurodegeneration. Therefore, the roles of proteins indicative of neuronal, axonal, and glial loss such as neurofilaments, tau, 14-3-3 proteins, and N-acetylaspartate are all under investigation, as are proteins affecting remyelination and regeneration, such as Nogo-A. With the increasing awareness of cognition dysfunction in MS, molecules such as apolipoprotein and proteins in the amyloid precursor protein pathway implicated in dementia are also being examined.

Serum biomarkers that help monitor therapeutic efficacy such as the titer of antibody to β-interferon, a first-line medication in MS, are established in clinical practice. Ongoing work with biomarkers that reflect drug bioavailability and factors that distinguish between medication responders and non-responders are also under investigation.

The discovery of new biomarkers relies on applying advances in proteomics along with microarray gene and antigen analysis and will hopefully result in the establishment of specific biomarkers for MS.

Harris VK, Sadiq SA. Disease biomarkers in multiple sclerosis: potential for use in therapeutic decision making. Mol Diag Ther 2009; 13 (4): 225-44

22. Salivary Biomarkers for Clinical Applications

For clinical applications such as monitoring health status, disease onset and progression, and treatment outcome, there are three necessary prerequisites: (i) a simple method for collecting biologic samples, ideally noninvasively; (ii) specific biomarkers associated with health or disease; and (iii) a technology platform to rapidly utilize the biomarkers. Saliva, often regarded as the 'mirror of the body', is a perfect surrogate medium to be applied for clinical diagnostics. Saliva is readily accessible via a totally noninvasive method. Salivary biomarkers, whether produced by healthy individuals or by individuals affected by specific diseases, are sentinel molecules

that could be used to scrutinize health and disease surveillance. The visionary investment by the US National Institute of Dental and Craniofacial Research, the discovery of salivary biomarkers, and the ongoing development of salivary diagnostic technologies have addressed its diagnostic value for clinical applications. The availability of more sophisticated analytic techniques gives optimism that saliva can eventually be placed as a biomedium for clinical diagnostics. This review presents current salivary biomarker research and technology developmental efforts for clinical applications.

Zhang L, Xiao H, Wong DT. Salivary biomarkers for clinical applications. Mol Diag Ther 2009; 13 (4): 245-59

23. A Proposal for a Pharmacokinetic Interaction Significance Classification System (PISCS) Based on Predicted Drug Exposure Changes and Its Potential Application to Alert Classifications in Product Labelling

Background and Objective: Pharmacokinetic drug-drug interactions (DDIs) are one of the major causes of adverse events in pharmacotherapy, and systematic prediction of the clinical relevance of DDIs is an issue of significant clinical importance. In a previous study, total exposure changes of many substrate drugs of cytochrome P450 (CYP) 3A4 caused by coadministration of inhibitor drugs were successfully predicted by using *in vivo* information. In order to exploit these predictions in daily pharmacotherapy, the clinical significance of the pharmacokinetic changes needs to be carefully evaluated. The aim of the present study was to construct a pharmacokinetic interaction significance classification system (PISCS) in which the clinical significance of DDIs was considered with pharmacokinetic changes in a systematic manner. Furthermore, the classifications proposed by PISCS were compared in a detailed manner with current alert classifications in the product labelling or the summary of product characteristics used in Japan, the US and the UK.

Methods: A matrix table was composed by stratifying two basic parameters of the prediction: the contribution ratio of CYP3A4 to the oral clearance of substrates (CR), and the inhibition ratio of inhibitors (IR). The total exposure increase was estimated for each cell in the table by associating CR and IR values, and the cells were categorized into nine zones according to the magnitude of the exposure increase. Then, correspondences between the DDI significance and the zones were determined for each drug group considering the observed exposure changes and the current classification in the product labelling. Substrate drugs of CYP3A4 selected from three therapeutic groups, i.e. HMG-CoA reductase inhibitors (statins), calcium-channel antagonists/blockers (CCBs) and benzodiazepines (BZPs), were analysed as representative examples. The product labelling descriptions of drugs in Japan, US and UK were obtained from the websites of each regulatory body.

Results: Among 220 combinations of drugs investigated, estimated exposure changes were more than 5-fold for 41 combinations in which ten combinations were not alerted in the product labelling at least in one country; these involved buspirone, nisoldipine and felodipine as substrates, and ketoconazole, voriconazole, telithromycin, clarithromycin and nefazodone as inhibitors. For those drug combinations, the alert classifications were anticipated as potentially inappropriate. In the current product labelling, many inter-country differences were also noted. Considering the relationships between previously observed exposure changes and the current alert classifications, the boundaries between 'contraindication' and 'warning/caution' were determined as a 7-fold exposure increase for statins and CCBs, and as a 4-fold increase for BZPs. PISCS clearly discriminated these drug combinations in accordance with the determined boundaries. Classifications by PISCS were expected to be valid even for future drugs because the classifications were made by zones, not by designating individual drugs.

Conclusion: The present analysis suggested that many current alert classifications were potentially inappropriate especially for drug combinations where pharmacokinetics had not been evaluated. It is expected that PISCS would contribute to constructing a leak-less alerting system for a broad range of pharmacokinetic DDIs. Further validation of PISCS is required in clinical studies with key drug combinations, and its extension to other CYP and metabolizing enzymes remains to be achieved.

Hisaka A, Kusama M, Ohno Y, et al. A Proposal for a pharmacokinetic interaction significance classification system (PISCS) based on predicted drug exposure changes and its potential application to alert classifications in product labelling. Clin Pharmacoket 2009; 48 (10): 653-66

24. Risk Management Policy and Black-Box Warnings: A Qualitative Analysis of US FDA Proceedings

Background: The US FDA increasingly applies risk management to drug safety policy. Little is known about the process by which the FDA approves labelling changes. Although advisory committees can recommend any of the risk management tools, including the use of 'black-box warnings', it is unknown whether they deliberate on these questions or how they apply the principles of risk minimization or management during their considerations of drug licensing.

Objective: To examine the process by which risk management is considered by the FDA, including the role of FDA advisory committees. We also aimed to identify and describe drug labelling changes and additions, including the prevalence of black-box warnings.

Methods: We electronically obtained publicly available information regarding drug approvals, drug revisions and advisory committee meetings over 3 years (2004–6) from the FDA. Data in the form of meeting transcripts and full histories of labelling changes were collected on drugs discussed by advisory committees. We then searched and qualitatively analysed the meeting transcripts to identify themes in the discussion. We also created a database of all prescription drug labelling changes for 3 years and examined which drugs have had the most changes. We describe the risk management consideration process and report the frequency and characteristics of labelling changes. Excerpts from the transcripts are selected to illustrate both typical and atypical features of the discussion.

Findings: A total of 174 black-box changes were made in the 3-year period of our study, of which 77 were new black-box warnings and 97 were revisions in black-box warnings. Of 77 new black-box warning additions, only 11 drugs were discussed by the advisory committees. Of the 17 most frequently revised drug labels in these 3 years, two were discussed in the advisory committee meetings. Advisory meeting discussions revealed confusion about black-box warnings and emphasized potential consequences of the warnings rather than their content.

Conclusion: The safety labelling of drugs on the market is changed often. Panels of advisors consider only a few drugs, rarely discuss the labelling requirements, and display confusion about applying black-box warnings. The creation and application of black-box warnings on prescription medications should receive closer attention from the FDA and its advisors.

Cook DM, Gurugubelli RK, Bero LA. Risk management policy and black-box warnings: a qualitative analysis of US FDA proceedings. Drug Saf 2009; 32 (11): 1057-66

25. 30 Years of Pharmaceutical Cost-Utility Analyses: Growth, Diversity and Methodological Improvement

Objective: To review and critically evaluate published cost-utility analyses (CUAs) pertaining to pharmaceuticals for the past 3 decades.

Methods: We examined data from the Tufts Medical Center Cost-Effectiveness Analysis Registry (www.cearegistry.org), which contains detailed information on English-language CUAs and their ratios (in $US, year 2008 values) published in peer-reviewed journals. We summarized study features using descriptive statistics for articles published from 1976 to 2006. Changes in study methodology over time were analysed by trend test. Analysis of ratios was restricted to those published from 2000 to 2006 from studies that correctly discounted future costs and benefits. Factors associated with having a favourable value (defined to be more than the median for all included ratios) were identified by logistic regression.

Results: Of 1393 CUAs published through 2006 640 (45.9%) pertained to pharmaceuticals. The proportion of CUAs that focussed on pharmaceuticals increased from 34% for the period 1990–5 to 47% for the period 2001–5. Investigations with a US perspective accounted for 51% of all CUAs, although this proportion has decreased over time. The UK perspective investigations accounted for nearly 16% of all studies, and this portion has increased over time. About 24% of all CUAs were sponsored by industry, 48% were sponsored by non-industry sources, and 28% did not disclose their funding. Adherence to good methodological practices is roughly similar for studies with industry and non-industry sponsorship. Adherence to these practices has increased over time. Among the 1969 ratios meeting our inclusion criteria, the median value was $US22 000 per QALY.

Logistic regression revealed that, while controlling for the intervention category (e.g. pharmaceutical, medical device, screening), ratios were more likely to be favourable if they were from studies sponsored by a pharmaceutical or device manufacturer (OR 1.53; 95% CI 1.07, 2.19). Ratios for pharmaceutical CUAs were less favourable than other ratios while controlling for sponsorship (OR 0.66; 95% CI 0.44, 0.98).

Conclusion: The number of published pharmaceutical CUAs has grown steadily and accounts for almost half of all published CUAs. Adherence to good methodological practices does not appear to differ by study sponsor. Ratios from industry-sponsored studies are more favourable than other ratios. The results highlight that there are many opportunities for efficient healthcare investment, among pharmaceutical and non-pharmaceutical interventions, just as there are many investments that are inefficient.

Neumann PJ, Fang CH, Cohen JT. 30 years of pharmaceutical cost-utility analyses: growth, diversity and methodological improvement. Pharmacoeconomics 2009; 27 (10): 861-72

26. A Cost-Effectiveness Analysis to Illustrate the Impact of Cost Definitions on Results, Interpretations and Comparability of Pharmacoeconomic Studies in the US

Background: There is a lack of a uniform proxy for defining direct medical costs in the US. This potentially important source of variation in modelling and other types of economic

studies is often overlooked. The extent to which increased expenditures for an intervention can be offset by reductions in subsequent service costs can be directly related to the choice of cost definitions.

Objective: To demonstrate how different cost definitions for direct medical costs can impact results and interpretations of a cost-effectiveness analysis.

Methods: The IMS-CORE Diabetes Model was used to project the lifetime (35-year) cost effectiveness in the US of one pharmacological intervention 'medication A' compared with a second 'medication B' (both unspecified) for type 2 diabetes mellitus. The complications modelled included cardiovascular disease, renal disease, eye disease and neuropathy. The model had a Markov structure with Monte Carlo simulations.

Utility values were derived from the published literature. Complication costs were obtained from a retrospective database study that extracted anonymous patient-level data from (primarily private payer) adjudicated medical and pharmaceutical claims. Costs for pharmacy services, outpatient services and inpatient hospitalizations were included. Cost definitions for complications included charged, allowed and paid amounts, and for medications included both wholesale acquisition cost (WAC) and average wholesale price (AWP). Costs were reported in year 2007 values.

Results: The cost-effectiveness results differed according to the particular combination of cost definitions employed. The use of charges greatly increased costs for complications. When the analysis incorporated WAC medication prices with charged amounts for complication costs, the incremental cost-effectiveness ratio (ICER) for medication A versus medication B was $US6337 per QALY. When AWP prices were used with charged amounts, medication A became a dominant treatment strategy, i.e. lower costs with greater effectiveness than medication B. For both allowed and paid scenarios, there was a difference in the ICER of over $US10 300 per QALY when medication prices were defined by WAC versus AWP. Ratios of medication costs to cardiovascular complication costs ranged from under 0.45 to over 1.7, depending upon the combination of costing definitions.

Conclusions: Explicitly addressing the cost-definition issue can help provide meaningful cost-effectiveness data to payers for policy development and management of healthcare expenditures. It can also help move the pharmacoeconomics and outcomes research fields forward in terms of both methodology and practical application.

Tunis SL. A cost-effectiveness analysis to illustrate the impact of cost definitions on results, interpretations and comparability of pharmacoeconomic studies in the US. Pharmacoeconomics 2009; 27 (9): 735-44

27. Comparing Three Software Tools for Implementing Markov Models for Health Economic Evaluations

Background: Various software packages are commonly used for the implementation and calculation of decision-analytic models for health economic evaluations. However, comparison of these programs with regard to ease of implementing a model is lacking.

Objectives: (i) to compare the assets and drawbacks of three commonly used software packages for Markov models with regard to ease of implementation; and (ii) to investigate how a technical model validation can be conducted by comparing the results of the three implementations.

Methods: A Markov model on chronic obstructive pulmonary disease was implemented in TreeAge, Microsoft® Excel and Arena® with the same assumptions on model structure, transition probabilities and costs. A hypothetical smoking cessation programme for patients in stage 1 was evaluated against usual care. The packages were compared with respect to time and effort for implementation, run-time, features for the presentation of results, and flexibility. Agreement between the packages on average costs and life-years gained and on the incremental cost-effectiveness ratio was considered for technical validation in the form of expected values (between TreeAge and Excel only) and Monte Carlo simulations.

Results: Ease of implementation was best in TreeAge, whereas Arena® offered the highest flexibility. Deterministic results were in agreement between TreeAge and Excel, as were simulated values between all three packages.

Conclusions: Excel offers an intuitive spreadsheet interface, but the acquisition of and the training in TreeAge or Arena® is worthwhile for more complex models. Double implementation is a practicable validation technique that should be conducted to ensure correct model implementation.

Menn P, Holle R. Comparing three software tools for implementing Markov models for health economic evaluations. Pharmacoeconomics 2009; 27 (9): 745-53

28. The Importance of Clinical Variables in Comparative Analyses Using Propensity-Score Matching: The Case of ESA Costs for the Treatment of Chemotherapy-Induced Anaemia

Background: The erythropoiesis-stimulating agents (ESAs) epoetin alfa (EA) and darbepoetin alfa (DA) have comparable efficacy in treating chemotherapy-induced anaemia (CIA). Therapy choice depends on many factors, including cost. Previous estimates of ESA cost differences have been derived from claims data. These data lack clinical variables, such as baseline haemoglobin (Hb) level, which are likely to influence choice of

ESA, dosing and costs. We estimated cost differences between DA and EA in patients with cancer receiving chemotherapy, using a propensity-score matched analysis of baseline patient characteristics with and without Hb values to assess the effect of this clinical variable on ESA cost estimates.

Methods: Data were extracted from electronic medical records in two US databases between January 2004 and December 2006. The study sample included 6743 patients receiving chemotherapy, with one or more visits during the study period, who received an ESA during a chemotherapy episode. Episodes of chemotherapy care were constructed using a 90-day gap in administration to identify the start and end. Patients receiving both DA and EA during their initial chemotherapy episode or with missing data were excluded, representing 42% of patients with CIA receiving an ESA. Drug costs were calculated from the cumulative dose multiplied by 106% of the average sales price (ASP) for DA or EA. Two propensity-score matches were conducted: first using variables available in administrative billing claims systems, then adding the baseline Hb test result. Regression-adjusted cost differences were estimated with and without baseline Hb, using generalized linear models.

Results: Using baseline Hb levels resulted in a better match of the baseline characteristics for the EA and DA treatment groups than the original sample or the matched sample without Hb variables. Mean ESA costs (year 2007 values) for the original sample were $US4171 for EA and $US3811 for DA (mean difference $US360; $p < 0.001$, standard error [SE] $US99). With propensity-score matching without Hb variables, mean estimated costs were $US3836 for EA and $US3599 for DA (mean difference $US237; $p = 0.053$, SE $US123). With propensity-score match including Hb variables, mean costs were $US3965 for EA and $US3536 for DA (mean difference $US429; $p = 0.001$, SE $US125). Cost differences in sensitivity analyses ranged between $US102 ($p = 0.201$) and $US261 ($p = 0.003$).

Conclusions: Addition of baseline Hb level as a variable in propensity score and ESA cost models affects ESA treatment cost estimates in patients with cancer receiving chemotherapy. Cost comparisons based on observational data should use analytical methods that account for differences in clinical variables between treatment groups.

Polsky D, Eremina D, Hess G, et al. The importance of clinical variables in comparative analyses using propensity-score matching: the case of ESA costs for the treatment of chemotherapy-induced anaemia. Pharmacoeconomics 2009; 27 (9): 755-65

29. Utilities of the EQ-5D: Transferable or Not?

Background: Within the framework of economic evaluations, the transferability of utility scores between jurisdictions remains unclear. The EQ-5D is a generic instrument for measuring health-related quality of life in economic evaluations, which can be used for comparing utility scores across countries. At present, the EQ-5D has several national value sets or tariffs. Nevertheless, utility estimates from foreign studies are often used directly for cost-effectiveness estimates, without adapting by applying the appropriate national value set. It is unclear if this practice is advisable, due to dissimilarities between the national value sets.

Objective: To examine the effects of differences in national EQ-5D value sets on absolute and marginal utilities of health states, and determine to what degree these differences can be explained by methodological factors.

Methods: First, the relative importance of the EQ-5D domains for the utility estimates was compared across the 15 value sets. Second, two hypothetical health states for a depressed patient and a pain patient (21232 and 33321) were selected for additional analysis, by comparing the utilities as scored by the value sets. The marginal influence of a one-level deterioration in a domain of these health states on the utility estimate was then determined. Third, the differences between the value sets were examined in more detail by using multilevel analysis to examine the role of methodological differences in the valuation studies.

Results: Differences can be perceived between the national value sets of the EQ-5D in the preferences for the domains. The utilities of the two hypothetical health states show that the value sets differ substantially. Furthermore, the differences between the marginal values of the deteriorations are large, which can be explained partly by the type of valuation method. Other methodological differences also influence the value sets.

Conclusion: All results indicate that the differences between the EQ-5D value sets are considerable and should not be ignored. The differences can largely be explained by methodological differences in the valuation studies. The remaining differences may reflect cultural dissimilarities between countries. Therefore, further research should focus on investigating the transferability of utilities across countries or agreeing on a standard to perform valuation studies. For the time being, transferring utilities from one country to another without any adjustment is not advisable.

Knies S, Evers SM, Candel MJ, et al. Utilities of the EQ-5D: transferable or not? Pharmacoeconomics 2009; 27 (9): 767-79

30. Using Self-Regulation Theory to Examine Patient Goals, Barriers, and Facilitators for Taking Medication

Background: Self-regulation theory predicts that patient behavior is determined by the patient's assessment of his/her

condition (illness presentation) and related health goals. Patients will adapt their behavior to achieve those goals. However, there are multiple levels of goals. In such cases, those lower-level goals (health goals) that are strongly correlated with higher-level goals (i.e. quality of life [QOL]) are more likely to drive patient behavior. Medication non-compliance is a health behavior that challenges healthcare practitioners. Thus, the primary aim of this paper is to explore the relationship between the lower-level goals for taking medication with higher-level goals. This paper also identifies patient-perceived barriers and facilitators toward achieving goals as they may relate to patients' illness representation.

Objectives: To identify lower- and higher-level goals associated with medication use for chronic conditions. To determine if there is a relationship between higher-level (global) goals and lower-level (health-related) goals. To identify patient-perceived facilitators and barriers to achieving those goals.

Methods: This was a prospective, observational study using a mailed survey. The setting was a US Midwestern state-wide survey. Participants were patients living in the community with hypertension, heart disease, diabetes mellitus, or arthritis, and taking prescription medication for any one of those conditions. The main outcome measures were lower- and higher-level goals related to medication use. The survey asked the participants if they had achieved their goals and to identify factors that may pose as barriers or facilitators to achieving them. Pearson correlation was used to test the relationship between the lower- and higher-level goals at $p < 0.05$.

Results: Responses from 292 qualifying patients were obtained. A significant relationship between lower- and higher-level goals existed ($p = 0.03$). Preventing future health problems was the most important lower-level goal for almost half of the respondents. Approximately 43% of the respondents said 'improving or maintaining quality of life' was their most important higher-level goal. Elderly respondents (65 years or older) said that being able to carry out daily activities on their own was their most important higher-level goal. To achieve this goal, they identified 'preventing future health problems' as the associated lower-level goal. One-third of the respondents stated that they had not yet achieved their medication-related goals. Patients identified good communication with their physicians (35%), the effectiveness of the drug product (32%), and their ability to monitor their condition (20%) as important factors toward helping them achieve their goals. Medication costs (30%), drug adverse effects (25%), and the lack of drug effectiveness (22%) were factors that patients identified as barriers to achieving their goals.

Conclusion: There is a significant and positive relationship between the lower- and higher-level goals. Healthcare providers can work with their patients to achieve their goals. Both good communication with the prescriber and the effectiveness of the drug product were identified as the most important facilitator by one-third of the respondents. Future research should study if relating the impact of good symptom control or the reduction of future health risks to QOL or longevity, as deemed relevant by the patient, influences medication adherence behavior.

Kucukarslan SN, Thomas S, Bazzi A, et al. Using self-regulation theory to examine patient goals, barriers, and facilitators for taking medication. Patient 2009; 2 (4): 211-20

31. First Things First: Difficulty with Current Medications is Associated with Patient Willingness to Add New Ones

Background: Inadequate BP control remains prevalent. One proposed explanation is 'clinical inertia,' often defined as the failure by providers to initiate or intensify medication therapy when otherwise appropriate. However, patients could contribute to clinical inertia by signaling an unwillingness to consider medication intensification.

Objective: To explore co-variates of patient attitudes likely to predict patients' willingness to intensify (WTI) their medication regimen.

Methods: A cross-sectional survey was conducted in nine Midwestern US Veterans' Administration medical facilities as part of a prospective cohort study of clinical inertia in hypertension treatment. 1062 patients with diabetes mellitus, identified as having BP ≥140/90 mmHg, were surveyed. Primary outcome was participants' indicated WTI BP medications if their provider noted elevated BP levels. Potential co-variates assessed included BP control (actual and perceived), perceived importance of BP control, BP management self-efficacy, competing demands, medication factors (adherence and management issues), trust in provider, and sociodemographic factors.

Results: While 64% of participants reported complete WTI BP medications, 36% of participants expressed at least some unwillingness. In ordered logistic regression analysis, WTI was negatively associated with medication concerns, particularly concern about adverse effects (odds ratio [OR] 0.49; 95% CI 0.42, 0.59) and adherence or management problems (OR 0.72; 95% CI 0.57, 0.91), and positively associated with perceived dependence of health on BP medications (OR 1.50; 95% CI 1.26, 1.79) and trust in provider (OR 1.30; 95% CI 1.10, 1.54).

Importance of BP control had a weaker, nonsignificant association with WTI (OR 1.17; 95% CI 0.99, 1.40). Competing demands, current BP control, current number of medications prescribed, and self-efficacy were not associated with WTI medications.

Conclusions: Patients' willingness to consider intensification of BP medications appears primarily determined by how well patients are managing their current medications, rather than patients' perceived importance of BP control, their self-efficacy, or their prioritization of BP control versus other health demands. Greater attention to patients' pre-existing medication issues may improve providers' ability to intensify BP medication therapy when medically appropriate while simultaneously improving patient satisfaction with care.

Zikmund-Fisher BJ, Hofer TP, Klamerus ML, et al. First things first: difficulty with current medications is associated with patient willingness to add new ones. Patient 2009; 2 (4): 221-31

32. Using the Pediatric Asthma Therapy Assessment Questionnaire to Measure Asthma Control and Healthcare Utilization in Children

Background: The usefulness of questionnaires to assess asthma control in clinical practice is recognized in recent international guidelines. While several questionnaires have been developed to measure asthma control in adults, there has been little study of the performance of such instruments in children.

Objective: To determine whether there is an association between asthma-related healthcare use and poor asthma control, as determined by categorical score on the control domain of the Asthma Therapy Assessment Questionnaire for children and adolescents (the pediatric ATAQ).

Methods: An analysis of a 1998 mailed survey of parents or caregivers of children aged 5–17 years with asthma enrolled in three large managed-care organizations in the Northeast and Midwest US was conducted. Pediatric ATAQ control domain score (reported for the past 4 weeks) was the main outcome measure. The pediatric ATAQ control domain was scored from 0 to 7, with 0 indicating no asthma control problems as measured by the questionnaire, and higher scores indicating increasing asthma problems. The hypothesis of an association between pediatric ATAQ control domain score and asthma-related healthcare use (hospitalizations, ER or urgent care facility visits, and doctor visits for worsening asthma in the past 12 months) was examined.

Results: 406 completed surveys were received. Asthma-related hospitalizations, ER/urgent care visits, and doctor visits were reported for 38, 173, and 319 children, respectively. Of the three control score categories (0, 1–3, and 4–7), children with a control score of 4–7 were more likely to have been hospitalized ($p = 0.01$), to have visited the ER or urgent care facility ($p < 0.0001$), or to have visited a doctor ($p = 0.0001$) because of asthma managed care.

In multivariate models including demographic variables and a measure of general health status, higher odds of ER/urgent care visits (odds ratio [OR] 3.47, 95% CI 1.92, 6.26) and doctor visits (OR 7.14; 95% CI 2.40, 21.2) was observed for children with an asthma control score of 4–7 than for children with no identified asthma control problems (score of 0). An asthma control score of 4–7 was significantly associated with hospitalization in a multivariate model including only demographic variables (OR 3.06; 95% CI 1.28, 7.33) but not in a model that included general health status (OR 2.44; 95% CI 0.96, 6.16). Relative to an excellent health status, a fair or poor health status was significantly associated with asthma-related hospitalization (OR 7.03; 95% CI 1.71, 28.87). Compared with White race, Black race was significantly associated with hospitalization (OR 2.30; 95% CI 1.05, 5.04) and ER/urgent care visits (OR 2.89; 95% CI 1.67, 5.01).

Conclusions: Children identified as having poor asthma control using the pediatric ATAQ instrument had significantly higher rates of asthma-related hospitalizations, ER or urgent care visits, and doctor visits than those with good control. This asthma control measure may be useful in identifying children in need of more intensive asthma management.

Diette GB, Sajjan SG, Skinner EA, et al. Using the pediatric asthma therapy assessment questionnaire to measure asthma control and healthcare utilization in children. Patient 2009; 2 (4): 233-41

33. Patients' Preferences for Generic and Branded Over-the-Counter Medicines: An Adaptive Conjoint Analysis Approach

Background: Despite increased use of generic medicines, little is known about either the attitudes of patients towards them or the decision-making process surrounding them. Young adults use over-the-counter (OTC) analgesics relatively often.

Objective: To assess the preferences of patients for generic and branded OTC pain medicines, to identify clusters with different preference structures, and to estimate the price elasticity of a generic alternative among university students.

Methods: Finnish university students ($n = 256$; students in courses at the Helsinki School of Economics) responded to an adaptive conjoint analysis (ACA) questionnaire on the choice

between branded and generic OTC ibuprofen products. Product attributes of price, brand, onset time of effect, place of purchase and source of information were included in the questionnaire on the basis of the literature, a focus group and a previous pilot study. Several socioeconomic and health behavior descriptors were employed. Individual-level utility functions were estimated, preference clusters were identified, and the price elasticity of the generic medicine was assessed.

Results: Five clusters with characteristic individual-level preferences and price elasticity but few differences in socioeconomic background were detected. Approximately half of the respondents were strongly price sensitive while the others had other preferences such as brand or an opportunity to buy the medicine at a pharmacy or to have a physician or a pharmacist as an information source.

Conclusion: The study provided new information on the concomitant effects of brand, price and other essential product attributes on the choice by patients between branded and generic medicines.

Halme M, Linden K, Kääriä K. Patients' preferences for generic and branded over-the-counter medicines: an adaptive conjoint analysis approach. Patient 2009; 2 (4): 243-55

34. How do People with Different Levels of Activation Self-Manage their Chronic Conditions?

Background: People with chronic conditions are better able to self-manage if they are more engaged, informed, and confident. Healthcare providers are increasingly offering support for self-management, and there is interest in improving the efficacy of these efforts by tailoring them to a person's knowledge, skill, and confidence to self-manage – so-called 'activation'.

Objective: To explore how people with chronic conditions at different levels of 'activation' (as measured by the Patient Activation Measure) understand successful self-management, what barriers to self-management they face, and what strategies they employ to manage their condition and to cope with stress.

Methods: Face-to-face semi-structured interviews were conducted with a stratified convenience sample of respondents with at least one chronic condition (n = 27) who were non-faculty staff at the University of Oregon (Eugene, OR, USA). Stratification was performed using the level of patient activation. Interviews took place in February and March 2006 in a private office on the university campus.

Results: Those people lower in activation tended to see successful self-management as compliance whereas those at higher activation levels saw it as being in control. People with lower activation levels indicated that lack of knowledge and lack of confidence were barriers for them. Both the high and low activated could be derailed by stress. People with lower activation levels talked about a more limited number of strategies for coping but both the high and low activated had learned strategies from professionals and by trial and error.

Conclusions: Some aspects of self-management support may need to be tailored for people at different levels of activation to ensure that differences in their understanding, knowledge, and confidence are addressed. However, there are also likely to be some types of self-management support such as stress-coping strategies and problem-solving skills that are beneficial for all patients with chronic conditions regardless of activation level.

Dixon A, Hibbard J, Tusler M. How do people with different levels of activation self-manage their chronic conditions? Patient 2009; 2 (4): 257-68

35. Using Qualitative Research to Inform the Development of a Comprehensive Outcomes Assessment for Asthma

Background: Qualitative research can inform the development of asthma patient-reported outcome (PRO) measures and user-friendly technologies through defining measurement constructs, identifying potential limitations in measurement and sources of response error, and evaluating usability.

Objective: To inform the development of a comprehensive asthma PRO assessment with input from patients and clinical experts.

Methods: Self-reported adult asthma patients recruited from a 3000-member New England area research panel participated in either one of three focus groups (n = 21) or individual cognitive item debriefing interviews (n = 20) to discuss how asthma impacts their health-related quality of life (HR-QOL), and provide feedback on a preliminary set of asthma impact survey items and prototype patient reports. Focus groups and cognitive interviews were conducted using traditional research principles (e.g. semi-structured interview guide, probing, and think aloud techniques). An expert advisory panel (n = 12) including asthma clinical specialists and measurement professionals was convened to review results from the focus group and cognitive interview studies, and make recommendations for final survey and report development.

Results: Domains of health impacted by asthma included physical (recreation, play, competitive sports, and exercise), social (activities, family relationships), emotional (anger, upset, frustration, anxiety, worry), sleep, role (recreational/leisure activities, work), and sexual functioning. Most items in the

impact survey were easily understood, covered important content, and included relevant response options. Items with contradictory examples and multiple concepts were difficult to comprehend. Suggestions were made to expand survey content by including additional items on physical and sexual functioning, sleep, self-consciousness, stigma, and finances. Reports were considered useful and participants saw value in sharing the results with their doctors. Graphic presentation of scores was not always understood; participants preferred tabular presentation of score levels with associated interpretative text. Display of inverse scores for different measures (higher scores equaling better health on one scale and worse health on another) shown on a single page was confusing. The score history section of the report was seen as helpful for monitoring progress over time, particularly for those recently diagnosed with asthma.

Expert panelists agreed that displaying inverse scores in a single summary report could be confusing to patients and providers. They also stressed the importance of comprehensive interpretation guidelines for patients, with an emphasis on what they should do next based on scores. Panelists made recommendations for provider and aggregate-level reports (e.g. 'red flags' to indicate significant score changes or cut points of significance; identification of subgroups that have scored poorly or recently got worse).

Conclusion: Incorporating input from patients, clinicians, and measurement experts in the early stages of product development should improve the construct validity of this PRO measure and enhance its practical application in healthcare.

Turner-Bowker DM, Saris-Baglama RN, DeRosa MA, et al. Using qualitative research to inform the development of a comprehensive outcomes assessment for asthma. Patient 2009; 2 (4): 269-82