eJIFCC

The clinical and health economic value of clinical laboratory diagnostics

Bruce Jordan, Cheryl Mitchell, Andy Anderson, Norbert Farkas, Richard Batrla

Roche Diagnostics Ltd, Rotkreuz, Switzerland

ARTICLE INFO

Corresponding author:
Bruce Jordan
Roche Diagnostics
CH-6343
Rotkreuz
Switzerland
e-mail: bruce.jordan@roche.com

ABSTRACT

The ultimate goal of diagnostic testing is to guide disease management in order to improve patient outcomes and patient well-being. Patient populations are rarely homogenous and accurate diagnostic tests can dissect the patient population and identify those patients with similar symptoms but very different underlying pathophysiology that will respond differently to different treatments. This stratification of patients can direct patients to appropriate treatment and is likely to result in clinical benefits for patients and economic benefits for the healthcare system. In this article we look at the clinical and economic benefits afforded by clinical laboratory diagnostics in three disease areas that represent substantial clinical and healthcare burdens to society; heart failure, Alzheimer's disease and asthma.

The relative spend on diagnostics compared with pharmaceuticals indicates that diagnostic tests are underappreciated in relation to the medical and economic value that they deliver. Clinical laboratory diagnostics should be viewed as a pivotal part of the healthcare system and valued accordingly. The skills available in clinical laboratories around the world should be harnessed to ensure the continued development of accurate tests that inform the healthcare community with respect to the pathophysiology of disease and facilitate the screening, diagnosis, appropriate treatment and monitoring of patients

INTRODUCTION

Clinical laboratory diagnostics are central to the integrated management of many different diseases. Without accurate diagnosis, appropriate treatment is not possible. However, the central role of clinical diagnostics is often underappreciated because the impact on patient care is not as readily apparent as medical intervention.

European expenditure on diagnostic procedures represents just 0.8% (€10.8 billion) of total healthcare expenditure (~€1,350 billion). Moreover, patients across Europe have unequal access to *in vitro* diagnostics because resources spent on these tests vary from €3.6 (Romania) to €43.5 (Switzerland) per capita per annum [1]. This expenditure belies the importance of clinical diagnostics, which is said to influence more than 60% of clinical decision making. Accurate diagnosis, based on detection of biomarkers and other tests, with subsequent guided therapy can result in clinical benefits for patients and economic benefits for the healthcare system [2,3]. As the population expands and ages, clinical laboratory diagnostics can help to reduce the associated healthcare costs by directing care and resources to those who are most likely to benefit.

Although automated platforms have accelerated the testing procedure and reduced the necessary labour intensity, many tests still require highly trained, skilled clinical scientists to interpret the results and relay these effectively to the clinician responsible for a patient's care. These clinical scientists should be viewed as highly valued members of the broader healthcare team.

The purpose of this article is to highlight the value of the diagnostic work conducted by clinical laboratories from two key perspectives; clinical and economic. The impact of clinical laboratory diagnostics is examined in three key areas; heart failure (HF), Alzheimer's disease (AD) and asthma.

IMPACT OF DIAGNOSIS ON UNDERSTANDING MEDICINE: HOW LESSONS FROM THE PAST ENABLE TREATMENT IN THE FUTURE

An understanding of diseases has always been fostered by a better understanding of underlying causes. In one of the earliest examples, diabetes mellitus (meaning 'honey-like'), was able to be separated from diabetes 'insipidus' (meaning 'tasteless') based on the observation that ants are attracted to the urine from a patient with diabetes mellitus [4,5]. Such an individual and definitive diagnosis is fundamental in separating patients with similar symptoms into subgroups with very different underlying pathophysiology.

Understanding how these diseases develop is key to appropriate patient management. It improves understanding of clinical symptoms and in turn improves early and accurate diagnosis of disease through the identification of at-risk groups. This is a progressive, iterative process with individual developments continually refining the initial wider spectrum diagnosis.

Asthma is an example of progressive refinement of diagnosis. Traditionally treatment of asthma has largely been symptomatic with increases in symptoms leading to escalation of therapy, with no knowledge or understanding of the different pathological causes responsible for symptoms in different patient groups. As a consequence, the cause of symptoms was not addressed and treatment response was suboptimal. Subsequent recognition that asthma patients can be eosinophilic or non-eosinophilic based on the presence or absence of sputum eosinophilia is leading to a better understanding of response to treatment in these patients [6]. However, this necessitates sputum testing for eosinophilic status becoming more widely accepted so that patients more likely to respond to therapy can be identified.

More recently further dissection of the patient population based on observed heterogeneity of interleukin-13 (IL-13) expression has identified a group of patients with high levels of periostin who are more likely to respond to therapy with lebrikizumab, an anti-IL-13 medicine currently in Phase III clinical development [7].

AD, the most frequent cause of dementia [8,9], may be a further example of such refinement. One characteristic of AD is the presence of amyloid-beta plaques. In the past a definitive diagnosis could only be made through identification of these plaques at autopsy, although more recently there has been a shift towards *in vivo* diagnosis based on amyloid-binding positron emission tomography (PET) tracers and cerebrospinal fluid (CSF) biomarkers. However, studies comparing clinical diagnosis and autopsy findings have shown that an incorrect diagnosis is made in as many as 12–23% of cases [10], and up to 32% of patients with clinically probable AD have shown no amyloid pathology on PET [11–13]. The potential impact of this was observed in the EXPEDITION 1 and 2 studies, which investigated the use of the humanized analogue of the murine antibody, solanezumab, in patients with mild-to-moderate AD [14]. In this study, there was no significant improvement in cognition or functional ability. However, 22% of the patient population did not meet the cut-off for being amyloid positive [15] and probably did not have AD. This may have diluted the efficacy. Using a biomarker like amyloid-beta it is possible to identify a purer population of the specific disease and gain an understanding of their disease progression and ability to be targeted with specific therapies, such as anti-amyloid therapy, that may be effective in this selected population. In fact, a subanalysis of these patients has demonstrated a trend to respond in amyloid-beta-enriched patients and the ongoing EXPEDITION 3 study is looking into this further [NCT01900665].

The understanding of the role of the specific Tau proteins in disease progression may further aid the understanding of the pathophysiological causes of AD. Stronger investment into biomarker research and provision of these biomarkers to physicians in the form of reliable and accessible diagnostic tools may be an effective route to developing a better understanding of the disease and ultimately help to develop more specific and effective therapies. For this reason the imbalance of expenditure on diagnostics and interventional drugs needs to be reduced. Diagnostics needs to play a more prominent role in medicine and these innovations should receive greater recognition by the healthcare community.

HEALTH ECONOMIC IMPACT: HOW THIS IS MEASURED

Problems central to the provision of healthcare include the scarcity of resources and the need to contain costs within healthcare systems against a background of increasing demand as a result of an ageing population, poor diet, increasing rates of obesity and other healthcare megatrends. Since the 1960s, expenditure on healthcare has risen faster than the general rate of inflation [16].

Health economic evaluations help decision makers to allocate scarce resources based on cost vs benefit. This mainly involves undertaking prospective and retrospective comparative studies and/or economic modelling [17]. Economic modelling falls into four major categories: cost minimization, cost-effectiveness, cost utility and cost-benefit analysis. Analysis can be performed from different perspectives; societal/economic perspective, healthcare system perspective, social insurance perspective or from the perspective of specific providers, such as hospitals. In general, choice of comparator must be appropriate for the specific analysis.

Costs are usually described in monetary units, while associated benefits are described in terms of quality-adjusted life years (QALYs) gained or lost [17]. The relationship between the two is the incremental cost-effectiveness ratio (ICER). Threshold values for 'willingness to pay' (e.g. approximately £20–30 k/QALY gained in the UK) could inform decision makers as to whether the technology in question is 'good value for money', keeping in mind the budgetary implications on the healthcare system.

Health economic evaluation of diagnostic technologies is complex, involving combined modelling of diagnostics and treatment, timing of tests and different test cut-off points, and is further complicated by the lack of universally accepted general guidelines and methodologies.

IMPACT OF CLINICAL LABORATORY DIAGNOSTICS: CLINICAL AND ECONOMIC PERSPECTIVES

Without reliable diagnostic tests appropriate clinical decisions cannot be made. Point of care tests allow these decisions to be made within hours, if not minutes. A single test can identify the need for additional tests, indicate that further tests are futile, or be sufficient to rule-out a disease and discharge a patient. They can be used to monitor treatment progress and to indicate when or whether treatment should be initiated or stopped as well as informing the optimal dose or treatment frequency needed to achieve a desired therapeutic effect in an individual patient.

A diagnosis based solely on clinical symptoms, as described above, can lead to the wrong conclusion. Laboratory diagnostics provide an objective measure. This is particularly important in areas where key symptoms are non-specific, such as dyspnoea or headache, and where diagnosis is problematic based on clinical history alone. Dyspnoea is one of the most common

symptoms. It is also one of the most non-specific; the online diagnostic tool, DiagnosticPro, lists close to 500 causes of dyspnoea, which can be challenging to distinguish between. Laboratory diagnostics, together with the clinical assessment, can give a definitive answer, or at least narrow down the options. For example, although acute coronary syndrome usually presents as dyspnoea associated with chest discomfort, it may typically present as dyspnoea alone. In this circumstance, cardiac markers are important for diagnosis and directing treatment. Nowadays, diagnostic tests can be performed at a centralized laboratory, in hospital, in the clinic, and at work or home, offering flexibility around clinical decision making.

Diagnostic tests have the ability to safeguard public health as well the health of an individual by providing rapid information during public health emergencies to confirm the presence of infectious disease, triage and treat accordingly. Evidence-based clinical practice guidelines are increasingly recommending the use of specific diagnostic tests because of their role in informing healthcare decision making.

Clinical diagnostics allow for the stratification of patients with heterogeneous diseases to enable targeted therapy for patients most likely to respond. Not only can diagnostic tests in some cases predict therapeutic efficacy, but they may also predict those who are more likely to experience adverse events. Thus, they inform the risk: benefit trade-off that is central to healthcare.

The real health economic benefit of clinical laboratory diagnostics is evident when the impact on tertiary care is examined. In particular, clinical laboratory diagnostics can be used effectively to triage patients to the appropriate level of care with a related reduction in costs associated with hospitalisation [3]. Additional cost benefits of clinical laboratory diagnostics may be realized through a reduction in the number needed

to treat, a reduction in drug costs associated with identifiable non-responders, avoided costs from predictable side effects, improved compliance and persistence and improved health outcomes [18]. Thus, clinical laboratory diagnostics play a key role by influencing the quality of patient care, health outcomes and downstream resource requirements. These considerations will become more and more important as the global population expands and ages. Using the example of AD, with an estimated projected worldwide patient population of 115 million by 2050 [8], employing a diagnostic test to exclude the proportion of patients unlikely to respond to therapy alone has the potential to drastically reduce associated healthcare costs.

The clinical benefit of an accurate diagnosis is apparent for all diseases. An associated health economic impact is most relevant in diseases that are highly prevalent or resource-intensive to manage. Three examples are HF, AD and asthma.

CLINICAL AND HEALTH ECONOMIC IMPACT OF LABORATORY DIAGNOSTICS IN HEART FAILURE

HF is one of the most costly medical conditions to manage, due to high prevalence and frequent and prolonged periods of hospitalization; in the US, in patients aged 18–64, each hospitalization due to HF costs an estimated $23,077 [19]. Although HF-related hospitalization rates are declining [20], HF remains one of the leading causes of hospitalization among people aged >60 years [21], with patients staying on average 4 days longer in hospital than for other diseases [21,22]. In addition, over one-quarter of patients are readmitted within 30 days of initial discharge [23].

The prevalence of HF increases with age. In the UK, analysis from the British Heart Foundation estimates that 0.9% of men and 0.7% of women suffer from HF, rising to 13.1% of men and 11.9% of women aged over 75 years [24]. Thus, as is the case in the US, HF constitutes a substantial burden on the National Health Service (NHS), accounting for one million inpatient bed-days (2% of the NHS total) and 5% of all emergency hospital admissions [25]. Given the age-related prevalence of HF, as well as age-related increases in recognised risk factors, such as hypertension, coronary heart disease, obesity, diabetes and hyperlipoproteinaemia, associated costs can be expected to increase. Indeed, the American Heart Association predicts that by 2030 the prevalence of HF will be 3.5%, equating to $77.7 billion in direct costs [26].

A cardinal symptom of HF is dyspnoea. As noted above, this symptom is non-specific and subjective and patients presenting with dyspnoea may have multiple comorbidities that complicate diagnosis. This means that patients with HF may be missed or that patients may be misdiagnosed or hospitalized unnecessarily. Each of these consequences has clinical and economic implications. In a study of 592 dyspnoeic patients, clinical uncertainty (a diagnostic certainty estimate between 21% and 79%) for acutely destabilized HF was associated with increased morbidity and mortality. Significantly more patients in the clinical uncertainty group were admitted to hospital (86% vs 71%; P<0.001) and median length of stay in hospital was also longer (6.6 days vs 5.4 days; P=0.02). In addition, in the clinical uncertainty group >90% of patients were discharged within 14 days compared with 9 days in the clinical certainty group [2]. Clinical uncertainty was found to be an independent predictor of death (hazard ratio [HR] 1.88 [95% confidence interval {CI}: 1.02–2.25; P=0.05]) as well as death or hospitalization within one year (HR 2.18 [95% CI: 1.71–2.49; P=0.01]) [2]. Although not evaluated directly in this study, the observed increased hospitalization of patients

in the clinical uncertainty group is highly likely to be associated with increased healthcare spend.

Value of measuring N-terminal prohormone of brain natriuretic peptide

The data in the study by Green and colleagues [2] suggest that reducing diagnostic uncertainty has the potential to improve patient outcomes as well as reducing costs associated with hospitalization. This can be achieved by including other tests to inform diagnosis and not relying on non-specific clinical symptoms, such a dyspnoea, alone.

Echocardiography is the most reliable method for assessing cardiac pathology. However, echocardiographic assessment of all dyspnoeic patients is likely not to be cost-effective, with many patients referred for evaluation showing no evidence of significant heart disease [27,28]. Tests that can accurately and rapidly confirm or rule-out a diagnosis of HF have potential to improve subsequent patient management and

significantly reduce the costs associated with clinical uncertainty. A number of biomarkers have been identified as being associated with HF. Among these, the natriuretic peptides are of proven diagnostic/prognostic value, based on the observation that levels increase following atrial or ventricular dilatation [29].

Brain natriuretic peptide (BNP) is derived from pre-prohormone of brain natriuretic peptde, which is cleaved to remove the 26 amino acid signal protein and then subsequently to produce active BNP and its inactive N-terminal portion, NT-proBNP [29]. Both BNP and NT-proBNP have been shown to be of considerable utility for the clinical evaluation and risk prediction of HF [30]. NT-proBNP, however, does have a number of advantages over BNP, including a substantially longer half-life [30], higher circulating concentrations [30], greater stability [31], lower vulnerability to circadian variation [32] and more flexible sampling [30]. Unlike BNP, the

Table 1	Optimal NT-proBNP cut-points for the diagnosis/exclusion of acute HF among dyspnoeic patients [34]					
Category	Optimal cut-point	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Confirmatory (rule-in) cut-points						
<50 years (n=184)	450 pg/mL	97	93	76	99	94
50–75 years (n=537)	900 pg/mL	90	82	83	88	85
>75 years (n=535)	1,800 pg/mL	85	73	92	55	83
Rule-in overall		90	84	88	66	85
Exclusionary (rule-out) cut-points						
All patients (n=1,256)	300 pg/mL	99	60	77	98	83

available NT-proBNP assays are standardized and show relatively reproducible results [33].

In the first large-scale international analysis of NT-proBNP testing in the evaluation of patients with suspected HF, NT-proBNP was a sensitive and specific indicator of HF [34; Table 1]. Measuring NT-proBNP levels can reduce the uncertainty associated with HF diagnosis based on clinical symptoms alone [2] and thereby ensure appropriate care [35]. In the study described above [2], among the 185 patients in the clinical uncertainty group, 103 (56%) had acutely destabilized HF. In this group, the value of clinical judgement alone, determined by the area under the receiver operating characteristic curve (ROC AUC) was found to be 0.76 compared with 0.88 in the clinical certainty group (P<0.001). In the same population, measurement of NT-proBNP had an overall sensitivity of 90% (95% CI: 81%–94%), 84% specificity (95% CI: 72%–88%) and a positive predictive value of 86% for the diagnosis of acutely destabilised HF [2]. ROC AUC for NT-proBNP was 0.91 and 0.96 in the clinical uncertainty and clinical certainty groups, respectively (Table 2). Combining NT-proBNP with clinical judgement improved diagnostic accuracy in both the clinical certainty (ROC AUC 0.98) and clinical uncertainty groups (ROC AUC 0.94; Table 2) [2].

The IMPROVE CHF (Improved Management of Patients with CHF) trial evaluated the clinical and economic impact of NT-proBNP testing in addition to usual care compared to usual care alone on the management of 500 patients presenting to the emergency department with dyspnoea. This study also demonstrated increased diagnostic accuracy when combining NT-proBNP measurement with clinical judge-ment (ROC AUC of 0.90 [95% CI: 0.90–0.93] vs 0.83 [95% CI: 0.80–0.84]; P=0.00001) [35]. Overall, the median duration of the initial visit to the emergency department was significantly shorter in the NT-proBNP group compared with usual care (6.3 vs 5.6 hours; P=0.0309). There were no significant differences in initial hospitalizations, length of hospital stay, time in intensive care or initial and 60-day mortality. However, a significant reduction in the number of patients readmitted within 60 days was observed (13% vs 20%; P=0.0463). In addition NTpro-BNP-guided therapy resulted in a 15% reduction in total direct medical costs to 60 days follow up ($6,129 vs $5,180; P=0.0232) [35].

The studies above describe how the addition of NT-proBNP testing to clinical judgement based

Table 2	Accuracy of clinical judgement and NT-proBNP-guided judgement in dyspnoeic patients according to clinical certainty of a diagnosis of acutely destabilised HF [2]

Judgement	ROC (95% CI)	
	Clinical certainty (n=407)	Clinical uncertainty (n=185)
Clinical	0.88 (0.83–0.92)	0.76 (0.69–0.83)
NT-proBNP-guided	0.96 (0.94–0.97)[a]	0.91 (0.87–0.96)[a]
Clinical plus NT-proBNP	0.98[b]	0.94[b]

[a] *P<0.001 compared with clinical judgement;*

[b] *P<0.05 for comparison with each of clinical and NT-proBNP-guided judgement alone*

on symptoms and other evaluations improves the accuracy of diagnosis and can reduce direct medical costs. Other studies have demonstrated the value of NT-proBNP measurements in the stratification of patient care, also with the accompanying benefit of reducing associated healthcare costs. The PROMPT study resulted in improved stratification of patient care, with knowledge of elevated NT-proBNP levels resulting in early and more aggressive patient management. More patients with high levels of NT-proBNP (>1,800 pg/mL) were likely to be admitted to a higher level of care if the physician was aware of the NT-proBNP level than if they were not (21.9% vs 12.9%; P=0.037). Patients with a low NT-proBNP level (<150 pg/mL) were less likely to be admitted (4.6% vs 13.8%; P=0.036). There was no difference in admission rates in those patients with intermediate values of NT-proBNP [3]. In addition, compared with low levels, high levels of NT-proBNP were associated with higher rates of hospital admission (odds ratio [OR] 2.9), longer hospital stays (8.5 days vs 3.5 days, P<0.01), higher rates of in-hospital death (3.9% vs 0%, P<0.01), greater likelihood of re-hospitalization within 6 months (OR 5.1, P < 0.001), and greater likelihood of death or re-hospitalization within 6 months (OR 5.7). Overall, NT-proBNP levels were associated with better stratification of patient care and were strongly correlated with subsequent utilization of hospital resources and prognosis [3]. In agreement with these observations, a cost-utility analysis of NT-proBNP-guided therapy in Canada found that NT-proBNP-guided intensive HF patient management, in addition to multidisciplinary care, not only reduced death and hospitalisation but was cost effective compared with multidisciplinary care alone or usual care, without adverse effects on safety [36]. NT-proBNP-guided intensive management cost less per patient compared with usual care and

multidisciplinary care (CAN$55,946 vs $57,729 and $61,500, respectively). Quality-adjusted life-years were also greater (3.20 vs 2.36 and 3.04 for usual care and multidisciplinary care, respectively).

Taken together, these studies clearly demonstrate the considerable value of NT-proBNP testing from both a clinical and health economic perspective.

CLINICAL AND HEALTH ECONOMIC IMPACT OF LABORATORY DIAGNOSTICS IN ALZHEIMER'S DISEASE

According to the World Alzheimer's Report (2010), the global economic burden of dementia - which affects 36 million people around the world - has been estimated at $604 billion [37]. The strongest risk factor for the development of AD is advancing age [8]. Therefore, increasing life expectancy will result in more and more people becoming affected by the disease; the number of people suffering from AD is estimated to reach 65.7 million by 2030 and 115.4 million by 2050 [37]. This same report predicts a rise of 85% in costs associated with dementia by 2030. As the most common cause of dementia, responsible for 60–80% of cases [9], AD is the largest contributor to this clinical and economic burden.

In Europe, annual costs per person with dementia vary widely. Based on Eurocodes estimates for dementia prevalence, a cost model based on published European cost of illness papers determined that the total cost of illness in the European Union in 2008 was €160 billion, which equates to €22,000 per person with dementia per year [38]. This annual burden varied from €4,473 in Eastern Europe to €35,987 in Northern Europe.

In the US, Medicare costs for beneficiaries with AD were $91 billion in 2005 and reached a staggering $160 billion in 2010. While direct medical

costs are substantial, the costs from lost wages of patients and families and the costs for non-nursing home patients is $120 billion annually in the US. In high-income countries, informal care (45%) and formal social care (40%) account for the majority of costs, while the proportionate contribution of direct medical costs (15%) is much lower.

In the US, development of an intervention found to delay onset of AD by 5 years is estimated to result in a 57% reduction in the number of people affected and to almost halve projected annual Medicare costs from ~$630 to ~$340 billion [8]. Currently, however, there are no effective disease-modifying drugs that will prevent the disease, slow its progression or delay its onset [8]. In the absence of such drugs, early symptomatic treatment is the optimal strategy. Studies have shown that a patient's level of function will be preserved for longer if managed earlier and that community-dwelling patients with AD incur less societal cost than those who require long-term institutionalisation [39]. Early intervention, however, requires early diagnosis. As discussed earlier, diagnosis based on clinical signs and symptoms alone is incorrect in a substantial proportion of patients [10–13].

Biomarkers have diagnostic value in AD. Although several have been studied, evidence for three is strongest [8,40]; the 42 amino acid species of amyloid-beta (amyloid β42 [Aβ42]), which is the principal constituent of amyloid plaques, and total Tau (t-Tau) and phosphorylated Tau (p-Tau), which aggregate to form intra-neuronal neurofibrillary tangles and are associated with neuronal degeneration or injury. Both are measured in CSF. Aβ42 has been shown to have an inverse correlation with plaque load at autopsy, and whereas t-Tau and p-Tau are generally highly correlated and typically elevated in individuals with Alzheimer's disease, p-Tau may be more specific for AD as, unlike t-Tau, elevations are not observed in traumatic brain injury,

stroke or Creutzfeldt–Jakob disease [8]. Indeed, low circulating Aβ42 and high levels of Tau have been shown to have diagnostic and prognostic value in AD and are able to predict which individuals with mild cognitive impairment (MCI) and asymptomatic/preclinical AD are likely to progress to AD [8].

The ability to identify individuals whose disease is likely to progress using clinical laboratory assessment of biomarkers is important. Even in the absence of effective disease-modifying therapies, the timely detection of AD can be cost effective because treatments that are available can improve symptoms sufficiently to reduce healthcare costs by keeping patients living in the community for longer [41]. Because few treatments are available, this study modelled the effects of two hypothetical interventions; one modestly effective symptomatic treatment, and another that halted cognitive decline for a short period. Although hypothetical, the study demonstrates that early intervention is necessary for current symptomatic treatments to maximise cost-effectiveness. For disease-modifying drugs, maximal cost-effectiveness is achieved by intervening early enough to anticipate the period of rapid cognitive decline [41]. A diagnostic and economic evaluation of new biomarkers for AD is ongoing, which aims to assess the diagnostic test accuracy of current clinical diagnostic work-up and emerging biomarkers, perform a cost-consequence analysis and assess long-term cost-effectiveness using an economic model [42].

Recently, the use of AD pathology biomarkers has been included in the new consensus research diagnostic criteria for AD, MCI, and preclinical AD, proposed by the National Institute on Aging and the Alzheimer's Association. These new criteria take into account that AD dementia is part of a continuum of clinical and biological phenomena [43–45]. The new International Working Group (IWG) criteria, IWG-2,

recommend the use of either CSF biomarkers or PET imaging for the evaluation of AD patients [46]. In Europe, the Committee for Medicinal Products for Human Use published a number of qualification opinions on the use of biomarkers in the context of AD for enrichment of clinical trials in pre-dementia and mild-to-moderate AD [47]. The use of AD biomarkers for clinical trial enrichment is also supported by the recent FDA draft guidance for treatment of early AD; at this point the role of clinical laboratory diagnostics can be expected to be central in the effective clinical and cost-effective management of patients with AD.

CLINICAL AND HEALTH ECONOMIC IMPACT OF LABORATORY DIAGNOSTICS IN ASTHMA

Asthma is a highly heterogeneous disease. It is a global public health problem and the prevalence is increasing in most countries [48]. According to the Global Asthma Report, as many as 334 million people may be affected and the burden of disability is high [49]. Asthma was once considered a disease of high income societies, but this is no longer the case and rates of asthma are increasing fastest in low to middle income societies [49]. It is responsible for an estimated 1% of the worldwide disability-adjusted life years lost [50] and ranks 22nd worldwide, similar to other chronic diseases, such as diabetes [48]. In Western Europe one in four patients requires either an emergency room or unscheduled urgent care visit, and in North America this figure reached 40% [50]. In the US, patients with asthma exacerbations had significantly higher total healthcare costs compared with those who did not ($9,223 vs $5,011; P<0.0001). Asthma-related costs were also significantly higher ($1,740 vs $847; P<0.0001), and they tend to have co-morbidities such as sinusitis, pneumonia, and mental disorders [51].

In the UK, the NHS spends around £1 billion a year for the treatment of patients with asthma. In the year 2008/2009 up to 1.1 million working days were lost due to lung problems [52,53]. Asthma exacerbations led to over 50,000 hospital admissions with an annual spend of £800 million on pharmaceutical therapy alone [54]. In Germany, the direct and indirect medical costs reached €2.74 billion during 1999. Age-specific hospital costs per admission ranged from €564 (in those <5 years of age) to €2,800 (in those ≥75 years of age) [55]. Moreover, despite the availability of effective preventive therapy, costs associated with asthma appear to be increasing [56].

The heterogeneity of the disease makes it a challenge to manage. Patients present with different clinical, inflammatory and immunological phenotypes, the identification of which is key to providing effective treatment. Traditional diagnostic techniques rely on clinical judgement and pulmonary function tests, despite the limitations of both [57]. Associated exacerbations, defined as the need for courses of high-dose oral corticosteroids or hospitalization, are a major cause of morbidity as a result of an accelerated decline in lung function [58,59] and are associated with high healthcare costs comparable to diabetes and hypertension [59,60]. Approximately 5–14% of the total asthma population have severe asthma [61,62] (Table 3) and this population is associated with disproportionate healthcare use and costs [62,63], both in terms of direct and indirect costs [64,65] (Figure 1). Disease exacerbations, in particular hospitalizations, account for 55% of direct costs in the EU.

It is not possible to predict the risk of exacerbation based on asthma phenotype without the use of biomarkers. However, along with a patient's clinical history, biomarkers may help identify individuals at risk of exacerbations, which may in turn improve patient care and reduce associated healthcare costs. Currently

| Table 3	Severe asthma is associated with disproportionate healthcare use and costs [32]	
Asthma severity	**% Asthma population**	**Mean direct costs* (€)**
Mild	13.7	263
Moderate	33.3	686
Moderate–severe	38.9	1,196
Severe	14.1	2,782

Direct costs of asthma: mean costs of goods and services except hospitalization.

available biomarkers for clinical practice, such as those in bronchial lavage, bronchial biopsies, sputum or fraction of exhaled nitric oxide (FeNO) are limited due to invasiveness or lack of specificity [66], and there is a need for easily interpreted biomarkers that can be exploited in clinical laboratory diagnostic tests to assess the nature and severity of disease.

Serum total IgE and allergen specific IgE are biomarkers to define phenotype in asthmatic patients [67]. Serum periostin, a systemic marker of T2-derived asthma, is upregulated by IL-13 and may be the marker with a highest accuracy for identifying eosinophilic airway inflammation in asthma [68–70]. Lebrikizumab, a monoclonal antibody to IL-13, has been shown to have a more pronounced anti-asthmatic effect in patients with elevated periostin [7]. Thus, diagnostic tests for periostin have the potential to identify a subgroup of asthma patients who will benefit from treatment with lebrikizumab. IL-5 has also been proposed as a potential therapeutic target in eosinophilic asthma. FeNO may

Figure 1	Asthma-related direct (drug; physician visits; emergency department/hospitalization) and indirect annual costs per patient by severity of asthma
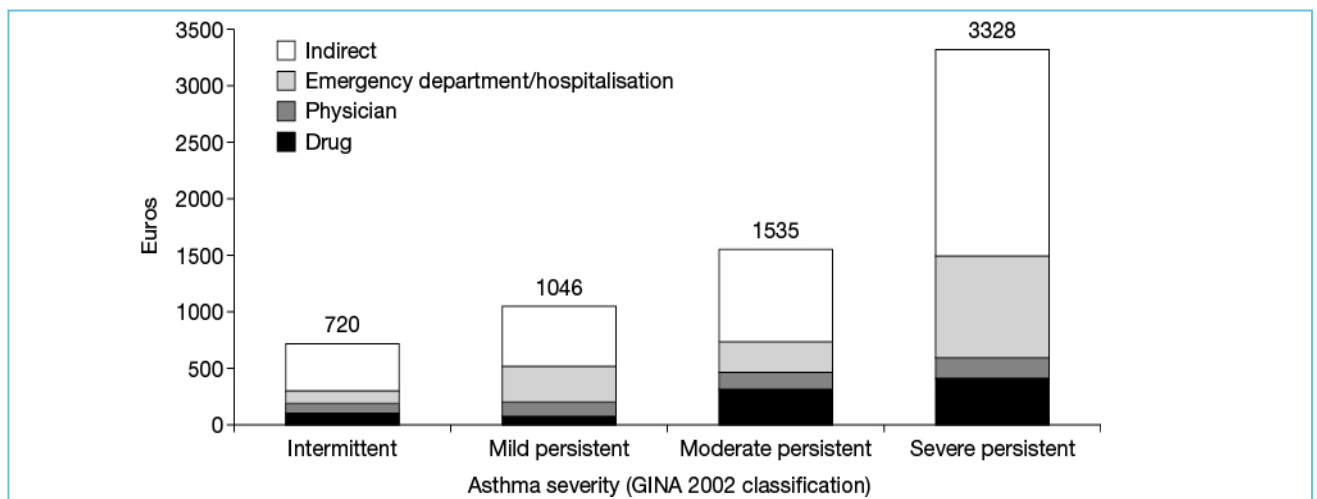
Reproduced by permission of the European Respiratory Society: Eur Respir J May 2004; 23: 723–29; doi:10.1183/09031936.04.00004904.

help predict exacerbations and may identify patients most likely to respond to inhaled corticosteroids [71], although results are conflicting.

Treatment directed by serial sputum eosinophil count measurements has been shown to prevent exacerbations in patients with severe asthma, resulting in fewer hospital admissions [72]. In this study, compared with treatment based on symptoms and spirometry, sputum count-directed corticosteroid therapy resulted in fewer exacerbations (47 vs 79; P=0.04), a longer period until first exacerbation (607 days vs 394 days) and fewer exacerbations requiring prednisolone (78% occurred in the symptoms and spirometry group). Since exacerbations are responsible for a substantial proportion of asthma-related costs, these observations may be expected to reduce healthcare expenditure.

As well as identifying those most likely to respond to certain therapies, eosinophil counts can similarly be used to identify patients likely to have a poor response to corticosteroids [73]. Identifying subpopulations of patients with improved clinical response to specific drugs allows targeted therapy and is likely to reduce costs. Individualized management plans have been shown to improve asthma control and reduce hospitalization (relative risk [RR] 0.64 [95% CI: 0.50–0.82]) and emergency room attendance (RR 0.82 [95% CI: 0.73–0.94]) as a result of exacerbations [74] as well as reducing the number of days off work (RR 0.79 [95% CI: 0.67–0.93]).

Clinical laboratory diagnostics clearly have a central role to play in the appropriate, cost-effective management of patients with asthma. The heterogeneity of the asthma phenotype requires clinical laboratory diagnostic tests for a biomarker panel to improve disease diagnosis [67].

DISCUSSION

The literature reviewed in this paper is not exhaustive. However, in the three therapeutic areas discussed there appear to be clear clinical and/or economic benefits to guided therapy facilitated by accurate clinical laboratory diagnostics. NT-proBNP-guided therapy has the potential to triage patients to the appropriate level of care [3], and to reduce costs associated with hospitalization [2,35]. Earlier intervention with symptomatic treatments in AD based on diagnosis with $A\beta42$ and Tau has the potential to reduce associated costs by keeping patients functioning in the community for longer [41]. When disease modifying drugs do become available, they have the potential for substantially reducing the financial impact of AD [8,41]. In asthma, emerging biomarkers, such as periostin, have the potential to dissect the heterogeneous asthma population and to direct care to those most likely to respond to therapy [7]. However, these apparent benefits of individualized healthcare need to be balanced against costs associated with this approach. These include additional costs associated with the true and false positive patients, the costs associated with expanding patient populations through screening and prevention, which will need potentially costly therapeutic intervention, and increased spending on diagnostics [18].

Diagnosis is a vital part of medical innovation and novel diagnostic tools enable the identification of patients with a specific pathophysiological cause within a group of patients with similar symptoms. This, in turn, fosters better understanding of the disease and perpetuates the cycle of medical innovation; provision of innovative and reliable/reproducible diagnostic tools to physicians is crucial for reliable outcomes in this process.

The clinical laboratory is thus central to the provision of effective patient care, identifying

disease, guiding treatment, and monitoring response. The skills within clinical diagnostic laboratories must be used to further refine diagnostic processes and realize the promise to identify patients more or less likely to respond to a particular therapy and to ensure appropriate, targeted therapy for all. This in turn should help to control healthcare costs associated with an expanding ageing population. To achieve this, manufacturers will need to focus on developing diagnostic tests that better predict clinical outcomes and deliver savings in healthcare costs and improve patient management. They will also need to collaborate more systematically to demonstrate the significant contribution of diagnostics to improving delivery of healthcare to patients.

The relative spend on diagnostics compared with pharmaceuticals underlines the fact that currently diagnostic tests are in general underappreciated in relation to the medical and economic value that they deliver. Unlike the 'value-based' reimbursement of innovative pharmaceuticals, in many markets *in vitro* diagnostics have been treated as low-margin commodities with low reimbursement rates that are based solely on the method of testing and not according to value brought to the patient [75]. In addition, in most healthcare systems, codings are non-specific, covering procedures, rather than technologies or brands, and new tests are linked to existing Diagnosis-Related Group codes [75].

The ultimate goal of diagnostic testing is to guide disease management in order to improve patient outcomes and patient well-being. Clinical laboratory diagnostics should be viewed as a pivotal part of the healthcare system and valued accordingly. The skills available in clinical laboratories around the world should be harnessed to ensure the continued development of accurate tests that inform the healthcare community with respect to the pathophysiology of

disease and facilitate the diagnosis, appropriate treatment and monitoring of patients. Laboratory medicine will need to form alliances with clinicians, healthcare managers and insurers, as well as the general public, and gain these stakeholders as advocates for valuing laboratory medicine according to the information it delivers to facilitate optimum clinical care.

REFERENCES

1. European IVD Market Statistics Report. Available at: http://www.edma-ivd.eu/index.php?mact=EuropeanIVDMarketStatistics,me8bc7,view,1&me8bc7details=26&me8bc7returnid=104&page=104. [Accessed November 2014].

2. Green SM, Martinez-Rumayor A, Gregory SA, Baggish AL, O'Donoghue ML, Green JA, et al. Uncertainty, diagnostic accuracy, and outcomes in emergency department patients presenting with dyspnea. Arch Intern Med 2008; 168: 741–8.

3. Luchner A, Möckel M, Spanuth E, Möcks J, Peetz D, Baum H, et al. N-terminal pro brain natriuretic peptide in the management of patients in the medical emergency department (PROMPT): correlation with disease severity, utilization of hospital resources, and prognosis in a large, prospective, randomized multicentre trial. Eur J Heart Fail 2012; 14: 259–67.

4. Lindholm J. Diabetes insipidus: historical aspects. Pituitary 2004; 7: 33–8.

5. Lakhtakia R. The history of diabetes mellitus. Sultan Qaboos Univ Med J 2013; 13: 368–70.

6. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, Fahy JV. Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. Am J Respir Crit Care Med 2012; 185: 612–9.

7. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. N Engl J Med 2011; 365: 1088–98.

8. Fagan AM. CSF Biomarkers of Alzheimer's disease: Impact on disease concept, diagnosis, and clinical trial design. Adv Geriatr 2014; Article ID 302712: doi:10.1155/2014/302712.

9. Alzheimer's Association. 2013 Alzheimer's disease facts and figures. Alzheimers Dement 2013; 9: 208–45.

10. Gaugler JE, Ascher-Svanum H, Roth DL, Fafowora T, Siderowf A, Beach TG. Characteristics of patients misdiagnosed with Alzheimer's disease and their medication

use: an analysis of the NACC-UDS database. BMC Geriatr 2013; 13: 137.

11. Doraiswamy PM, Sperling RA, Coleman RE, Johnson KA, Reiman EM, Davis MD, et al. (AV45-A11 Study Group). Amyloid-β assessed by florbetapir F 18 PET and 18-month cognitive decline: a multicenter study. Neurology 2012; 79: 1636–44.

12. Devanand DP, Mikhno A, Pelton GH, Cuasay K, Prad-haban G, Dileep Kumar JS, et al. Pittsburgh compound B (11C-PIB) and fluorodeoxyglucose (18 F-FDG) PET in patients with Alzheimer disease, mild cognitive impairment, and healthy controls. J Geriatr Psychiatry Neurol 2010; 23: 185–98.

13. Nelissen N, Van Laere K, Thurfjell L, Owenius R, Vandenbulcke M, Koole M, et al. Phase 1 study of the Pittsburgh compound B derivative 18F-flutemetamol in healthy volunteers and patients with probable Alzheimer disease. J Nucl Med 2009; 50: 1251–9.

14. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. Alzheimer's Disease Cooperative Study Steering Committee; Solanezumab Study Group. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 2014; 370: 311–21.

15. Dean R, Shaw LM, Waligorska TW, Korecka M, Figur-ski M, Trojanowski JQ, et al. Inclusion of patients with Alzheimer's disease pathology in solanezumab expedition 3 using florbetapir PET imaging or inno-bia AlzBio3 CSF aβ1-42. Alzheimers Dement 2014; 10: 811.

16. Meltzer MI. Introduction to health economics for physicians. Lancet 2001; 358(9286): 993–8.

17. National Institute of Clinical Excellence. Guidance for Manufacturers and Sponsors. London: NICE, 2001. Available at: http://www.gserve.nice.org.uk/niceMedia/pdf/technicalguidanceformanufacturersandsponsors.pdf.[Accessed December 2014].

18. Faulkner E, Annemans L, Garrison L, Helfand M, Holtorf A-P, Hornberger J, et al, for Personalized Medicine Development and Reimbursement Working Group. Challenges in the development and reimbursement of personalized medicine—payer and manufacturer perspectives and implications for health economics and outcomes research: A report of the ISPOR Personalized Medicine Special Interest Group. Value Health 2012; 15: 1162–71.

19. Wang G, Zhang Z, Ayala C, Wall HK, Fang J. Costs of heart failure-related hospitalizations in patients aged 18 to 64 years. Am J Manag Care 2010; 16: 769–76.

20. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998–2008. JAMA 2011; 306: 1669–78.

21. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al, Study Group on Diagnosis of the

Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003; 24: 442–63.

22. Organisation for Economic Co-operation and Development (OECD). Average length of stay in hospitals. In: Health at a glance 2011: OECD indicators. OECD, 2011. pp88–89.

23. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med 2009; 360: 1418–28.

24. British Heart Foundation Health Promotion Research Group. Coronary heart disease statistics: 2012 edition, London: British Heart Foundation, 2012. p.81. Available at: https://www.bhf.org.uk/publications/statistics/coronary-heart-disease-statistics-2012. [Accessed December 2014].

25. National Institute for Health and Care Excellence. NICE Guideline CG108 Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. London: NICE, 2010. Available at: http://www.nice.org.uk/guidance/cg108. [Accessed December 2014].

26. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al.. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 2011; 123: 933–44.

27. Hobbs FD, Jones MI, Allan TF, Wilson S, Tobias R. European survey of primary care physician perceptions on heart failure diagnosis and management (Euro-HF). Eur Heart J 2000; 21: 1877–87.

28. Khunti K. Systematic review of open access echocardiography for primary care. Eur J Heart Fail 2004; 6: 79–83.

29. Januzzi JL Jr. Natriuretic peptides as biomarkers in heart failure. J Investig Med 2013; 61: 950–5.

30. Steiner J, Guglin M. BNP or NTproBNP? A clinician's perspective. Int J Cardiol 2008; 129: 5–14.

31. Yeo KT, Wu AH, Apple FS, Kroll MH, Christenson RH, Lewandrowski KB, et al. Multicenter evaluation of the Roche NT-proBNP assay and comparison to the Biosite Triage BNP assay. Clin Chim Acta 2003; 338: 107–15.

32. Bruins S, Fokkema MR, Römer JW, Dejongste MJ, van der Dijs FP, van den Ouweland JM, Muskiet FA. High intraindividual variation of B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with stable chronic heart failure. Clin Chem 2004; 50: 2052–8.

33. Clerico A, Zaninotto M, Prontera C, Giovannini S, Ndreu R, Franzini M, et al. (Study Group on Cardiovascular Risk Biomarkers of the Italian Society of Clinical Biochemistry). State of the art of BNP and NT-proBNP im-

munoassays: the CardioOrmoCheck study. Clin Chim Acta 2012; 414: 112–9.

34. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006; 27: 330–7.

35. Moe GW, Howlett J, Januzzi JL, Zowall H. (Canadian Multicenter Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF) Study Investigators). N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation 2007; 115: 3103–10.

36. Moertl D, Steiner S, Coyle D, Berger R. Cost-utility analysis of nt-proBNP-guided multidisciplinary care in chronic heart failure. Int J Technol Assess Health Care 2013; 29: 3–11.

37. Alzheimer's Disease International. World Alzheimer Report 2010. Available at: http://www.alz.co.uk/research/files/WorldAlzheimerReport2010.pdf. [Accessed December 2014].

38. Wimo A, Jönsson L, Gustavsson A, McDaid D, Ersek K, Georges J, et al. The economic impact of dementia in Europe in 2008 - cost estimates from the Eurocode project. Int J Geriatr Psychiatry 2011; 26: 825–32.

39. Leifer BP. Early diagnosis of Alzheimer's disease: clinical and economic benefits. J Am Geriatr Soc 2003;51:S281–8.

40. Humpel C. Identifying and validating biomarkers for Alzheimer's disease. Trends Biotechnol 2011; 29: 26–32.

41. Barnett JH, Lewis L, Blackwell AD, Taylor M. Early intervention in Alzheimer's disease: a health economic study of the effects of diagnostic timing. BMC Neurol 2014; 14: 101.

42. Handels RL, Aalten P, Wolfs CA, OldeRikkert M, Scheltens P, Visser PJ, et al. Diagnostic and economic evaluation of new biomarkers for Alzheimer's disease: the research protocol of a prospective cohort study. BMC Neurol 2012; 12: 72.

43. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging - Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 263–9.

44. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al.The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging - Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 270–9.

45. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 280–92.

46. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014; 13: 614–29.

47. Isaac M, Vamvakas S, Abadie E, Jonsson B, Gispen C, Pani L. Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: cerebro-spinal-fluid related biomarkers for drugs affecting amyloid burden--regulatory considerations by European Medicines Agency focusing in improving benefit/risk in regulatory trials. Eur Neuropsychopharmacol 2011; 21: 781–8.

48. Bousquet J, Khaltaev NG. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. World Health Organization, Geneva, 2007. Available at: http://www.who.int/gard/publications/GARD%20Book%202007.pdf. [Accessed November 2014].

49. Global Asthma Network. Global Asthma Report 2014. Available at: http://www.globalasthmareport.org/ [Accessed December 2014].

50. Global Initiative for Asthma. Global Burden of Asthma, 2004. Available at: http://www.ginasthma.org/documents/8. [Accessed December 2014].

51. Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol 2012; 129: 1229–35.

52. Asthma UK. Asthma facts and FAQs. Available at: http://www.asthma.org.uk/asthma-facts-and-statistics [Accessed December 2014].

53. National Health Service. An Outcomes Strategy for COPD and Asthma: NHS Companion Document. Department of Health, 2012. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216531/dh_134001.pdf. [Accessed December 2014]

54. National Health Service. 2013/14 standard contract for respiratory:severe asthma (adult) Available at: http://www.england.nhs.uk/wp-content/uploads/2013/06/a14-respiratory-sev-asthma.pdf. [Accessed December 2014]

55. Stock S, Redaelli M, Luengen M, Wendland G, Civello D, Lauterbach KW. Asthma: prevalence and cost of illness. Eur Respir J 2005; 25: 47–53.

56. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM. Economic burden of asthma: a systematic review. BMC Pulm Med 2009; 9: 24.

57. Taylor DR. Biomarkers of inflammation in asthma: a clinical perspective. Semin Respir Crit Care Med 2012; 33: 620–9.

58. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. Eur Resp J 2007; 30: 452–6.

59. Thomson NC, Chaudhuri R. Identification and management of adults with asthma prone to exacerbations: can we do better? BMC Pulm Med 2008; 8: 27.

60. Lane S, Molina J, Plusa T. An international observational prospective study to determine the Cost Of Asthma eXacerbations (COAX). Resp Med 2006; 100: 434–50.

61. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343–73.

62. Braman SS. The global burden of asthma. Chest 2006; 130(1 Suppl): 4S–12S.

63. Godard P, Chanez P, Siraudin L, Nicoloyannis N, Duru G. Costs of asthma are correlated with severity: a 1-yr prospective study. Eur Respir J 2002;19: 61–7.

64. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. Respir Med 2006; 100: 1139–51.

65. Antonicelli L, Bucca C, Neri M, De Benedetto F, Sabbatani P, Bonifazi F, et al. Asthma severity and medical resource utilisation. Eur Respir J 2004; 23: 723–9.

66. Vijverberg SJ, Hilvering B, Raaijmakers JA, Lammers JW, Maitland-van der Zee AH, Koenderman L. Clinical utility of asthma biomarkers: from bench to bedside. Biologics 2013; 7: 199–210.

67. Fatemi F, Sadroddiny E, Gheibi A, Mohammadi Farsani T, Kardar GA. Biomolecular markers in assessment and treatment of asthma. Respirology 2014; 19: 514–23.

68. Jia G, Erickson RW, Choy DF, Mosesova S, Wu LC, Solberg OD, et al. (Bronchoscopic Exploratory Research Study of Biomarkers in Corticosteroid-refractory Asthma (BOBCAT) Study Group.) Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. J Allergy Clin Immunol 2012; 130: 647–54.

69. Nair P, Kraft M. Serum periostin as a marker of T(H)2-dependent eosinophilic airway inflammation. J Allergy Clin Immunol 2012; 130: 655–6.

70. Parulekar AD, Atik MA, Hanania NA. Periostin, a novel biomarker of TH2-driven asthma. Curr Opin Pulm Med 2014; 20: 60–5.

71. Dweik RA, Sorkness RL, Wenzel S, Hammel J, Curran-Everett D, Comhair SA, et al. Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. Am J Respir Crit Care Med 2010; 181: 1033–41.

72. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemière C, Pizzichini E, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. Eur Respir J 2006; 27: 483–94.

73. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids.Thorax 2002; 57: 875–9.

74. Gibson P, Powell H, Coughlan J, Wilson A, Abramson M, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev 2003; 1: CD001117.

75. Fugel HJ, Nuijten M, Postma M. Stratified medicine and reimbursement issues. Front Pharmacol 2012; 3: 181. doi: 10.3389/fphar.2012.00181.