PORTRAIT OF A HEALTH ECONOMIST

ESSAYS BY COLLEAGUES AND FRIENDS OF

BENGT JÖNSSON

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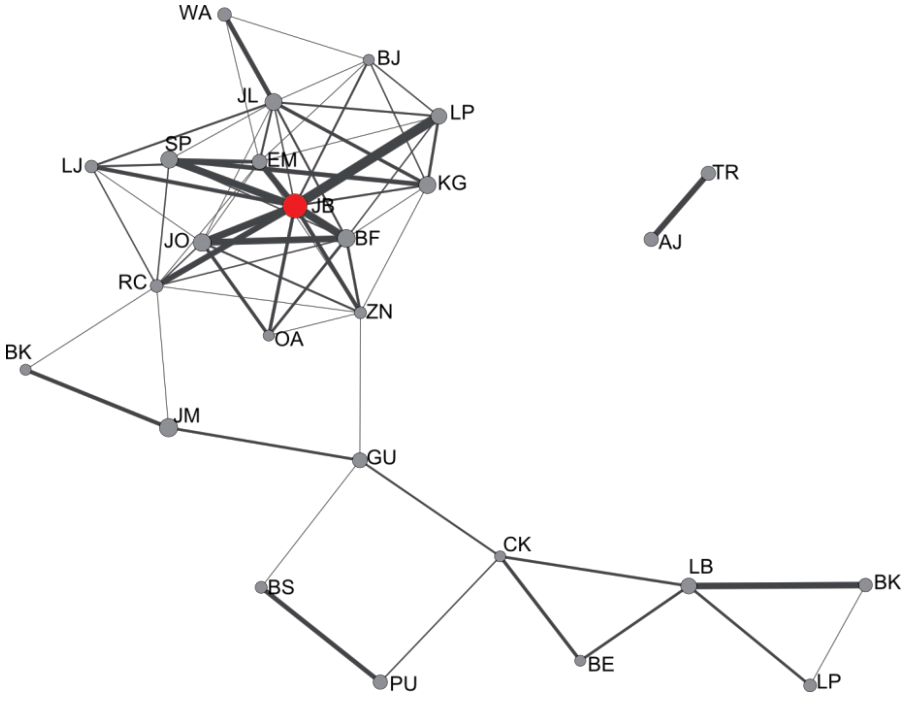
"Festschrift" in honour of Bengt Jönsson, May 2014

Edited by Anthony J Culyer and Gisela Kobelt



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FOREWORD

This book is offered to friends and colleagues of Bengt Jönsson and, indeed, to all with an interest in health economics or more generally in things Swedish, as a token of our affection and esteem for this King of Scandinavian health economics on the occasion of his seventieth birthday.

Bengt lectured at the University of Lund in Southern Sweden from 1969 to 1979 and defended his thesis “Cost-benefit analysis in public health and medical care” in 1976. His analyses and visions have lost nothing of their vitality and relevance almost 40 years since then. In 1979 he founded The Swedish Institute for Health Economics (IHE), and in 1982 became professor of health economics as the University of Linköping, where he founded the Centre for Medical Technology (CMT). Both IHE and CMT are today the focal institutions for health economics in Sweden. In 1991 he moved to the Stockholm School of Economics where he is now Professor emeritus. Emeritus or not, he is as active as ever. Bengt’s list of publications is somewhere around 500 – he doesn’t know the precise number!

The idea for this “Festschrift” was born over dinner in a Stockholm restaurant while Bengt was otherwise occupied, and immediately took flight. The immediate tasks were to: find a publisher and funds, build a list of invitees (we hope we missed nobody who would have liked to have contributed). Later, the tasks were to: chase authors for their manuscripts, edit, format and finally print the collection. All of it, of course, was to be done without Bengt’s knowledge…

We are very grateful to all those who answered positively and who actually produced a contribution. We got very few 'Nos', which attests to the respect and friendship of all for Bengt.

We also found the funding, both for the book and for the health economics conference where it will be launched. Our sincere thanks go to the sponsors (AbbVie Sweden, EFPIA, European Health Economics France, The Swedish Institute for Health Economics Sweden, Lundbeck Denmark and Vifor Pharma Switzerland).

Producing this Festschrift was huge fun – we trust you will find the reading enjoyable as well. Most of all, we hope that Bengt will find it an interesting keepsake of a happy occasion and of a magnificent career.

Tony Culyer and Gisela Kobelt

Stockholm, May 22, 2014

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QALYs AND BEYOND

Martin Buxton

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Bengt Jönsson's career in health economics began, like mine, when the rigorous application of economic evaluation to health care was in its infancy (indeed a mere babe in arms). He in Sweden and I and other pioneers in the UK and elsewhere, were promoting ideas that initially appeared quite alien to many of the clinicians we began to work with. To the policy-makers we wished to influence they perhaps seemed less alien, but their application involved an ambitious, indeed some would have said 'heroic,' step towards achieving a much more rational basis for allocating health resources. It was indeed a brave new world where the costs of health care needed to be judged against the outcomes they produced. We were arguing that it was no longer justifiable to undertake an intervention:

> 'Not for the good it may do
>
> But that nothing be left undone
>
> On the margin of the impossible.' (T S Eliot 1939)

Instead, difficult lines had to be drawn to ensure that resources were not devoted to interventions for which the outcomes did not justify the costs (and hence did not justify the benefits forgone elsewhere in the health-care system).

The clinicians that we began working with, when focussed on patient outcomes, generally used a variety of different clinical measures, many specific to particular clinical areas. Comparisons between studies even in a single clinical area were difficult and it was nigh on impossible to compare cost-effectiveness of interventions in different clinical specialties. Bengt and colleagues reviewed the

issues of outcome measurement and emphasised the severe limitations of cost-effectiveness using a variety of partial natural units as endpoints (Johannesson, Jönsson and Karlsson 1996). For us, and most other health economists at that time, the concept of the QALY provided both an elegant conceptual solution and an empirical salvation to deal with comparisons of cost-effectiveness. I know that Bengt, like me, holds the late Alan Williams as one of our heroes and mentors (Jönsson 2008). We both admired the way that Alan persistently and unperturbably argued for the QALY, though Bengt took issue with him particularly on the question of whether a societal perspective of costs should be adopted (Johannesson et al 2009).

I don't think anyone really saw the QALY as a perfect concept, not least when we came to attempt to find systematic and reproducible ways of measuring it in empirical studies. It was a pragmatic solution to a problem: it was relatively crude tool but potentially powerful. Conceptually it focussed the health economics world, and the health care community that we hoped to influence, on a measure of outcome that incorporated both survival and morbidity, rather than on narrow clinical outcomes or indeed just on levels of clinical activity. The more decision-makers began to accept and use QALYs, the easier it made our lives as 'jobbing' health economists. In this brave new world the process of care was deemed unimportant: only the end can justify the means as Tony Culyer frequently reminded us (eg, Culyer 1992). It would make an interesting political science thesis, if it has not been done already, to look back and analyse systematically how the QALY concept gained such traction and wide, though not world-wide, acceptance from policy makers. Suffice it here to recognise that there can be no doubt that it has become the most widely used measure of efficacy or effectiveness for economic evaluations, to the point where, being seen as having an acceptable cost per QALY is almost as important to the success of a new pharmaceutical as getting a regulatory license. However, after the development of instruments to measure the utility dimension (notably the important stream of international research that established the EQ-5D as the most widely accepted measure and continues with work on the EQ-5D-5L), the concept of the QALY has really not progressed and has certainly not been superseded. Conceptually it remains almost unchanged from the ideas that Alan Williams presented in his seminal application published in the BMJ (Williams 1988).

But as only a partial and imperfect solution to the problem it addresses, the QALY leaves a number of really important research questions to address. In this Festschrift we need to look forward, as well as backward, and highlight what are some of the important research directions our younger colleagues might usefully pursue. In particular, what lies beyond the current QALY?

Bengt, I think, might still be favourably disposed to encouraging further use of contingent valuation to elicit monetary values for health outcomes from the public and then to use more standard cost-benefit analysis as conceptually and theoretically a superior way to evaluate interventions (Johannesson and Jönsson 1991). Others would promote the move towards measures of happiness as more encompassing and less prescriptive ways of valuing health (Dolan 2011). Whilst not denying the potential value of developments in both such directions, I would argue for a different route to progress economic evaluation in health care – an incremental route that builds on the QALY, but explicitly recognises that we have perhaps encouraged the pendulum to swing too exclusively towards outcomes when in fact the process of care matters as well.

We need to understand much better what values the public wish to see reflected in the way we analyse resource allocation in health care (Buxton and Chambers 2011). It is clear, and perfectly understandable, that both policy makers and the general public value characteristics of the way in which care is delivered and are probably willing to trade such 'process' characteristics against outcomes. If we look at what concerns Ministers of Health, it is as much about how, when and where health care is delivered as about what outcome it produces. A recently published analysis of impact assessments for policies introduced by the UK Department of Health identified eighteen categories of benefit other than QALY gains including choice and access, patient costs and convenience, public trust and confidence, etc (Shah et al 2012). In a short study for NICE on Innovation, Ian Kennedy (2009) emphasised the need for NICE to consider a range of health-related benefits that might include for example the convenience of the mode of drug administration, the location of care, enjoyment of greater dignity etc. Similarly, the main arguments for choosing to buy private medical insurance in the UK do not appear to be about expecting better health outcomes but about process characteristics: choice of consultants and hospitals, combined with speed and convenience of timing, and treatment with greater comfort and privacy. As Bengt and colleagues commented years ago, 'QALYs gained could be problematic for use in treatments that improve the patient's comfort during the treatment process' (Johannesson, Jönsson and Karlsson 1996). Yet, it remains the case, that most of the economic analyses that support NICE's decisions, though not necessarily all the decisions that follow from them, are predicated exclusively on QALY maximisation and take no account of the value of process characteristics.

A common response to this is to recognise that other factors should be taken into account in actual decision-making and to recommend that decision-makers use some form of formal multiple criteria decision analysis (MCDA) which includes not only consideration of QALYs but all other factors that are valued

(Hansen 2012). [Bengt has referred approvingly to Sweden's use of 'soft' QALYs as compared to the 'hard' (rather less flexible and singular focus on) QALYs that he observes in NICE.] But the use of MCDA, in itself, does not solve the problem. A real solution requires that we understand what relative value to place on these other characteristics, such as process, that we value. But at present there is little empirical evidence on such relative values to provide analytical leverage on the systematic incorporation of wider process characteristics of care. Health economists need to embrace process – not to the exclusion of outcomes - but in a way that enables analyses to understand which aspects of process are most highly valued and to reflect the values the public and/or patients place on process characteristics relative to outcomes. If we continue to rely on a singular focus on health outcomes we may be encouraged to pay for drugs that give marginal (but apparently cost-effective) increases in survival for cancer patients, rather than funding hospice care than can ensure that the last months of life can be enjoyed in dignity and with family rather than in the relative social isolation and the indignity that is so often characteristics of acute hospital care. Equally, it may lead us to reject a new drug that does not improve health outcomes but offers significantly greater convenience to patients. More generally and more worryingly, a health-care system that only values outcomes, and is planned and managed focussing on outcomes, may be much less sensitive to what is required and the capital and personnel investments that are needed to deliver a high quality process of care. Pessimistically, one has to consider whether health economics with its almost complete focus on outcomes and its relative denial of the importance of process, may a have contributed in a small way to the lack of attention that has it seems been paid in recent years to the appalling nature of the care sometimes provided by the health system. If the quality of the care process is not valued when we make resource allocation decisions, it should perhaps not surprise us if maintaining that quality of care becomes relegated as a day-to-day managerial priority.

Whether or not health economics' failure to value the process of care delivery means that it should take a share of the blame for such problems, I am convinced that health economists need to develop ways to systematically value and incorporate such process characteristics. Given the wide-spread use and understanding of QALYs it seems to me that it makes sense to use them as the common unit of value and to begin to value such characteristics in terms of their QALY equivalence, and to estimate empirically how many QALYs we should be prepared to sacrifice for a specific improvement in process benefits. At a micro level, this would provide an empirical and integrated way of determining what value should be placed on a new pharmaceutical that offers greater convenience through its mode of administration, and at a macro level it would provide a way of trading the non-outcome benefits from health-care system changes that offer improved access or greater convenience in the way health

care is delivered with the innovative treatments that offer direct QALY benefits. Of course, I am not the first to draw attention to this issue and there are a variety of potential ways it can be addressed. Jack Dowie (1995) suggested that 'we need to recognise that that health services generate outcomes before and during interventions as well as after them' and went on to propose 'the Service-Inclusive Quality Adjusted Life year or SIQALY'. But with a few notable exceptions these ideas have not been well explored and developed for general use and from my perspective, it would be an important step forward if the issue of process values was taken forward by our younger colleagues.

Are these ideas that Bengt would agree with and directions that he too would encourage? I believe so, but he can speak for himself. What I know is that Bengt, like me, takes as much pride in the advances that others, whom he has trained, mentored or influenced, have made and can in the future make to ensure that the application of health economics becomes even more valuable to, and pertinent to the needs of, our health-care systems. It would certainly be very disappointing to us both if health economics rested on past laurels and failed to continue to develop. The problems of resource allocation in health care have certainly not gone away!

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THE IMPORTANCE OF COST EFFECTIVENESS IN PRIORITISING DRUGS

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INTRODUCTION[1]

Thirty-eight years have passed since publication of the first Swedish thesis on economic assessment of health care and social services (Jönsson 1976). Initially, physicians and other decision makers in health care were suspicious and doubtful of health economic analyses. By the mid-1990s, suspicion had gradually turned into a growing interest. In 1997, Bengt Jönsson wrote a review article stating: "But the evidence so far is that formal cost-effectiveness studies have had a limited impact on the outcome of decisions. This is hardly surprising since the methodology and data for such studies have recently been available and efficient use of resources just recently has risen to the top of the health policy agenda" (Jönsson 1997, p 603).

Cost-effectiveness is a key concept in health economics, but only during the last decade has it become generally accepted in making health policy. In practice, both in Sweden and internationally, the strongest role played by health economics has been in the introduction of new pharmaceuticals (Carlsson et al 2006). The role for health economics has limitations. "However, the role for economic evaluations is to inform decision makers about issues related to efficient use of resources. They cannot and should not prescribe decisions; there are other goals and considerations that must be included in an overall assessment" (Jönsson 1997, p 604). We aim to present a brief overview concerning the use of economic analyses to prioritise drugs at various levels of

[1] This is modified version of a longer article: Borgquist L, Carlsson P, Kostnadseffektivitetens betydelse vid prioritering av läkemedel, Läkemedelsboken 2014, Läkemedelsverket.

decision making in Swedish health services and address the relative importance of such analyses amongst the other factors that decision makers consider.

COST-EFFECTIVENESS AND PRIORITISATION DECISIONS

In 1997 the Swedish Parliament included cost-effectiveness as part of the ethical platform that should be used to set priorities at all levels of health care (Socialdepartementet 1996/97). Cost-effective use of limited resources aims to achieve a reasonable relation between costs and health benefits (SBU 2013). For instance, in choosing drugs, this means selecting the option that requires the fewest resources in relation to the intended outcome, or selecting a more expensive option that produces better outcomes when the cost for the added effect is deemed reasonable.

At times, prioritisation decisions are relatively simple, for instance when the price between two equally effective drugs can be compared. At other times, the decision-making situation is more complex and may require further formal investigation via health economic analyses. The methodologies for such analyses have improved and become more uniform, mainly during the past two decades. For instance, to promote methodology that is as uniform as possible, the Dental and Pharmaceutical Benefits Agency (TLV) has published guidelines on how to conduct economic analyses when applying for subsidies (TLV 2003).

In setting priorities for drugs, the cost-effectiveness principle is one of three principles to be considered, the other two are the human dignity principle and the needs-solidarity principle (Socialdepartementet 2001/02, pp. 44-45). The human dignity principle states: “all humans have equal value and equal rights irrespective of their personal characteristics and functions in society” (Socialdepartementet 1996/97, pp. 18-26). Further, the government’s guidelines state: “it is important to establish that talent, social position, income, age, etc should not determine who should receive care, or the quality of care received”. However, it is consistent with the human dignity principle to take into consideration the circumstances that limit the patient benefits of medical interventions in individual patients.

The needs-solidarity principle states: “resources should be distributed according to need” (Socialdepartementet 1996/97, pp. 18-26). According to this principle, more of healthcare’s resources should be distributed to those with the greatest needs, the most severe diseases, and the poorest quality of life. Cost-effectiveness must be balanced against need, i.e. cost-effectiveness that encompasses patient benefits must be balanced against the severity level of the condition and other relevant aspects. Although the ethical platform for setting priorities applies to decisions at all levels, the priorities for drug-related decisions

are influenced by many factors that cannot be considered ethical principles, e.g. economic incentives, special interests, professional interests, staff expertise, and patient preferences.

FOUR DECISION LEVELS IN SETTING PRIORITIES FOR DRUGS

How do we perceive the reasoning used in practice by decision makers at different levels (national, regional, organisational, and individual/patient)? Do health economic analyses serve as a foundation? We illustrate this by four decision levels in setting priorities for drugs.

NATIONAL LEVEL - MANY ACTORS COMPETING FOR TERRITORY

Many actors at the national level aim to influence the utilisation of pharmaceuticals. In addition to national agencies such as the National Board of Health and Welfare, the Dental and Pharmaceutical Benefits Agency, and the Medical Products Agency is the Swedish Association of Local Authorities and Regions (SALAR), which has formed a new pharmacotherapy group (NLT) that makes recommendations to county councils concerning drugs used for inpatient care.

The Dental and Pharmaceutical Benefits Agency evaluates and decides which drugs and dental treatments should be included as benefits, i.e. covered by the insurance scheme once the patient pays the out-of-pocket maximum. The pharmaceutical board of the Dental and Pharmaceutical Benefits Agency assesses a drug's cost-effectiveness when making decisions regarding subsidies for pharmaceuticals or consumable items. Many decisions concern drugs that have similar effects to other drugs already included as benefits. In such cases, the prices or total costs of the respective treatments are compared. The health economic analysis then becomes relatively simple. In other cases, when the health benefits are minor and the added costs high, the question of cost-effectiveness comes to a head, particularly when the treatment targets patients with a severe disease. Then the board also considers the human dignity principle and needs-solidarity principle.

The cost-effectiveness of drugs varies across subgroups of patients. The decision may also address limitations. For instance, when introducing new pharmaceuticals to treat hypertension, a drug might be subsidised only for those patients who have already tried other specified drugs. Companies are responsible for providing the information used as basis for the decision. In turn, the staff of the Dental and Pharmaceutical Benefits Agency reviews the information before the board makes a decision regarding subsidisation. Prior to the decision, the companies have the opportunity to present oral or written testimony directly to the pharmaceutical board. The applicant corporation can

appeal decisions to the courts, which they often do. This is an important part of creating a legitimate priority setting process.

REGIONAL/COUNTY COUNCIL LEVEL - INCREASED CONTROL OF DRUGS THROUGH ECONOMIC INCENTIVES

The county councils attempt, in various ways, to promote cost-effective use of drugs through the organisation of local drug committees. Experts are linked to the local drug committees with the intent to work jointly towards medically appropriate, effective, safe, and economic use of drugs within inpatient and outpatient care, dental care and community health services. The most important tasks of the local drug committees are to develop a basic list of recommended drugs, act as medical experts for drug procurement, monitor prescription patterns and to educate.

The basic list of recommendations, which is usually revised annually, is based on scientific documentation addressing outcomes, safety, standard practice, and the cost-effectiveness of the drugs. According to the local drug committees in several county councils, when assessments reveal several medically equivalent alternatives, the cost aspect should be the deciding factor. The lists are dominated by fundamental drugs, i.e. drugs used to treat the most common diseases in primary care and consequently include many patients. Regardless of whether treatment starts in primary care or in hospital, these recommendations should be followed. All county councils use lists of recommendations and producer-independent information in their management approach.

Sometimes the local drug committee has been used to establish requirements for clinical monitoring of pharmaceuticals. A regional management and information system generates economic monitoring data, and the clinics' financial staff provides support. Drug costs per patient listed, by primary care centre, are used to measure cost-effective drug utilisation.

ORGANISATIONAL LEVEL - CONFLICT BETWEEN INTERESTS AND CONTROL SIGNALS IN DECISIONS ON DRUGS

When prioritising, decision makers are influenced by numerous research results and recommendations from agencies, professional organisations, and not least the companies marketing pharmaceuticals. Such recommendations can be based on considerations about cost-effectiveness. At the organisational level, the focus is more on cost control, which can conflict with cost-effectiveness when making decisions.

Most county councils have decentralised budget responsibilities for drugs, i.e. each clinic or primary care unit has its own pharmaceutical budget although the

designs can vary. The intent is for the organisation to adhere to the list of drugs recommended by the county council. Changes in practice can occur quickly, not least within hospital specialities, which means that new drugs not on the list can start to be widely prescribed before those responsible for the budget can react or adjust the budget. When the price of these new drugs is high, it creates an imbalance in the economy of the local healthcare units.

The Östergötland County Council was a pioneer in placing the pharmaceutical budget with the individual primary care centres and connecting the reimbursement system to the monitoring of established goals. Hence, individual prescribers and the primary care centres could directly see the economic effects of compliance towards the goals. Those that operated within the pharmaceutical budget could use any surplus for other purposes, e.g. expand the staff.

When responsibility for drug costs is decentralised downward in the organisation, the prescribing unit can manage the surplus/shortage within their budget framework. They have no direct incentive to consider the costs that fall outside of their own budget. Decentralisation increases self-determination and opportunities for redistribution but can also contribute towards a risk for tunnel vision and sub-optimisation.

CONSULTATION – FACTORS OTHER THAN COST-EFFECTIVENESS HAVE MAJOR IMPORTANCE

Many factors need to be considered in prescribing drugs for an individual patient. Factors of importance include the effects and side effects of the drugs, the patient's comorbidities, interactions between drugs, and the development of drug resistance, e.g. in prescribing antibiotics. During a consultation, treatment options other than drugs, e.g. lifestyle changes involving diet, exercise and changing habits, are often considered in combination with and without pharmacotherapy.

When consulting with a patient, the individual physician seldom focuses on the price of a particular drug or the cost of a treatment regimen. As a rule, the physician's price consciousness is guided by policy decisions and the pharmacy dispensing the cheapest equivalent agent. Many primary care centres use the physician's computerised medical record system to mark the drugs on the pharmaceutical list and the ones found to be most cost-effective. Although patients may not be aware of prices, they are often aware of the out-of-pocket maximum and the coverage period. Some healthcare units regularly review the prescription patterns of individual physicians.

Few systematic studies have examined physician prescriptions with regard to cost-effectiveness. A Norwegian study, however, reveals some interesting

findings concerning cost consciousness (Carlsen et al 2012). In this study, Norwegian physicians were allowed to prioritise several factors in choosing drugs. Even when physicians chose the drug with the best effects, irrespective of cost, the patient's preference also played a major role in the physician's medical decision. These findings are confirmed in other studies (Erntoft et al 2010; Arvidsson et al 2012).

THE ROLE OF HEALTH ECONOMICS IN PRIORITISING DRUGS

HOW FAR HAVE WE COME?

The rules, established by law, for using a health economic approach at the national level are most apparent in the Dental and Pharmaceutical Benefits Agency. Although cost consciousness has increased substantially in health services since year 2000, not least regarding the use of pharmaceuticals, no one can claim that cost-effectiveness thinking permeates health services (with the exception of simple price comparisons of similar agents). It is our impression that formal health economic assessments are systematically used only to a minor extent at levels other than the national level.

In the past 5 to 10 years, several studies have focused on local and regional medical decision makers and their use of health economic decision criteria (Erntoft 2010). These studies have revealed several barriers against using cost-effectiveness criteria at the regional and local levels, compared to the national level. For instance, one study found a sceptical attitude by the medical profession towards economic terminology and that resistance to changing routines created substantial barriers against the use of health economic information in decision making (Duthie et al 1999). Another study has shown that personal consequences, e.g. receiving bad press or acquiring enemies and opponents, which can cause decision makers to limit access to health care (Jan 2003). Moreover, short-term budget goals, the use of simple rules of thumb, e.g. price comparisons (Chen et al 2007), and the fear of disturbing the patient-physician relationship (Jansson and Anell 2006) can be important reasons why health economic assessments are not used more often in supporting decision making at the individual level.

A study from the priority setting initiative at the National Board of Health and Welfare suggests that the medical profession is paying greater attention to cost-effectiveness (Eckard 2011). Nevertheless the degree of severity and the expected benefits of an intervention, combined with the grade of evidence, carry the greatest weight in making decisions on priorities. The information on health economics had limited influence on the decision-making process. One barrier was that adequate health economic evidence was often lacking.

Pharmaceuticals have been the area most studied in terms of health economics; so one would expect greater economic awareness and control in drug decision making – even at decision-making levels beyond the national level. Other technologies, e.g. various types of medical devices or surgical methods, have been studied considerably less than drugs. These technologies seldom have economic control guidelines involving cost effectiveness, even at the national level. An exception would be the national guidelines from the National Board of Health and Welfare, which are being further integrated with the county councils' decision-making processes. Recently the Swedish government tasked the Dental and Pharmaceutical Benefits Agency with assessing the health economics of medical devices on a trial basis.

CONCLUSION

During the last decade cost-effectiveness has become a generally accepted concept in health policy making on national level. The cost-effectiveness principle is one of several considerations that must be included in an overall assessment. However cost-effectiveness has received relatively little attention at the consultant and organisational levels, although its acceptance appears to be increasing. In practice at the consultant level, many other factors often play a greater role when making decisions about drugs, e.g. patient-and profession-related factors. The weight of any indirect influence of cost-effectiveness via various guidelines is difficult to determine. Concurrently, the organisational level including clinics and other units is heavily managed by financial cost control. There is a risk that cost control in the organisation can lead to lower cost-effectiveness, just as the lack of cost control can contribute to ineffective use of resources.

Further progress towards increasing transparency in decision making and producing substantially more health economic assessments at the national level to support the county councils should be pursued. This should be complemented by further advancement of expertise in health economic thinking at the organisational level and amongst individual clinics.

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NEW PUBLIC MANAGEMENT IN THE DANISH HEALTH CARE SYSTEM

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INTRODUCTION

At a meeting of the Nordic Health Economists' Study Group in the late 1980s Professor Jönsson, as the discussant of a paper, commented that "new winds were blowing", implying that new ideas were emerging and being implemented in health policy. New initiatives in the Nordic health care systems at the time – and later - included free choice of GP or hospital, contracting services and some treatments out, decentralisation followed by direct control and responsibility, professional management and the introduction of new management tools, the introduction of diagnosis related groups (DRG) systems for allocating resources and policies to incentivise hospitals to increase production and productivity. Other changes included contracting between regions as third party payers and providers, benchmarking productivity and quality, the use of formal evaluation and balanced score-card tools, the introduction of individual incentives and the application of principal-agent models (Alban and Christiansen 1995; Klausen and Ståhlberg 1998). The new ideas were termed "modernisation" and later became known under the umbrella concept of New Public Management (NPM). The term was coined by Professor Christopher Hood in his seminal article (Hood 1991). NPM focuses on professional management and the use of market mechanisms tools in public sector management, in contrast to the former hierarchical administration and Weberian bureaucracy (Weber 2009). Institutional reforms created separate manageable units to which incentives could be applied and managers could be

held accountable. The market orientation implied that elements from markets, though not a complete market system, were introduced. Being a broad term NPM has different interpretations and has been implemented differently in different countries according to their individual contexts.

NPM emerged in the United States, the United Kingdom and New Zealand in the 1980s. Later, the Nordic countries followed this trend (Malmmose 2012). However, it is debatable precisely when NPM ideas began in the Nordic countries as the concept was not part of any fundamental reform, being introduced gradually. One reason underlying these changes in the UK and the Nordic countries was the wide recognition that the welfare state, as it was conceived after the Second World War, was financially unsustainable. In 1971 and 1974, this problem had already been comprehensively addressed in two Danish government reports on the future long-term economic development (PP I, 1971; PP II, 1974). Their aims have, however, been interpreted in various ways. Some have seen the objective as an attempt to consolidate the welfare state. Pedersen (2011) saw it as a sign of conversion of the welfare state to a "competitive state" which continuously responds to internal and external challenges arising from changing demographic structures and globalisation. This implied that budgeting management and professional leadership would become increasingly important. The content of NPM has changed over time, however. The internal market, as introduced in the UK and New Zealand, was replaced in 1996 with "cooperation". While quantitative objectives were introduced relatively early, quality indicators were later introduced to supplement the then purely quantitative goals (Malmmose 2012).

THE DANISH HEALTH CARE SYSTEM

The Danish health care system is a *Beveridgean* system with tax funding and universal coverage. Until 2007 public hospitals were run by counties, which were also responsible for the services of self-employed health care professionals. In 2007, the fifteen counties were reorganised into five regions, and the number of municipalities was reduced from 272 to 98, thereby creating larger local units. The larger municipalities were given increased responsibilities for health care outside hospitals, such as disease prevention and health promotion. In addition to the public system, a small private hospital sector continued. General practitioners and specialists as well as other health personnel in the private practice sector are contractors whose fees and terms of providing services are negotiated with the counties (Olejaz et al 2012).

Although NPM ideas were introduced gradually in the Danish health care sector, they permeate its organisation and governance principles today. Some key elements are described in what follows.

SUPPLY SIDE INITIATIVES

Since the late 1980s global budgeting has been the main method of allocating budgets to hospitals, which, in turn, allocate budgets to clinical departments. The global budgets replaced highly specified budgets which required politicians to deal with considerable detail. As a part of the decentralisation, some of the larger hospitals created management teams to replace the former hospital administration which had had little management authority. In other hospitals, a director was hired - often a health professional by profession. These new teams comprised a hospital manager, a chief doctor and a chief nurse. Clinical management teams at department levels, consisting of a doctor and a nurse, were also introduced. These changes were intended to increase efficiency in running the hospital and its separate departments.

To control the total spending within public budgets, a formal "budget cooperation" between the government and the counties and municipalities was introduced in 1980. This annual cooperation produced a negotiated agreement on budget limits and gradually evolved higher specification of the goals to be attained with the budget and, in some years, entailed disciplinary consequences in terms of a reduced budget in the following year in case of overspending.

To enhance efficiency further, in 1995 some counties introduced a management-by-contract principle through which negotiated hospital budgets were accompanied by a contract specifying production and quality requirements to be fulfilled in the fiscal year. Priority-setting thus became a political responsibility (Alban and Jeppesen 1995). Later, budget management was reinforced by new tools, such as improved information systems and a balanced score card.

While hospitals were financed through global budgets until 2002, the criteria for their allocation - as recommended by the government - have gradually changed, so that more emphasis is now placed on performance measurement. Thus, an activity-based payment system was introduced incrementally, until a fifty-fifty split between global payment and activity-based payment was attained in 2007. Activity became measured in monetary terms, based on a DRG system. The split balances incentives to increase production against a need to control total budgets though the extent to which the regions have followed these guidelines varies.

In 2002 the government also introduced an additional activity-based national grant to stimulate activity and hence reduce waiting times. The grant amounted to 2-3% of total hospital budgets, and grants were transferred to counties on the basis of additional activity compared to the previous year. Counties had the

authority to transfer these grants to their hospitals with whatever allocation formula they found appropriate.

Economic incentives have also been used to promote a shift from inpatient to ambulatory care to reduce costs and meet patient preferences. Thus, some regions have raised the payment for ambulatory care in their activity based reimbursement schemes, and over the last ten years the DRG system has gradually been changed to include more so-called “grey-zone” tariffs which cover care that can be performed either as in- or outpatient treatment. The tariff is an average of the costs of these two types of treatment and, since ambulatory treatment has the lower costs, hospitals are incentivised to shift to ambulatory care.

Since 2006 the Ministry of Health has regularly published reports comparing productivity across hospitals (Ministeriet for Sundhed og Forebyggelse 2011), thereby creating incentives through benchmarking. Quality indicators, including hospital mortality, have been published since 2007 (Ministeriet for Sundhed og Forebyggelse, 2013).

To encourage municipalities to take up prevention, rehabilitation, and health promotion, differential fees were charged by the regions from the municipalities for private individuals’ use of all types of health care since 2007. In particular, the use of in-patient hospital days had high fees (34% of the DRG tariff with a maximum of 14,337 DKK in year 2014) while GP consultations carried a 10% charge (Bekendtgørelse, 2013).

DEMAND SIDE INITIATIVES

To enhance patient choice and increase hospital accountability, information on expected waiting times is published on a webpage with easy search functions. The information shows maximum expected waiting times in weeks for patients with uncomplicated health problems. Hospital wards are required to report routinely to a central data base which is updated on a monthly basis.

Waiting times had been a key concern to the public for a long time when incentives were introduced to shorten them in the 1990s. To even out waiting times, and to accommodate patients’ preferences, a free choice of public hospital for elective patients has been in place since 1993. The choice was originally limited to hospitals at the same level of specialisation as the one to which the patient was referred, within or outside the patient’s home county or region (Sundhedsloven 2010, chapter 19).

From 1993, elective patients were promised a waiting time of no more than three months from referral to beginning of treatment. By 2002 the target wait had been

reduced to two months and became formulated as a “guarantee” (though not in any judicial sense). By 2007 the “guarantee” had fallen to four weeks, regardless of disease type or severity. Along with the change in 2002, an extended free choice of hospital was introduced whereby the free choice was extended to private hospitals when public hospitals could not perform the treatment within the target, provided that the regions had a contract. Regions are expected to negotiate contracts with private hospitals and clinics (Christiansen and Bech 2013).

Expected waiting times were published on the Internet by the National Board of Health to inform patient and to put pressure on any hospitals with long lists. Since 2013 the waiting time guarantee promises a guarantee of diagnosis within one month from referral, and a flexible waiting time for treatment of either one or two months depending on the severity of the health problem. The argument was that the general guarantee had unnecessarily given a priority to non-severe diseases (Christiansen and Bech 2013).

To increase competition in the health sector, the Liberal-Conservative government coalition in 2002 introduced a preferential tax payment rule for employees with a private employer-paid insurance premium (the employer could still deduct the premium payment as an operating cost when calculating taxable income). Following this the number of individuals taking out private supplementary health insurance increased rapidly. According to some estimates, more than 1 million people had employer-paid health insurance in 2011, when the preferential tax treatment was abolished by a new Social Democratic-Social Liberal-Socialist government coalition. Private insurance could not (and still cannot) be used outside the private sector, as public hospitals are not allowed to receive private payment. As a consequence, the number and turnover of private hospitals and clinics increased substantially until the 2011 change in policy (Christiansen and Bech 2013). Since then, the number and activities of private hospitals has decreased.

DISCUSSION

The introduction of NPM ideas was associated with marked health care reforms in the UK (under the Thatcher regime) and New Zealand (Ashton 1993), whereas in Denmark the ideas were introduced gradually. The initial aim was to increase efficiency and provide more value for tax money through decentralised decision making. The market forces approach has been reinforced by increased insistence on the documentation of processes and the use of outcome indicators to control performance. Objectives and standards have been established and evaluation processes implemented to make decentralised management accountable (Malmmose 2012). The implementation and application of NPM

have in particular been in the hands of public administrators with a background in either economics or political science. That is why critics have given this trend a nickname that derived from the acronym of their union called “DJØF”, hence “djøfisation”. Among the critics are those who lost influence due to the reforms, such as politicians, who claim that their democratic influences has diminished, and professionals, including hospital doctors, with the emergence of professional management. It has also been claimed that users have lost influence in the public sector and that the application of NPM tools has resulted in too many meetings and reports without real influence on the daily running of institutions. Malmmose (2012) has demonstrated that the budget management terminology, with its use of quantitative terms, has permeated the health policy debate, implying that health professionals have conflicts of interest due to their traditional ethical emphasis on the individual patient. In recent years, a certain tendency towards recentralisation has emerged (Martinussen et al. 2009), especially in finance, planning and regulation.

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ARE THERE *REALLY* TEN GOOD ARGUMENTS FOR A SOCIETAL PERSPECTIVE IN THE ECONOMIC EVALUATION OF MEDICAL INNOVATIONS?

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"If economists could manage to get themselves thought of as humble, competent people, on a level with dentists, that would be splendid!"

(Keynes 1932, p.373)

In 1986, Culyer and Jönsson argued thus: "… economists have customarily taken one of two alternative approaches. The first is the Paretian… the… second is the more pragmatic decision-making approach… Clearly, which of these two approaches is adopted by the economist is itself a political judgement – a 'high order judgement about where the political judgements are to come from" (Culyer and Jönsson 1986, pp. 1-2). Bengt Jönsson's important paper (Jönsson 2000) takes explicit sides, arguing that analysts ought to adopt a societal perspective in the economic evaluation of medical innovations, is perhaps the most compact case of its kind (other, longer, versions include the well-known texts by Drummond et al. 2005 and Gold et al. 1996; and Johannesson et al. 2009). In this paper I want briefly to argue, first, that the best argument for adopting a societal perspective is an eleventh argument and, second, that there are three presumptions underlying all eleven arguments that should engender a less confident approach by economists and other engaged in health technology assessments (HTAs), on both pragmatic and political

grounds, to the question of choosing a perspective from which to design and conduct a study.

The ten arguments are these:

- The societal perspective is necessary for making optimal societal decisions
- The societal approach is the classic approach to assessing societal investments and health benefits
- Costs should also be considered from the societal perspective
- The 'payer perspective' leads to suboptimal allocations of resources and cost shifting
- Ignoring consequences such as productivity gains and reduced informal care costs leads to underinvestment in health care resources
- Payer perspectives vary widely and are not unique even within a single jurisdiction
- QALYs should reckon only pure health changes and ought not to include productivity effects
- Changes in political decision makers means that the payer perspective on costs will vary over time and across technologies with consequential arbitrariness in calculated costs per QALY
- The societal perspective enables distributional matters to be investigated, together with their behavioural consequences
- The societal perspective facilitates international comparisons and public understanding.

My proposed eleventh argument is this:

Only if the societal approach is adopted will decision makers be confronted with a full information set of the costs and consequences of alternative actions; anything less comprehensive will necessarily be subject to omitted variable bias, probably of unknown sign and size, causing either over- or under-investment in new technologies (as well as in old ones).

In some ways this is a generalisation of several of Bengt's more specific arguments but is, I suggest, somewhat more persuasive by virtue of *not* relying on precedent as do his two first arguments: that regulatory agencies actually adopt the societal perspective (itself an arguable point) and therefore so ought HTA studies; and that the societal perspective is the 'standard' approach in environmental and transport studies (also an arguable fact). The fact that something has been a common practice in the past is scarcely a powerful warrant for continuing with it on that ground alone.

The three underlying presumptions that cause me concern may be baldly stated:

(1) *To insist upon the societal perspective is to ignore the information costs of HTA*. Conscientiously to search out the most precise estimates of *all conceivable* costs and consequences of a decision, which is what the societal perspective requires, is to presume that the value of the expected improvement in the quality of the decision in question (somehow measured) is always and everywhere greater than the cost of acquiring the additional information that turns a 'narrow' perspective into a societal one. This point, which does not hinge on anyone's preferred measure of 'decision quality', seems so evident that it scarcely needs further elaboration: what economist could conscientiously so disown the marginal balancing of cost and benefit as applied to the practice of HTA itself? Nor does my argument depend on any specific *source of valuation* of the additional information, which may or may not be 'societal' in the sense of being rooted in patient preferences. Either way, however, in turning a 'narrow' perspective into a societal one, it is preposterous to assume that the value of the expected improvement of a decision is always and everywhere greater than the cost of acquiring the additional information that did the turning. But any compromise on the comprehensiveness of the dataset necessarily makes the analysis, to a greater or lesser extent, less than fully 'societal'. I therefore argue that a less than 'societal' approach is the rational approach.

(2) *Economists make better social value judgements than other people.* A perspective for HTA is a statement of the costs and consequences, together with their distribution across people and places,that are to be taken into account. For economists to seize authority to stipulate perspectives is presumptuous in the extreme. Stipulating perspectives is not a task for which economists are equipped by technical training, by their ethical rectitude or by political authority granted through due process. Economists are often quite good at *eliciting* the implicit perspectives and values of decision makers and other stakeholders, which is a useful – indeed highly desirable – early step in any HTA study, but this is not at all the same as *stipulating* them. In eliciting them they may also encourage decision makers to reconsider their own presumptions and even to weigh the case for adopting a 'societal' perspective. But the process is not, or ought not to be, one of *persuading* decision makers to accept the value judgements that happen to be those preferred by the economist (or, indeed any other analyst) unless they have (very unusually) been granted the that authority by a due process.

In any case, what is it that economists *mean* when they speak of a 'societal' perspective? What is generally in their minds is, I think, a specific philosophical view; one that is *consequentialist*, that is based upon *preferences*, and that is *individualistic*: one that as a matter of principle seeks to combine the preferences of all individuals in a 'society' over all the possible consequences of the decision in question in order to make a preference ranking. Merely to state

this is to call it into question as a complete and sufficient basis for public decision making in health policy (or, indeed, any other). I am not arguing against the careful consideration of consequences and of individuals' preferences, but I think they need careful *weighing* (are ill-informed preferences to count the same as well-informed ones? Are selfish preferences to count the same as generous ones? Are preferences about processes to count the same as preferences about outcomes? Are preferences about very minor matters to be dug out as assiduously as those concerning major matters? Is experienced utility to count the same as remembered utility or decision utility? And they may also need *supplementing* as well: we may want (or decision makers may want) to be satisfied that consequences, like the greater social integration of the lonely elderly or arranging for them to have a more supportive community, which are not states of being, like 'health', are also given appropriate consideration. These consequences are *contexts* of being rather than states of being. And the same goes for *transformations* and *changes between states* which can themselves be causes of great good or ill aside from the states to which or from which a person is transitioning (being obliged to quit and re-apply for one's old job, an experience common enough for health service employees in the UK, is hardly a consequence to be ignored, even though the starting state and the final state may be exactly the same in all respects). At the patient level, the same might be true of changes in the location of care or the pathway through which it is delivered; outcome may remain the same but one is unlikely to be indifferent to manner in which the change is managed and adaptation to it assisted (or not).

Ironically, the 'societal' perspective as 'classically' understood may thus be rather less comprehensive than may be considered proper even by economists who urge adopting the 'societal' perspective, let alone those with political accountability for service standards.

(3) *The political and constitutional context of health policy can be ignored*. In virtually all jurisdictions, and for reasons well-rehearsed by health economists over many years, arrangements have been adopted to combat the anti-social consequences of unregulated health care finance and provision: manifest inequity of financial burdens falling disproportionately on those least able to bear them, externalities, publicness, imperfect agency, monopoly, transaction costs of insurance, arbitrary management of moral hazard and adverse selection,... In most jurisdictions, one consequence is the creation of ministries of health with ministers appointed by a due process and accountable, at least in democracies, to a parliament or generally elected assembly of 'society's' representatives. Governments characteristically set budgets across broad categories of economic activity (health, education, the environment, etc.) and also set the rules determining how those budgets are to be spent, the consequences to be taken into account in allocating expenditures, and the processes of

accountability for decisions taken. One conspicuous consequence of these processes is that decision makers in such ministries nearly always adopt a 'narrow' perspective (or, worse, *more than one* such narrow perspective!) and even persist in it despite the 'arguments' of economists. Two questions therefore demand an answer: how does one account for this obtuseness (if that is what it is), and by what moral argument do non-elected, unaccountable, economists set themselves above elected and accountable public officers? An embarrassingly bold answer to this question was given years ago by that great student of Swedish economics, Ralph Turvey: "...the value judgments made by economists are, by and large, better than those made by non-economists." (Turvey 1963, p. 96).

But I ask you: who, apart from a few economists, would allow economists to make such a claim, let alone accord it any degree of credibility? At the end of the day, what's wrong with being pragmatic by risking – but thoughtfully! – some degree of omitted variable bias? And what's wrong with taking one's moral authority from a democratic process, as NICE does, rather than a priori from the somewhat questionable quasi-utilitarian welfarism upon which much of cost-effectiveness still rests? What's wrong with a dash of economic humility?

Herein lies an irony: Bengt Jönsson is among the most modest of men: despite his astonishing achievements as the founding father of Scandinavian health economics he himself never writes or behaves immodestly. But his claims for the societal perspective turn out to be highly immodest claims made on behalf of an entire profession! "Trust me, I'm an economist!" It doesn't ring true, does it? Nor should it.

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WHY HAS SWEDEN BEEN SO PROMINENT IN HEALTH ECONOMICS?

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INTRODUCTION

In January 2005 the Swedish government commissioned the Swedish Council for Working Life and Social Research (FAS) to carry out an analysis of Swedish Health Economics Research. The analysis was to include an inventory as well as an evaluation of research carried out in the area. It was to provide an assessment both of the scientific quality and policy relevance of the research.

I was fortunate enough to chair the evaluation team – a role passed on to me by Professor Alan Williams, my colleague at York. The other members of the team were Grete Botten, Director of Health Management and Health Economics, University of Oslo, Unto Häkkinen, National Centre for Health Economics, National Research and Development Centre for Welfare and Health (STAKES), Finland and Kjeld Møller Pedersen, Institute of Public Health, Health Economics Unit, University of Southern Denmark.

A Swedish reference group advised the evaluation team, consisting of Björn Smedby, Marianne Hanning, Olle Persson and Kerstin Carsjö. The team's report was published in the Scandinavian Journal of Public Health (Drummond *et al.* 2006). Our main finding was that, considering articles published in the top health economics journals (Journal of Health Economics (JHE) and Health Economics (HE)), Sweden ranked 5th in the world, whereas its average position across all scientific fields, is twelfth (see Table 1). Indeed, if one ranked the top 10 countries based on publications per head of population, Sweden would come

second. The citations per paper were also highest for Sweden, indicating that the papers were also highly regarded. Also, if one considered publications in journals in related fields, such as medicine, health services research and health technology assessment, the performance of Swedish health economics would have been even more impressive in terms of total publications and citations.

It was not within the remit of the evaluation team to comment on *why* Swedish health economics had been so prominent, but I explore this issue here.

TABLE 1 PAPERS BY COUNTRY IN JHE AND HE*

	1986 - 2004		**2000 - 2004**		**Mean citations per paper 1986 - 2004**	
Country	*Whole count*	*Fractional count*	*Whole count*	*Fractional count*	*Whole count*	*Fractional count*
USA	647	602	284	256	6.9	6.4
UK	319	270	169	134	5.9	4.7
Canada	93	71	54	36	5.6	3.9
The Netherlands	93	71	48	33	6.2	3.9
Sweden	64	54	28	23	10.5	8.6
Australia	54	38	29	19	2.8	1.7
Spain	46	38	23	20	2.0	1.9
Norway	42	35	21	16	2.9	2.1
Germany	32	23	17	12	5.4	2.2
Switzerland	29	17	18	11	8.3	4.9

**Data provided to the evaluation team by Olle Persson, University of Umeå.*

'Fractional counts' split multi-authored papers between countries if authors originate from more than one country

THE RIGHT ENVIRONMENT

Sweden has always had a well-developed approach to considering resource allocation decisions in health care. It was a pioneer in the field of health technology assessment (HTA), through the establishment of the Swedish Council for HTA (SBU) in 1987, under the leadership of Egon Jonsson and Swedish Planning and Rationalisation Institute (SPRI), the organisation founded by the government and the Federation of County Councils. SPRI published a booklet in 1979 called 'Hälsoekonomi', believed to be the first use of the term in Swedish. This well-developed approach to HTA provided a fertile environment for those who had an interest in health economics, particularly economic evaluation.

In addition, Sweden was one of the countries having an innovative medical school, in Linköping, in the same mould as McMaster in Canada and Maastricht in The Netherlands. A particular feature of these medical schools was to encourage multidisciplinary research, including health economics.

THE RIGHT PEOPLE

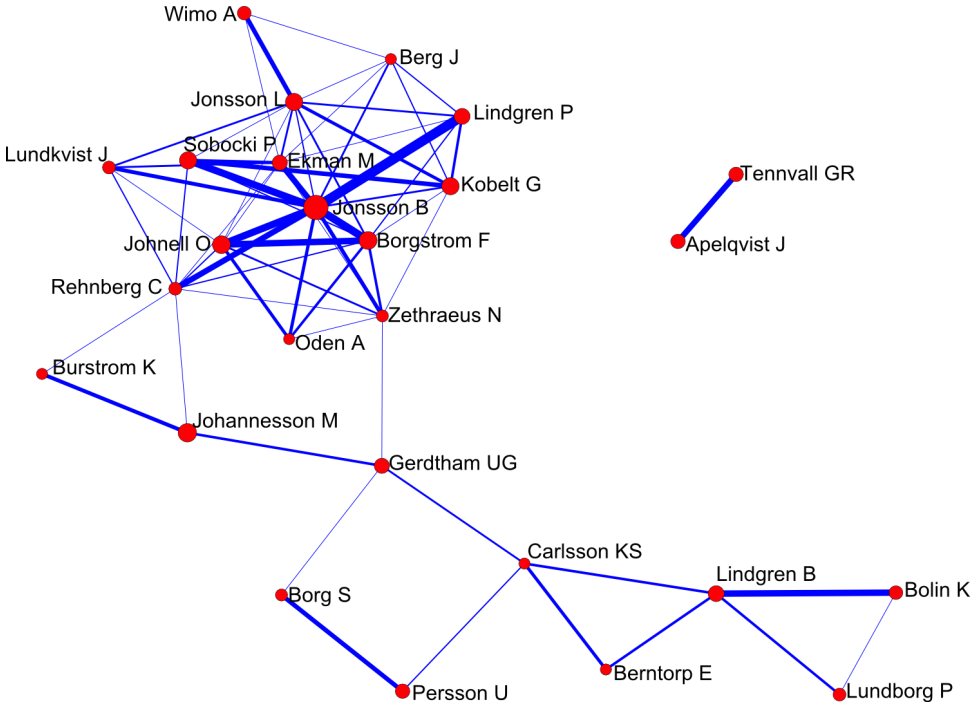
The early leader in Swedish Health Economics was Ingemar Ståhl from the University of Lund, but the person mainly driving Swedish success was Bengt Jönsson. After obtaining his PhD at Lund, Bengt took up a position as the first Swedish Professor of Health Economics in Linköping and later moved to the Stockholm School of Economics. According to an analysis of Swedish publications in health economics from 2000-2013, Bengt topped the list, with 75 publications and 2423 citations (Persson, 2013). Although Bengt's personal achievements speak for themselves, he also contributed greatly by bringing many others into the field, either as research collaborators or PhD students. These connections can be illustrated by bibliographic 'maps' based on co-publications or co-citations. These maps have been generated using the Pajek software, based on the same dataset.

Figure 1 shows the relationships in terms of co-publications. The size of the circles indicates the h-index value for each author, based on the number of publications 2000-2013. (The *h*-index (Hirsch, 2005) is the most widely used citation-based summary measure of scholarly influence, reflecting both the number of publications and the number of times they have been cited. An h-index of 20 means that an author has 20 publications to its name, each of which has been cited at least 20 times but does not have 21 articles with at least 21 citations each.) The width of the lines joining authors reflects the number of co-authorships.

Figure 2 shows the relationships in terms of co-citations. If authors are co-cited in papers of a research field we can assume that they are similar in terms of the type of research they publish. Therefore, a co-citation is mostly a citation relationship created by the citing behaviour of authors other than the co-cited ones. The size of the circles corresponds to the number of first author citations. The wider the lines on the map, the more the co-citations of the two authors joined by the lines. The number of lines has been reduced using a strongest link algorithm.

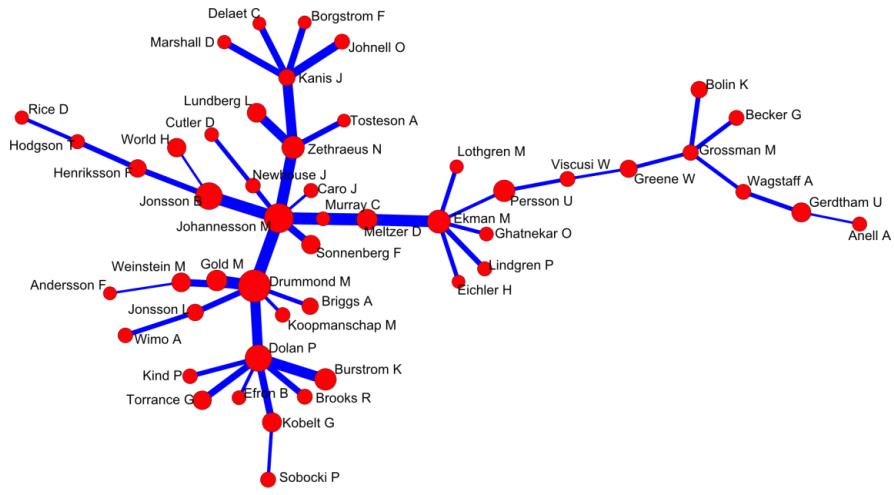
The assessment of citations in the JHE and HE by the evaluation team covered the period 1986 – 2004. During this period, the third and fourth most cited authors were Magnus Johannesson and Ulf Gerdtham, both of them Bengt's PhD students and subsequent collaborators.

FIGURE 1 CO-AUTHORSHIP OF PAPERS WITH SWEDISH AUTHORS



Source: Olle Persson, Umeå University, 2013

FIGURE 2 CO-CITATIONS IN PAPERS INCLUDING SWEDISH AUTHORS



Source: Olle Persson, Umeå University, 2013

THE RIGHT APPROACH

There are several things to admire about the way Swedish health economics has developed. First, there has been a strong emphasis in training in economic theory and principles. The evaluation team reported that 46 PhD students had defended their thesis in Swedish academic institutions between 2000 and 2005. Although no comparative data were available for other countries, the team felt that this was an excellent achievement.

Secondly, the connection between health economics research and health care decision-making has been maintained. At the national level, trained health economists have made important contributions to the work of the Dental and Pharmaceutical Benefits Agency (TLV) and the SBU. In addition, several of the health economics research units located in universities had also made important contributions to the work of County Councils in their locality.

Thirdly, many academically-trained health economists have entered the pharmaceutical industry and continued to publish in the international literature. Indeed, the evaluation team debated whether publications from individuals in the private sector should be included in the Swedish published 'output'. In the end it was decided to restrict the evaluation to the publications by individuals working in publicly-funded institutions.

The link between health economics research and the pharmaceutical industry has been continually reinforced by the existence of the Institute for Health Economics (IHE), founded by Bengt Jönsson in 1979. The IHE has been prominent in health economics research over this period and has produced numerous reports on health economics topics.

CONCLUSION

The rest of the world can learn a lot from the achievements of health economics in Sweden. You do not have to be a big country in order to make a big impact.

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TOWARD AN ECONOMIC THEORY OF ECONOMICS: SOME IMPLICATIONS

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There is a curious gap in economics, a small "hole in the heart" as it were. We have no theory of the discipline of economics itself, of the economic behaviour of economists. This realization first occurred to me during a visit to Bengt Jőnsson in Sweden, many years ago, where he and I discussed it with a few of his colleagues, but I did not follow up on the thought. Now seems a opportune time to re-open the question.

This lacuna is the more curious in that we have economic theories of just about everything else. Economists have been very imperialistic, applying the tools and techniques of economic analysis to virtually all forms of human activity. From their natural homes in commodity, financial and labour markets, industrial organization, the public finances and the like, economists years ago began to move into the "economics of" such fields as education, health and health care, defense, and even love, marriage and the family. Alan Blinder once satirized this casual colonization in a short note "On the Economics of Brushing One's Teeth". (In fact there *are* some interesting economic stories that could be told -- that have not been -- about the profitability of producing and marketing preventive dentistry of doubtful efficacy.)

Bengt and I are among those who have spent their careers studying and writing about the economics of health and health care, which economists first invaded in force during the 1960s. In my judgement this colonization process – which was sometimes strongly resisted by many of the natives, particularly physicians – has produced both significant enlightenment and significant disinformation, and it is a close call as to where the balance lies.

In general, where economists have arrived with "off-the-shelf" intellectual frameworks straight from the textbooks that take no account of local institutions

and circumstances, they have "darkene[d] counsel by words without understanding." But where we have intermarried (intellectually) with the natives, tried to understand what they have to tell us – which is usually quite a lot – and sought to modify and adapt our supposedly universal theories to provide a realistic account of the new territories we have come to occupy, we may sometimes see the opportunity to, like Alfonso X ("the Wise)" give good advice.

That is the spirit in which one might hope to approach a true theory of economics itself. We *are* the natives here, so the project is one of self-discovery, of applying the tools and techniques of economics better to understand ourselves.

Where to start? Well, what do economists do? Several definitions are offered to the beginning student, or were to this one. None seem very helpful. E.g. "Economics is whatever economists do." But what I and my colleagues do in our professional time is this: we transform *impressions* into *expressions*. We work pretty much exclusively with symbols rather than material objects. In the process we use up the scarce resources of our own time, energy and intellectual capital, as well as, of course, various forms of physical capital and human assistance. .

We read, listen, collect and assemble various types of data and process them in more or less formal ways. The processing is carried out within explicit or implicit intellectual frameworks (theories and ideologies). Some of these we are aware of, but not all, and there is a rough but very far from complete consensus among economists as to what constitutes "doing economics" as opposed to, say, amateur sociology. (Interestingly, there is a very good ethnographic study of economists done as satire, by Axel Leijonhufvud, an economist.)

When the impressions are formed, we convert them to expressions in written or spoken form – articles, books, lectures, reports, consultations. The process is more or less interactive. In a well-functioning seminar the interaction of expression is simultaneously generating or modifying impressions. And the process of expression itself can modify impressions – the pen is sometimes wiser than the word.

So if that is what we do all day, why do we do it? What is the objective function that drives this production process? The theory textbooks give a straightforward answer – for the money. We all know the basics of microeconomic theory and can reproduce them in our sleep. (And many do.) We are maximizing our individual utilities, which are functions of our commodity consumption baskets. Shift to an indirect utility function, and utility depends on income and exogenous commodity prices. There may be other arguments in the utility function, but in the textbooks these do not matter at the margin. Nor is this just in the

introductory texts; in advanced theory for graduate students the math becomes more complex but the behavioural story remains the same.

This is rather awkward. If economists are at the margin converting impressions into such expressions as will maximize their incomes (subject to time and energy constraints), then a true economist will say anything s/he is paid to say. A group presenting themselves as an academic discipline are simply a collection of intellectual whores.

Some might argue that there is a degree of empirical support for this. But things are not really that bad. The simple textbook model of income maximization is fundamentally wrong on at least two levels. First, there is a lot more in the individual utility functions (ours and everyone else's) than simply income – professional respect, genuine intellectual curiosity, even beneficence. These other arguments do interact with income to influence expressions. We are not all simply liars for hire. And secondly, the process of utility maximization has a collective dimension that makes it much more interesting and complicated. Why, after all, should anyone believe anything we say, let alone pay or otherwise support us for saying it? Yet clearly at least some people do, because economists are quite well paid for their expressions.

One response might be that in the course of the long and rigorous training that most of us undergo, we have acquired significant human capital that gives us special insight into the behaviour of economic phenomena, enabling us to predict and to some extent measure the likely effects of public or private policies. (But not, alas, the stock market!) Such knowledge is obviously valuable, and to the extent that it is or is perceived to be derivative from the extensive human capital accumulated by economists through their training and work experience, we can earn a quasi-rent on that capital. (A darker view would be that economists vary considerably in the weights that they attach to the various arguments in their utility functions. Some are, indeed, pretty close to liars for hire, or more politely specialized public relations staff for various organizations, either for-profit corporations, professional or trade associations, or "think tanks" with a commercial clientele).

The earning of collective quasi-rent depends on preserving and enhancing the perception that economists *qua* economists know something special and valuable to others. We thus have a collective interest in protecting the brand, so to speak, and in expanding its market.

Protecting the brand, and the quasi-rents it generates, offers possible explanations for several peculiar features of economist behaviour. The imperialistic urge to expand the scope of the "mainstream" intellectual framework of economic theory and to privilege it even in fields where its core

assumptions fit very badly, if at all, is a way of expanding access to additional quasi-rents without incurring the cost of acquiring additional human capital relevant to those fields. One can, of course expand by cooperating with the natives, but interdisciplinary work implies – requires -- recognition of the value of human capital from other disciplines and might require sharing the quasi-rents. It also requires more work.

The effort to create and preserve a privileged position for the economics brand underlies another common collective behaviour, the attempt to portray our discipline as a science. This shows up most vividly in the annual Nobel Prizes in science. It is widely believed, and routinely reported in the press, that there is a Nobel Prize in economics just as in the sciences of Physics, Chemistry, and Medicine. But this is not quite true. The prize in economic sciences (sic), which dates only from 1969, is given not by the Nobel Foundation but by the central bank of Sweden, and is formally the Sveriges Rijksbank Prize in Memory of Alfred Nobel.

The creation of the prize was presumably intended to recognize the status of economics as a real science. Its practitioners' expressions should therefore be accorded the same respect as is given to those or, say, physics. (Economists have long suffered from physics-envy, with good reason.) But on closer examination the history of the award has demonstrated the exact opposite. Economics is not, and cannot be, a true science like those recognized by the original Nobels.

The difference emerges clearly from the 2013 prize in physics, awarded to Francois Englert and Peter Higgs for the discovery of the Higgs boson. Higgs and others proposed the existence of such a particle in 1964, and its importance was immediately recognized. But the prize was not awarded until their proposal was confirmed experimentally, forty-nine years later. There are no prizes for good ideas, or even brilliant ones, unless and until they are confirmed by conclusive observation.

The contrast with economics is stark. For example, the 1997 economics prize went to Myron Scholes and Robert Merton for the derivation of the so-called Black-Scholes equation. This is a quite complex bit of mathematics enabling the rigorous and presumably reliable calculation of prices for future options in markets for financial assets of all kinds. Its developers assembled a hedge fund, Long Term Asset Management, in 1994 to apply and exploit their new tool in the real world. Initially the fund was very successful, being worth several billion dollars at the time the Nobel prize was awarded. But the financial weather turned stormy. Within a year the huge profits were almost all lost and the fund was wound up. The equation, when more rigorously tested, was flawed. The Nobel prize was not, however, returned.

The unscientific basis for the prize had been flagged long before. The 1974 prize was awarded jointly to Gunnar Myrdal and Friedrich von Hayek for their studies of the welfare state. Unfortunately their views and conclusions were diametrically opposed to each other. They were both engaged in essays in persuasion, to borrow Keynes' title, and at least one of them was simply in error.

The award was a political compromise, not a recognition of scientific achievement. Myrdal took the occasion to write an essay arguing (persuasively, in my view) that there should not be a prize in economics.

Now in fact the label of the award, "economic sciences", is a tip-off. It is an example of "persuasive definition", a rhetorical device intended to persuade others that a particular field of intellectual activity deserves the credence given to the sciences. There are a number of other examples.

"Political science" is relatively innocuous, and Christian Science at least produced a quality newspaper. But "creation science" is deliberately deceitful, and "nursing science" is just confused.

This is not to say that there are not works of outstanding scholarship in economics, whether or not rewarded by the Swedish bank prize. Of course there are, and always have been, and some have been appropriately recognized. (Other awards, however, do seem rather banal.) Either way, however, they do not meet the rigorous confirmation test of science.

But do the labels matter? If some economists try to puff themselves up as scientists, and work away on ever more abstruse mathematical models of social behaviour in the hope of looking like real scientists, so what? *Caveat emptor*, after all, and non-economists seem to have little difficulty generating a healthy skepticism about the pronouncements of economists. And if economists themselves, driven by physics-envy or a cargo-cult illusion, spend too much time and intellectual effort generating and analyzing economies that do not exist, never have existed, and never could exist, well where is the harm in what one of my former colleagues called "recreational mathematics". (He was quite good at it.)

Most of the time it probably does not matter. Nonetheless there are, I think, some very real and very large dangers inherent in "scientism" in economics. These have been powerfully demonstrated by the experience of world financial markets over the last generation.

Starting in the late 1960s, a revolution in macro-economics began in the leading graduate schools. The late Keynesian orthodoxy was overturned and eventually replaced with "Ratex", behavioural models built on so-called Rational

Expectations theory. These were more mathematically rigorous than the previous rather fuzzy Keynesian consensus. But the "new thinking" was in fact intellectually retrograde in harking back to an imaginary world of fully informed transactors in self-regulating markets that, if not perfect, necessarily yielded better results than any efforts at public regulation. *Laissez-faire* was back, with more mathematics

As the careers of those who had imbibed the new thinking brought them to the levers of power, financial regulatory structures were dismantled and the rest is history. Like Myron Scholes in 1998, Alan Greenspan by 2008 had "found a flaw" in his theoretical framework. But Scholes and his colleagues lost only their own money. Greenspan was chairing the United States Federal Reserve Board, and the flaw in his theory led into the world-wide financial crisis and recession, with massive and continuing consequences. Bad economics can do enormous damage.

It can also kill. At almost the same time as the Ratex revolution in macroeconomics, economists began moving in force into the fields of health and health care. Bengt and I were part of that colonization effort, and we have laboured in that vineyard for most of our professional careers. But this field was already occupied by well-organized and intellectually powerful natives. The result has been a generation-long "struggle for the soul" of the discipline of health economics.

The core of the contention has been over the appropriate frameworks of understanding for interpreting the behaviour of participants in the health care system, and guiding the formation of public policy in this area. All of the new colonists brought with them the tools and techniques of economics, but some simply applied these models pretty much off-the-shelf. The models were adapted to take account of the risk associated with ill-health and the corresponding presence of insurance, but not much more. A false trail was laid at the outset by a confusion between risk and Knightian uncertainty. But at their heart these models did not get much beyond intermediate price theory, if at all.

Fully informed consumers (not patients) were imagined as transacting in free competitive markets but responding to price signals distorted by (private) insurance. Great attention was and is devoted to estimating elasticities of demand in order to fine-tune hypothetical private insurance contracts and minimize the resulting "welfare burdens".

To other newcomers, however, these efforts represented "the impercipient in pursuit of the irrelevant". In this new country, the economic frameworks must be adapted to take account of not only the incentives faced by patterns, but the asymmetry and inherent incompleteness of information – true uncertainty, not

simply quantifiable risk. Further, it made no sense to assume away the very peculiar institutions in the health care sector, of public and particularly private regulation, as if they either did not exist or had no impact on economic behaviour or outcomes. Nor are those peculiar institutions random accidents or aberrations of social policy. For good or ill, they are rooted in ideologies, some shared and some conflicting. This must also be taken into account in trying to understand and predict behaviour, and propose and evaluate policy. These complexities are very difficult, well actually quite impossible, to capture in the precise mathematical formulae and precise predictions required by a more "scientific" economics. On the other hand, the more precise models, however intellectually satisfying, tend to be precisely wrong.

My sense is that any struggle has now died down, as the contending parties simply do not bother to talk to each other. Those championing the "mainstream" theoretical approach dominate the discipline in the United States (with some outstanding exceptions) while in Canada and northern and western Europe most health economists have to a greater or lesser degree "gone native" (again with exceptions).

But again, does it matter? It is quite obvious that there is a strong, though not perfect, correlation between the methodological predilections of health economists, and the institutions in the countries where they are located. But is it fair to hold American health economists responsible for `the notoriously costly, inefficient and inequitable health care system? It is true that their preferred analytic models tend to provide intellectual support for that system, but surely they were not decisive? (The flies around a dead horse did not kill the horse.) And the flaws in "Obamacare" are surely traceable not so much to American health economists as to the concessions demanded by an overly powerful private insurance industry that can buy economists wholesale – and sometimes does.

But conversely how much credit do health economists in other countries, such as Bengt Jönsson or myself, deserve for helping to understand and improve our own far from perfect but far more humane and efficient health care systems? A question for another time. Skol!

THE HEALTH ECONOMICS OF DIABETES

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INTRODUCTION

Diabetes mellitus comprises a heterogeneous group of disorders characterised by elevated blood glucose levels (National Diabetes Data Group 1995). The disease has probably been known for at least 2000 years (Agardh et al 1994). According to the classification system by WHO (Alberti and Zimmet 1998), the disease is mainly divided into the two primary sub-groups, type 1 diabetes and type 2 diabetes. Type 1 diabetes is an autoimmune inflammatory disease categorised by a destruction of the pancreatic beta-cells, whereafter the patients are entirely reliant on exogenous insulin-replacement therapy. In contrast, type 2 diabetes affects several different metabolic parameters including blood glucose, serum lipids, serum urea, fibrinolytic parameters and insulin secretion as well as insulin sensitivity (Alberti and Zimmet 1998).

International forecasts have suggested that diabetes prevalence may exceed 300 million by the year 2025 (King et al 1998). The increase is mainly attributable to Asia, Africa and North America, but an increase of about 50% in the prevalence is also expected for Europe (Zimmet 2000).

The chronic nature of diabetes, the high prevalence and increasing incidence, the high degree of co-morbidity and excess mortality are all factors that lead to diabetes imposing a major economic burden on society, in terms of use of health care resources and loss of productivity (Pagano et al. 1999). One of the first and groundbreaking cost-of-illness studies in diabetes was a Swedish study performed by Bengt Jönsson using data from 1978 (Jönsson 1983).

COST-OF-ILLNESS STUDIES IN DIABETES

The study by Bengt was a retrospective top-down cost-of-illness study using public registries to collect data. To ease the data collection and avoid double counting of costs, only the main diagnosis was used for the data collection. The study included both direct and indirect costs. The total cost of diabetes according to this study is shown in Table 1.

TABLE 1. THE COST OF DIABETES IN SWEDEN IN 1978 (MSEK AND PER CENT)

Resources	**MSEK**
Direct costs	568 (43%)
hospital care	358
ambulatory care	82
drugs	108
medical devices	20
Indirect costs	749 (57%)
sickness absence	134
early retirement	438
mortality	176
Total costs	1 317

Source: Jönsson 1983

The study showed the importance of taking a societal perspective in the analysis. Loss of production, i.e. costs outside the health care system, dominated. One important approach in the study was also to divide the cost of diabetes into the management/control of diabetes and the cost due to complications of diabetes. It was shown that the cost due to complications accounted for approximately ¾ of the total cost. A replica of this study was performed later with data from 1994 (Henriksson & Jönsson 1998), using exactly the same methodology. Surprisingly, the cost structure was identical between the two studies, including the split between costs due to management/control and the cost due to complications, despite the fact that 16 years had passed between the two studies.

The two studies showed how public databases and registries can be used to calculate the burden of disease. This was an important finding since Sweden always has been famous for having good quality public registries. However, there were several shortcomings in the studies. As outlined in the introduction, type 1 and type 2 diabetes are two very different diseases, and it does not make

sense to put them together. Also using diabetes as main diagnosis misses a lot of cases in which diabetes is a secondary diagnosis. There are resources used that are not present in the public registries, like paramedical services. Furthermore, the registries do not allow for a deeper analysis of how patients are treated, the cost of complications, quality of life and so forth.

To fill these gaps a pan-European multicenter study was started with the aim to increase the knowledge specifically for type 2 diabetes and a focus on the economic aspects (The CODE-2 study: the Cost of Diabetes in Europe - type 2). The study was sponsored by SmithKline Beecham and performed in eight European countries (Sweden, UK, Germany, the Netherlands, Belgium, Italy, Spain and France) in 1998 including more than 7000 patients with type 2 diabetes. The methodology and results for the entire European sample is presented below (taken from Jönsson, 2002).

THE CODE-2 STUDY (TYPE 2 DIABETES)

Methods

The study used a bottom-up, prevalence-based design, which optimised the collection of data at a national level while maintaining maximum international comparability. Effort was made to ensure consistency in terms of data specification, data collection tools and methods, sampling design, and the analysis and reporting of results. The main source of data collection was two questionnaires, one sent to the patients and the other to the responsible physician. The questionnaires captured clinical data, patient characteristics, treatments, diabetes related complications, quality of life and resource utilisation. Resources were valued using unit costs from different public sources. The cost for the sample of patients in each country was extrapolated to the entire diabetes type 2 population in that country using national prevalence figure.

Results

Table 2 shows descriptive statistics of the CODE-2 sample. Total direct medical costs in the eight European countries were estimated at € 29 billion per year (1999 values). The estimated average yearly cost per patient was € 2834 per year. Of these costs, hospitalisations accounted for the greatest proportion (55%, range 30–65%) with a total cost for the eight countries of € 15.9 billion. In contrast, drug costs for managing type 2 diabetes were relatively low, with antidiabetic drugs and insulin accounting for only 7% of the total healthcare costs.

TABLE 2. CODE-2 DEMOGRAPHIC DATA

Country	Study population (patients)	Age (years±SD)	Gender (% M/F)	Mean BMI (kg/m^2±SD)	Mean time since diagnosis (years±SD)
Belgium	735	66.0 ± 11.7	42/58	29.3 ± 6.1	7.6 ± 6.9
France	751	64.0 ± 11. 5	52/48	28.7 ± 4.8	9.1 ± 8.0
Germany	809	67.1 ± 1.6	48/52	28.4 ± 0.1	8.0 ± 0.9
Italy	1263	65.7 ± 9.5	50/50	28.0 ± 4.6	13.0 ± 8.7
Netherlands	909	64.8 ± 11.6	49/51	28.1 ± 5.1	6.4 ± 6.0
Spain	1004	67.4 ± 10.0	44/56	29.6 ± 4.9	10.1 ± 8.1
Sweden	777	67.6 ± 11.6	50/50	28.5 ± 4.8	8.3 ± 7.0
UK	756	63.3 ± 12.0	61/39	30.0 ± 5.8	7.8 ± 7.0
CODE-2	7000	65.9	50	28.7	9.3

This study not only enabled cross-country comparisons but also in-depth analyses of country specific data. This is the most relevant part, since treatment decisions are made locally and the country specific data can be used to support these decisions and improve the care of patients with type 2 diabetes. For illustrative purposes, the main results from the Swedish sub-stud are summarised here (Henriksson et al 2000).

The Swedish sub-study

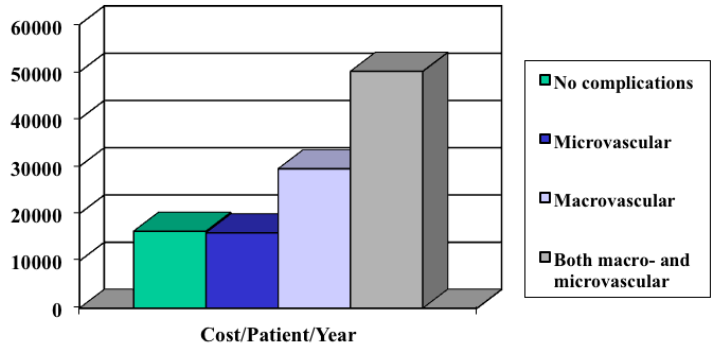
In Sweden, 777 patients were randomly selected from medical records from nine primary care centers in different parts of the country. The total cost for patients in 1998 was approximately SEK 7 billon, or SEK 25,000 (Table 3). Hospitalisation accounted for 42%, ambulatory care for 31% and drugs for 27% of total costs. Interestingly, it was not antidiabetic drugs that were most costly but drugs for treating hypertension and dyslipidemia.

TABLE 3. COST OF TYPE 2 DIABETES IN SWEDEN IN 1998

	Total cost	Hospitalisation	Ambulatory care	Drugs
Type 2 population	6,995 MSEK	2,968 MSEK	2,161 MSEK	1,866 MSEK
Per patient	24,983 SEK	10,599 SEK	7,719 SEK	6,665 SEK

One important aim of the study was to find potential cost drivers in type 2 diabetes. The study confirmed the earlier findings by Bengt (Jönsson 1983) that diabetes-related complications are dominating the cost of the disease as shown below.

FIGURE 1. COST PER PATIENT WITH DIFFERENCE COMPLICATIONS (SEK, 1998)



Patients who have developed both micro- and macrovascular complications have an annual cost of around SEK 50,000, which can be compared to a patient with no complications, who has a cost of SEK 16,000. Hence, the presence of micro- and macrovascular complications increases the cost by more than a factor of three and the explanation for this increase is mainly because complications lead to more hospitalisations, which are costly.

CONCLUSIONS

Cost-of-illness studies are used to calculate the societal burden of diseases. The studies in diabetes, independently of when they were performed and which methodology was used, show that diabetes-related complications are the main cost driver. These findings are important for decision making about how to diagnose and treat the disease. Early detection and good glycemic control is good not only for patients but also for reducing the cost of the disease. New technology may have a huge impact on how a disease is handled and thereby on the absolute cost and on the cost structure. The studies discussed here are from the late 1970th to the late 1990th, but during recent years new drugs and new technologies have been introduced, e.g. DPP-4 inhibitors or new insulin pumps. Forthcoming studies will show if and how these can affect the long term outcome and hence the cost of diabetes.

The studies led by Bengt have been ground breaking in more than one aspect. They have for the first time clearly identified the cost-drivers. They have shown

that it is possible to collect data both from clinicians and patients. They have provided evidence that, similar to clinical trials, descriptive economic studies can be performed with a common protocol on an international level. Finally, they have illustrated the importance of collecting systematically real life data to support decision making, both for outcome and cost assessment of current drugs and for estimating the potential impact of new technologies.

Bengt has during his entire career promoted the use and/or generation of solid data for research and decision making. Many cost of illness studies, not the least in diabetes, attest to this. He was and is right. Today decision makers share the same beliefs, and many efforts to collect real life data are ongoing, be it in cohort studies, post-marketing surveillance studies or registries.

It has been an honour to participate in these efforts with Bengt.

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ADDRESSING THE SECOND GAP IN TRANSLATION

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INTRODUCTION

One challenge in health economic assessment is getting results implemented in policy. In his 2006 report, Sir David Cooksey set out a vision for invigorating the translation of knowledge into everyday practice. He identified two important gaps: The first was in the transmission from benchmark to bedside; the second was in the translation of HTA findings into health service and general healthcare improvement (Cocksey 2006).

A good example that illustrates Bengt Jönsson's early contribution in addressing this second gap is the "*Cost-Benefit Analysis of Hepatitis B Vaccination: A Computerized Decision Model for Spain"*, published in 1991 (Jönsson et al 1991). As a health economist and leader of an interdisciplinary working group of medical specialists, epidemiologists and local health experts, he developed a generally applicable computer model as a tool for decision-making in alternative vaccination strategies against hepatitis- B, an important public health problem in Spain at that time.

The problem of hepatitis- B vaccination was particularly relevant for two reasons:

A) THE BURDEN OF DISEASE RELATED TO HEPATITIS-B INFECTION

The prevalence of hepatitis B varies throughout the world. It is categorised into low (< 2%), medium (2% - 5%), and high (> 5%). Countries in the Mediterranean region such as Spain (population about 40 million) – or Italy and Greece – show an intermediate endemicity of this type of jaundice.

The acute disease is generally asymptomatic and resolves without treatment. However, individuals who progress to chronic infection are at risk of increased morbidity and mortality. It was estimated that 60,000 new infections occurred every year. In addition, serological evidence showed that about half a million people are chronic virus carriers, the prevalence being especially high in young adults in urban areas. They form the main reservoir of the virus. Several serological studies have confirmed that the risk of vertical transmission of the disease from hepatitis-B carriers to dependants, spouses and children, is also very high (Bruguera et al 1990). Moreover, chronic hepatitis -B infection is the leading cause of cirrhosis and hepatocellular carcinoma, and 15% to 25% of these patients die because of the liver disease. Years of life lost represent more than 90% of the burden of disease (Garcia-Fulgueiras et al 2011).

In the past, the main method available to reduce the morbidity was vaccination with a vaccine derived from human plasma. In addition, it is common to give hepatitis B immune-globulin after accidental exposure. Regarding vaccine, its availability was limited and the price was high. Therefore, until the early 1990s, prevention was based exclusively on selective vaccination of individuals of high-risk groups, a strategy that proved inadequate in reducing the incidence and the prevalence rate of the disease (de la Torre 1998).

B) THE TECHNOLOGICAL PROGRESS

In 1986 a new hepatitis-B vaccine (HBV) obtained by genetic engineering became available, with an efficacy identical to that of the vaccine derived from plasma. The average protection against becoming a chronic carrier has been estimated at about 90%. The original vaccine restraints have disappeared; the new vaccine could be obtained in unlimited amounts and at a substantially lower price (Antonanzas et al1992). The technological progress warranted a new medical and economic assessment of the costs and benefits for Spain. With the reduced costs, mass vaccination became affordable and it became essential to develop and to evaluate different programmes with the aim of controlling the disease.

THE STUDY

To assess costs and benefits of different immunisation strategies, medical and economic data from Spain were collected. With the support of the National Centre of Microbiology and Virology in Madrid, it was possible to get access to the latest epidemiological statistics. Detailed information on the costs (or prices) of screening and vaccination, and on the costs for treatment of the different

stages of the disease, were available with the help of medical specialists and hospital administrators. The collection of data was performed on the spot, and the discussion with the local experts and all key stakeholder groups took place throughout the entire process of the evaluation.

A general decision model was developed to estimate costs and benefits of different vaccination strategies. Because screening was mandatory in public hepatitis vaccination programmes in Spain, the model started with the decision node for the alternatives “screen” or “not screen”. It included opportunities for screening, prophylaxis after exposure, cost and administration of the vaccine, side effects, time costs, and variations in compliance with the vaccination schedule. Because HBV infection is common among economically active groups of the population, indirect costs seemed very important and were also included. Local data were used to calculate lost earnings, dependent on age, gender, and employment situation.

A detailed analysis was performed for the entire health care personnel, the largest high-risk group for hepatitis-B in Spain. In this population, epidemiological data and data on direct costs were readily to hand. Moreover, reliable information on absence from work could be obtained.

As expected, the costs of a possible infection with HBV varied according to the patient’s history, and to the degree of severity of the clinical consequences. Calculations obtained with the model indicated that a vaccination programme would reduce direct expenditures for hepatitis-B if the attack rate in the target population is higher than 4.9%. The major benefit, however, results from increase in life expectancy. If indirect costs are included, the benefit threshold was reduced to 0.9%. If the probability of markers is lower than 0.19%, it will be less expensive to vaccinate without prior screening. The results were very sensitive to the cost of the vaccine, and to the compliance of the individuals.

The study was the first of its kind in Spain and was supported by a pharmaceutical company. A series of subsequent studies followed in close succession, often financed by public money. Two of them explicitly referred to the study by Bengt and his group:

- In 1995, a team of well-known Spanish health economists published the C/E ratio of three different HBV strategies in Catalonia. The index of efficiency used in their analysis was the cost of avoided case of HBV infection. The study found mass immunisation to be most effective. Regarding the question of generic effectiveness measures, or QoL years gained, they referred to the calculations of Jönsson et al. Their study was funded by the Department of Health and Social Security of the Catalonia Regional Government (Antonanzas et al1995).

- In 1997, an interdisciplinary team of health specialists and economists presented another C/E analysis in order to determine the effectiveness of mass immunisation with the new recombinant vaccine against the hepatitis-B virus in Spain. In this case decision trees supported by Markov models with Monte Carlo simulation were used for the calculation of the costs of the disease. Mass adolescent vaccination showed the best cost-effectiveness. The explicit aim of this study was “to contribute to the economic evaluations previously performed in our country on HBV vaccination” (including Jönsson et al. by name). This study was financed by the Health Research Fund of Spain (Garuz et al 1997).

FOLLOW-UP AND CONCLUSION

In rapid succession, prevention measures against HBV infection were introduced. The generalised vaccination of health care personnel in the ‘90s resulted in a drastic reduction in new cases of hepatitis-B in hospitals. The screening of blood donors for HBV markers has virtually eradicated post-transfusion hepatitis (Bruguera 2006).

Over the last 20 years, all Spanish regions have adopted vaccination programmes among newborns and adolescents, and today, the vast majority of school children are vaccinated. Recently, high coverage rates (>95% in children) confirmed the high performance of hepatitis vaccination programmes. Thanks to the implementation of mass vaccination for adolescents, the country has seen a steady decrease in annual HBV incidence (Brown et al 2004; Pachon et al 2007).

This short account of the development of successful vaccination strategies in Spain illustrates the potential of a well organised HTA study based on a series of sound principles or conditions:

- the obvious need for the intervention
- the timeliness of the study
- a multidisciplinary collaboration was assured from the outset (without specific information one simply cannot proceed with efficiency evaluation of the intervention)

But knowledge production by providing high quality evidence base is not enough. Crucial in translating the findings into practice was

- the identification of strategies that are effective and simultaneously appropriate for general use,
- triggering the financial support for the process of implementation into routine.

Bengt has always been actively involved in strengthening the impact of HTA studies. By delivering results suitable to shareholders, and meeting needs of decision makers, he facilitated the application of new technologies. The study in Spain illustrates that he was also an early pioneer in addressing the Second Gap in translation.

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THE PRACTICAL IMPORTANCE OF THE COSTING PERSPECTIVE FOR REIMBURSEMENT DECISIONS

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INTRODUCTION AND OBJECTIVES

The choice of costing perspective is a heavily debated issues in the application of economic evaluation for decision making in health care (Jönsson 2009). It is a key premise in societal cost-benefit analysis that all resource use should be included and valued by its opportunity costs, irrespective of who the payer is (Jönsson 1976). This is a necessary condition for cost-effectiveness analysis to inform socially optimal decisions regarding the use of health technologies: only if all costs are considered will decisions made on the basis of incremental cost-effectiveness analysis be consistent with the maximisation of social welfare (Johannesson 1997a). The US panel on cost-effectiveness in health and medicine (Weinstein 1996) was one of the first attempts to provide guidance on the principles and practice of economic evaluation, advocating a societal perspective with the inclusion of productivity costs (indirect costs). Meltzer (1997) and Johannesson (1997b) demonstrated that for life-extending interventions, the analysis should also incorporate all consumption and production in added life-years.

Despite strong support in academic literature for adopting a societal perspective, guidelines for reimbursement submissions frequently recommend a narrower health care payer perspective, in addition to or instead of the societal perspective (Jönsson 2009). Table 1 lists current recommendations regarding costing perspective for reimbursement agencies and other decision-making bodies internationally.

TABLE 1. RECOMMENDED COSTING PERSPECTIVE IN SUBMISSION GUIDELINES (ISPOR 2013)

Societal perspective preferred	**Third-party payer perspective preferred**	**Both (no preference stated)**
	Baltic states (Latvia, Lithuania, Estonia)	
Finland	Belgium	Italy
France	Brazil	Norway
Portugal	Canada	Poland
Sweden	NICE (England & Wales)	Russia
Cuba	Germany	Spain
The Netherlands	Hungary	
	Israel	
	New Zealand	
	AMCP (US)	

A principal argument for the health-care payer perspective has been that economic evaluation should present evidence of relevance for the decision maker, who typically has responsibility only for a limited budget, e.g. direct medical expenses. Claxton and others (2010) emphasised the importance of health care budgets as an expression of social preference regarding allocation of resources to health care. With fixed budgets, cost-effectiveness analysis should have a more limited role of maximising health outcomes subject to the constraints set by the health care budget, and thus only costs that fall on this budget should be included in the analysis.

Further, it has been argued that including costs that are unrelated to the intervention being evaluated will unfairly penalise patients with expensive underlying medical conditions. For example, it would be close to impossible to show cost-effectiveness for any life-saving intervention in patients with chronic kidney disease requiring dialysis (Grima 2012). This position has however been criticised as inconsistent (VanBaal 2013).

Estimating costs from a societal perspective is associated with methodological as well as empirical challenges (Roy 2008). With the societal perspective, each resource should be valued at its opportunity cost, i.e. the value in its best alternative use. Market prices are typically taken as a proxy for opportunity cost, but there is a lack of established methodology to correct market distortions to prices, and lack of data on actual opportunity cost of resources. There is also

controversy regarding the valuation of lost productivity; the Dutch reimbursement agency advocates the friction cost method (CVZ 1999) while most other agencies recommend productivity costs to be measured using the human capital method (ISPOR 2013).

However the methodological issues with adopting a narrow costing perspective can be just as challenging. Departures from the societal perspective will usually require some element of judgment regarding which costs to include and which to exclude; the distinction between direct vs indirect costs, related vs unrelated costs etc. is rarely unambiguous.

Productivity costs constitute large share of burden of illness, in particular in chronic conditions affecting patients in early age. For example, a 2012 report found that productivity costs amount to 40% of the total economic burden of brain disorders (Olesen 2012).

The extent to which the consideration of productivity costs and future costs actually impacts reimbursement decisions is less well established. In practice, the societal perspective differs from a third-party perspective mainly due to inclusion of effects on work productivity and inclusion of production and consumption in added life-years (future costs). This paper reviews recent decisions by the Swedish reimbursement agency, the Dental and Pharmaceutical Benefits Agency (TLV), with the objective of determining to which extent adopting a societal perspective rather than a health-care payer perspective impacts actual reimbursement decisions. TLV is one of very few reimbursement agencies explicitly requiring a full societal perspective in the base-case, including future costs (TLV 2003). The decisions by TLV are further compared with decisions on the same products by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. The NICE methodology of technology appraisal is very similar to the guidelines produced by TLV in virtually all respects except for costing; NICE requires the reference case be presented from the National Health Service perspective (NICE 2013).

METHODS

All TLV decisions in the period September 2010-September 2013 were reviewed, excluding decisions that only concerned the reimbursement of new package sizes, new formulations or where the active substance was already reimbursed under a different brand. The motivation for each reimbursement decision was examined to determine whether costing perspective might have been a factor influencing the decision, i.e. whether the decision considered indirect costs and/or costs in added life-years. Although the published reimbursement decisions do not contain all the details of the consideration of the evidence, the

main aspects considered in the decision-making process are stated. ICERs were converted to EUR to allow comparison using the exchange rate of 8.77 SEK/EUR and 0.847 GBP/EUR[2].

RESULTS

Of the 71 decisions reviewed, 41 (58%) were granted general reimbursement, 20 (28%) restricted reimbursement and in 10 cases (14%) reimbursement was refused. Overall, 20 decisions (28%) were potentially influenced by costing perspective, meaning that decisions were based on ICERs that may include productivity costs or costs in added life years (though this was not always explicitly stated). There were very few decisions where indirect costs were quoted as a factor in the reimbursement decision. A notable exception is the decision for general reimbursement of the vaccine Rotarix against rotavirus infection, which was largely motivated by reductions in lost production for parents (TLV 2012a).

Restricted reimbursement decisions were more likely to be based on cost-effectiveness analyses where costing perspective may play a role (50%), compared to decisions of general reimbursement where only 15% of decisions were potentially influenced by costing perspective.

More than two out of three decisions were taken without the explicit calculation of an incremental cost-effectiveness ratio; in most cases the submission concerned a drug with similar effect and the same or lower price as a drug that is already under general reimbursement. For example, in the evaluation of apixaban for stroke prevention in atrial fibrillation, the drug was considered equally efficacious as another drug, dabigatrian, which has received general reimbursement. Since the price for apixaban did not exceed that for dabigatran the drug was granted general reimbursement with no further consideration of cost-effectiveness (TLV 2012b). ICERs for drugs receiving general or restricted reimbursement were all below 1 million SEK, while ICERs for drugs that were refused reimbursement were all above this level.

Among the 20 drugs reviewed by TLV where the costing perspective may have influenced the reimbursement decision, 8 have also been reviewed by NICE. The ICERs calculated in NICE technology appraisals were generally lower than the ICERs quoted in TLV's decisions. These discrepancies do not appear to be mainly driven by the differences in costing perspective; rather, lower drug prices and higher costs of other health care services (driven by higher compensation to

[2] Currency exchange rates from www.oanda.com, accessed Oct 18 2013

health professionals) in the UK may have contributed to this result (Brekke 2012).

There was close to complete concordance between NICE and TLV with respect to reimbursement decisions, with only one exception: while NICE recommended the use of vemurafenib for malignant melanoma, TLV decided against reimbursing this drug. The TLV decision was motivated by poor cost-effectiveness; the ICER for vemurafenib vs. standard of care was just over 1 million SEK (€120,000). By contrast, the NICE technology appraisal estimated the ICER to between 44,000-51,800 GBP (€52,000-€61,000). Since the two evaluations were based on the same clinical data, and the main drivers of the results were survival benefits and the drug cost, it is likely that the inclusion of costs in added life-years in the Swedish analysis is the main reason for the difference in results.

DISCUSSION AND CONCLUSIONS

The costing perspective is a key methodological issue in economic evaluation, and the high contribution of productivity costs to the total costs of illness, in particular in chronic disorders, leads to the expectation that the costing perspective has important consequences for the results of evaluations and decisions made on the basis of these results. However, this review does not lend support to the hypothesis that the costing perspective is a principal determinant of reimbursement decisions. Comparing decisions by two agencies in Sweden and the UK, decisions were largely consistent in spite of differences in costing perspective. The consideration of net consumption in added life-years for life-extending interventions may be a more important factor for reimbursement decisions than the consideration of effects on productivity. To explain this, consider that in Sweden the net consumption in the highest age group (85 years and above) is about 300,000 SEK (www.tlv.se, www.scb.se), and the average health utility in this group is 0.74 (Burström 2001). Assuming that the threshold willingness to pay per QALY is 1 million SEK, the net value of extending life by one year is 440,000 SEK (1,000,000*0.74-300,000), considering the effects of costs in added life years. Thus incorporating costs in added life-years reduces the value of life-extending interventions by about 40%. Even an intervention that extends life at zero cost would have a cost-effectiveness ratio of over 400,000 SEK/QALY (€46,000/QALY).

The inclusion of costs in added life years is a relatively easy modelling exercise and requires no or little in terms of additional data collection. The consideration of intervention effects on productivity, however, requires investment in terms of data collection. In several decisions, TLV were asking the manufacturer to provide additional data on productivity costs since none were presented in the

initial reimbursement submission. As only reimbursement agencies in few smaller markets today recognise the inclusion of productivity costs, and there is no consensus on appropriate methodology, manufacturers may not prioritise the investment in building evidence for an effect on productivity costs. Conversely, the presentation of high-quality evidence on effects on productivity could lead to a more pronounced role in decisions and a closer adoption of the societal perspective where this is the aim.

Irrespective of the preference of a decision-maker or agency for a particular costing perspective, it should be considered best practice in economic evaluation to present results from a societal perspective in addition to any other perspective. This allows the decision-maker and other stakeholders to see the consequences of adopting a narrow costing perspective. For life-extending interventions, ICERs from a societal perspective may be considerably higher than from a health care payer perspective due to the inclusion of net consumption in added life-years. Conversely, including intervention effects on productivity costs may lead to lower ICERs from a societal perspective.

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A JAPANESE-STYLE APPROACH TO VALUE-BASED PRICING: SCIENTIFIC BASIS AND THEORETICAL POTENTIAL

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INTRODUCTION

Extensive discussion of value-based approaches to reimbursement and pricing are often heard in western countries. The UK's NICE, for example, announced an introduction of value-based pricing after 2014 to reform NICE decisions on reimbursement in terms of incremental cost-QALY ratio for a single threshold. Although France and Germany are less positive towards the cost-QALY threshold, both of them have been converging on similar methods, which so far consider the relative clinical benefit and cost-benefit ratios to determine the reimbursement rates (e.g. "SMR/ASMR" in France).

In Asia, the UK NICE method using a threshold cost-QALY ratio for health technology assessment (HTA) has been established in some countries such as Korea, Taiwan, and Thailand. Among those HTA systems, however, the issue of value-based pricing has not explicitly arisen as yet. Over the next few years, it is expected that Asian countries will follow the western countries in developing VBP approaches to pricing and seek a solution satisfying local requirements specific to their own system. In 2011 Japan officially announced the start of serious consideration being given to the use of cost-effectiveness methods for

pricing new medical technologies, with a pilot introduction in 2014. As of the beginning of 2014, the new policy on the details of cost-effectiveness methodology has not been determined, except for a summary agreement in the government committee that suggested employing an HTA methodology similar to that of NICE, but leaving the details for future discussion. Also the pilot introduction was postponed until 2016. Regarding the changing situation, this article seeks to begin to fill this gap by interpreting the current Japanese pricing issues in pharmacoeconomic language and sets a basic frame of theory for Japan-style value-based pricing in the future.

PRICING AND REIMBURSEMENT IN JAPAN

Pricing of new technology (drugs and devices) is controlled and determined by rules in the Ministry of Health, Labour and Welfare (MHLW). Once the price of a new drug is determined by the government, it is also approved for inclusion in the National List for reimbursement. Price revisions are conducted biennially. The discount rate in re-pricing is politically determined by MHLW. Since a constant reimbursement rate of 70% is applied automatically to all drugs after listing on the National List, there is no scope for discussing the issue of reimbursement rates after approval. Hence, value-based approaches to pricing and reimbursement for new drugs in Japan have been historically focused on how to improve the pricing calculations made by the government.

The methods used in official pricing do not consider economic evidence of cost-effectiveness. It is not a prescriptive requirement, since the equations have been developed in political and experience-based ways in the Ministry of Health. This lack of a scientific basis partly explains why Japan is not regarded as a country with a modern HTA system, although Japan has a complex HTA system of its own style that has had a long history over fifty years.

CURRENT METHODS FOR COST-BENEFIT CONSIDERATIONS IN PRICING

The pricing rules in Japan are characterised by the concept of a "premium" for a higher price, which is added to the baseline price to reflect the additional usefulness of a new drug (Kamae and Kobayashi 2010). The pricing mechanism reflects a value-for-money assessment based on subjective judgment, It also considers price-volume impact on the national budget over two years. We might call it "quasi value-based pricing" (quasi VBP). There are two types, Type-I for initial pricing and Type-II for re-pricing every two years. As shown at Table 1, the quasi VBP is characterised by various categories and different premium rates according to requirements that are defined for each category.

A survey of 106 new drugs on the National Health Insurance price listing in 1998-2013 (12 antihypertensive, 25 antidiabetic, 52 antibiotic, 17 psychotropic drugs) reported that 2 (17%) antihypertensives, 5 (20%) antidiabetics, 16 (31%) antibiotics and 4 (24%) psychotropics obtained a premium (Kamae et al 2013). The survey also revealed that the category of “Usefulness II” was given to 85% of all drugs gaining the premium with a 3% to 20% rate, and only one drug obtained the premium of “Innovativeness” with a premium rate of 30%.The reason for 30% premium being determined in the applicable range of 70% to 120% was not reported. Such decisions, having so inadequate a basis, inevitably arise in the absence of numerical criteria. Government policy, requires following the conditions for a new drug to receive a premium for innovativeness:

1. to be clinically useful with a new mechanism of action
2. to show objective evidence of greater efficacy and safety than the comparator
3. to show objective evidence of an improved treatment method for the indicated disease or trauma.

The statements, however, are too descriptive to give unambiguous guidance as to whether the innovativeness premium could be applied. Also they do not provide any information on how any single point within the range of 70 to 120% reflects a specific degree of innovation provided by the new drug.

Although the Japanese quasi VBP lacks a scientific basis for the premium, it can be formulated in the following way:

New price = Baseline price x (1 + Premium rate), (1.1)

= Baseline price + Baseline price x Premium rate, (1.2)

= Baseline price + Premium, (1.3)

despite the different categories, rates and conditions of each premium.

TABLE 1 QUASI VALUE BASED PRICING IN JAPAN 2012

Type	Name of Method	Category of Premium	Premium Rate
I: Initial Pricing	Similar efficacy comparison	Innovativeness	70-120%
		Usefulness	Usefulness I 35-60%
			Usefulness II 5-30%
		Marketability for orphan drugs	Marketability I 10-20%
			Marketability II 5%
		Pediatric use	5-20%
	Cost accounting	Operating profits	19.1% with plus-minus 50% (i.e., 9.55%-28.65%)
II: Re-pricing	Regular revision	Premium for promotion of new drug creation,	2.5-7.5% depending on the categories
		Premium for pediatric or orphan drugs,	
		Premium for genuine clinical effectiveness	
	Others	market expansion re-pricing, etc.	2.5%

RELATION BETWEEN ICER AND JAPANESE PREMIUM

The incremental cost-effectiveness ratio (ICER) is defined as an incremental cost, ΔC, divided by an incremental effectiveness, ΔE. That is,

$$ICER = \Delta C / \Delta E, \quad (2.1)$$

where $\Delta C = C_1 - C_0$, C_1: cost of a new technology and C_0: cost of a comparator.

This definition of the expression (2.1) can be transformed to:

$$\Delta C = ICER \times \Delta E. \quad (2.2)$$

By substituting $C_1 - C_0$ for ΔC, the expression (2.2) leads to:

$$C_1 = C_0 + ICER \times \Delta E. \quad (2.3)$$

When considering the relation between cost and price, in general, the expression (2.3) will be presented as:

$$g(P_1) = g(P_0) + \text{ICER} \times \Delta E, \qquad (2.4)$$

where cost C_i is defined as the function g of price, $Ci = g(P_i)$, i = 0, 1.

Supposed that the costs C_1 and C_0 simply represent the prices P_1 and P_0, respectively, of a new technology and its comparator, the expression (2.3) comes up to:

$$P_1 = P_0 + \text{ICER} \times \Delta E. \qquad (2.5)$$

Comparing the expression (2.5) with (1.3), the following relation between ICER and Japanese premium would be suggested:

$$\text{Premium} = \text{ICER} \times \Delta E. \qquad (2.6)$$

That is to say, the Japanese premium should be proportional to “relative clinical benefit" of the new technology assuming that the ICER term is constant. The expression (2.6), therefore, implies that it could give a scientific basis for Japanese premium with respect to the simplest assumption that cost is equal to price.

A more practical approach would be the assumption that cost should be a linear function of price, that is, $g(P_i) = a \times P_i + b$ (a, b: constant). Then, plugging it into the equation (2.4), the expression (2.5) will be slightly modified as follows:

$$P_1 = P_0 + (\text{ICER} \times \Delta E) / a. \qquad (2.7)$$

If we substitute k for 1/a, where k is a constant, the relation (2.6) becomes:

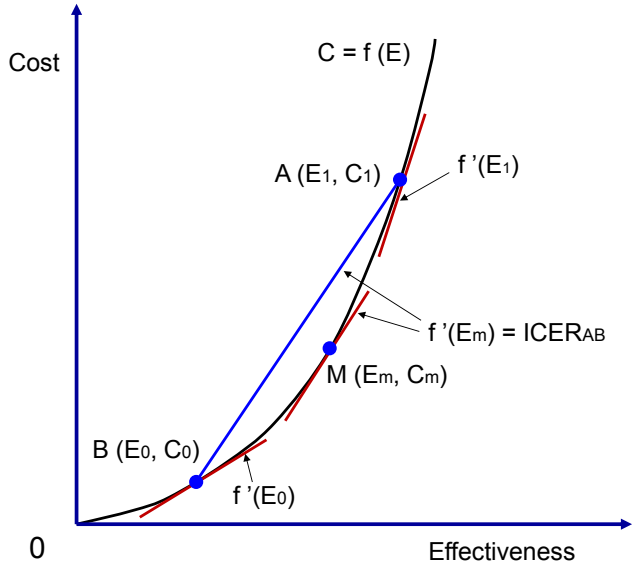
$$\text{Premium} = k \times (\text{ICER} \times \Delta E), \qquad (2.8)$$

Equation (2.8) has the same property as (2.6) in that the premium is proportional to relative clinical benefit ΔE, because both of k and ICER are constant. Another interpretation of the expression (2.8) is that the Japanese premium would be proportional to the product of ICER and ΔE. This interpretation may enable us to take a practical approach to the study of quantification of the Japanese premium in terms of ICER and clinical benefit, because the constant k of proportionality could be estimated based on the practical setting in Japan.

HIGHER PREMIUM INCORPORATING INNOVATION

An interesting interpretation of equation (2.8) would be the proportionality between the Japanese premium and the ICER, assuming the relative clinical benefit is constant. Namely, if we plug a higher value into the term of ICER in the equation (2.8), the premium will rise. This nature of the expression (2.8) may provide a useful clue about how an innovative technology should be rewarded with respect to higher pricing. Figure 1 illustrates the scheme for rewarding the innovation under the assumptions that the ICER is given with the slope of the line connected between Point A and Point B, both of which are located on the continuous efficiency-frontier curve, $C = f(E)$, on the cost-effectiveness plane (Kamae et al 2011).

Figure 1. ICER and continuous cost-effectiveness curve



Since the differential coefficient, $f'(E)$, of the cost-effectiveness function represents the tangent line at a point on the curve (Kamae et al 2007), the $ICER_{AB}$ defined between Point A and B can be equal to the tangent $f'(E_m)$ at the Point M according to the intermediate-value theorem. Hence, considering the tangents, $f'(E_0)$ and $f'(E_1)$ at Point B and A, respectively, we obtain the following inequality:

$$f'(E_0) < ICER_{AB} < f'(E_1). \qquad (3.1)$$

This inequality gives us certain lower and upper limits of the ICER defined between a new technology and its comparator. Accordingly, the upper limit $f'(E_1)$ might be interpreted as a "reasonable" candidate value to be substituted for the ICER value at the equation (2.8). Therefore, if we assume that the upper limit $f'(E_1)$ is k* times as large as the $ICER_{AB}$ (k*: constant), the revised higher premium rewarding innovation will be given as follows:

$$\text{Revised Premium} = k \times f'(E_1) \times \Delta E, \qquad (3.2)$$

by substituting $k^* \times ICER_{AB}$ for $f'(E_1)$, then

$$\text{Revised Premium} = k \times (k^* \times ICER_{AB}) \times \Delta E. \qquad (3.3)$$

As the order of k and k* is changeable, the expression (3.3) is also transformed to: $k^* \times (k \times ICER_{AB} \times \Delta E)$. As the blanket portion of $(k \times ICER_{AB} \times \Delta E)$ is identical to the primary premium before considering the upper limit of the $ICER_{AB}$, the expression (3.3) can be interpreted as:

$$\text{Revised Premium} = k^* \times \text{Premium before revision.} \qquad (3.4)$$

DISCUSSION

Formula (3.4) illuminates how the primary premium, which is determined by current premium rules, can be revised in use of the coefficient k* to reflect the degree of innovation associated with the cost-effectiveness function, $C = f(E)$.

One of the advantages of (3.4) is that it represents only a partial adjustment to the current system, which may be more politically acceptable than a total change of the system. Another is flexible applicability of the formula (3.4) (or (3.3)) for an arbitrary unit of clinical benefit. The term of ΔE can accept any clinical outcome including the QALY.

The coefficient k* can be estimated according to the equation $k^* = f'(E_1) / ICER_{AB}$ if the nominator $f'(E_1)$ is known. In general, the derivative cannot be calculated unless the consecutive cost-effectiveness function, $C = f(E)$, is known. As for the estimation of k*, therefore, a question is left for the further study on how to find the consecutive cost-effectiveness function, $C = f(E)$.

In the real world, of course, the framework of the theory needs to be refined and validated as to whether the assumptions could work to capture the complex

relation between a price and the actual cost. Those challenges are left for further investigations.

CONCLUSION

The theoretical development shown in this article is a suggestion for Japanese stakeholders to find a way to set a Japanese-style pricing mechanism based on the value of a new technology. In that process, pharmacoeconomic methodology must be carefully considered to provide the Japanese current system with more scientific basis, while maintaining the current rules as much as possible. Currently, many countries are witnessing a global shift in the way policymakers adopt value-based policy making in health care. It would not be an overstatement to suggest that the theoretical frame presented in this article indicates the potential to advance Japanese value-based approaches to pricing policy, and may even influence other countries when they seek their own way of developing a value-based HTA system.

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THE APPLICATION OF ECONOMICS TO OSTEOPOROSIS

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INTRODUCTION

One in three women and at least one in six men will suffer an osteoporotic fracture in their lifetime and it is estimated that more than ten million men and women are at high risk of osteoporotic fractures in the European Union (Hernlund et al 2013).

Osteoporosis and the 3.5 million fractures it causes cost the health care systems of Europe in excess of €39 billion each year (data for 2010). But numbers don't tell the full story. For the individuals who suffer fractures as a result of the disease, the stories are personal. Pain, disability, reduced mobility and long-term disability are all too frequent. Additionally, fractures related to osteoporosis result in death. About 43,000 deaths occur each year in Europe as a direct consequence of hip or spine fractures (Hernlund et al 2013).

Osteoporosis is young. As a disorder osteoporosis was only defined in 1993 at an international consensus conference, later adopted by the WHO in 1994 that provided an operational definition based on the measurement of bone mineral density (BMD) (Kanis et al 1994). This presaged the development of highly effective treatments such as alendronate, which first became available in September 29, 1995. Despite tools for the diagnosis and treatment of osteoporosis, interventions were ineffectively targeted, in part because osteoporosis belongs to no one specialty. The few 'full time' specialists have to cross specialty boundaries as well as technology boundaries, which is where Bengt Jönsson comes in, in the late 1990s.

At that time I assembled a small team funded by discretional grants to identify why patients were not being identified for treatment and to develop algorithms for the assessment of fracture risk. The expertise represented was clinical, epidemiologic, mathematic, statistical and economic. We were privileged to have Bengt as our economic collaborator. His collaboration allowed us as a team to make significant inroads to the development of fracture risk assessment, the formulation of intervention thresholds based on health economics, and to characterise the economic burden of disease in a systematic manner.

THE GESTATION OF FRAX – THE FIRST TRIMESTER

FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX) that calculates the 10-year probability of a major fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture. Fracture risk is calculated from age, body mass index and well validated dichotomised risk factors. Femoral neck bone mineral density (BMD) can be optionally input to enhance fracture risk prediction. Fracture probability differs markedly in different regions of the world so that FRAX is calibrated to those countries where the epidemiology of fracture and death is known (currently 50 countries). About 3 million calculations are performed yearly in 173 countries. Bengt was one of the major architects in formulating key concepts that shaped the eventual emergence of FRAX in 2008.

A first step was to identify the relevant risks. We thought it important to characterise the risk of fracture rather than the risk of osteoporosis. We began by investigating the performance of BMD measurements as a predictor of fracture risk (Kanis et al 200a; Kanis et al 2000b; Kanis et al 2000c). It became evident that the clinical utility of assessing fracture risk depended not only on BMD and fracture risk, but also on mortality. Thus, fracture probability would be low in an individual at very high fracture risk if the risk of death was even higher. We subsequently developed accurate methods for assessing lifetime risks of fracture (Odén et al 1998) and integrating the hazard functions of death and fracture (Kanis et al 2000d). The principle was extended to include BMD (Kanis et al 2000c, 2001b, 2002b) and the mortality consequences of fracture (Johnell et al 2004, Kanis et al 2004c), particularly deaths that could be attributed to the fracture event (Kanis et al 2003).

Having decided to adopt a probability-based approach to fracture risk assessment, it was important to determine the time horizon. One-year probabilities would yield numbers that were too low for clinical consumption (e.g. a 1 year probability of hip fracture of 0.3%). At the other extreme, lifetime probabilities, though much higher, did not increase with age despite a logarithmic increase in the incidence of hip fracture. The compromise was the

birth of a ten-year probability (Kanis et al 2001c, 2002c). This had the advantage of providing readily understandable numbers and was a time horizon favoured by Bengt that covered the duration of interventions together with the slow offset of effect once treatment had stopped (Jönsson 1999). We then reviewed the world literature on hip fracture risk and death (Kanis et al 2002b) and noted a greater than ten-fold variation in hip fracture probability worldwide. From this observation, it became clear that the assessment of fracture risk must take account of the global diversity of risk.

A further problem to be tackled was the output variable. Ideally this should include all osteoporotic fractures. But how should these be defined? In the absence of a gold standard we developed site-specific criteria based on their association with low BMD, their predictive value for other fractures and the pattern of incidence with age (Kanis et al 2001c) which have now become widely accepted. However, the epidemiology of many osteoporotic fractures is ill-defined. An example is rib fracture, which is notoriously difficult to diagnose. For this reason we focussed on the 'major osteoporotic fractures' (hip, clinical spine, forearm and proximal humerus) which accounts for about 80% of the fracture burden and for considerably more of the disutility and economic burden (Kanis et al 2001c, 2004b).

The choice of multiple endpoints created epidemiological challenges in the context of probabilities. If we were to develop the 10-year probability of a major osteoporotic fracture, then the metric of interest was the incidence of a first major fracture whether this be at the hip, spine, humerus or forearm. In the absence of empirical data, our colleague Olof Johnell characterised the incidence of a first major fracture from detailed information from all fracture cases in Malmo, Sweden (Kanis et al 2000d). From this we could derive correction factors to adjust the more usual estimates of age and sex specific incidence available in other regions of the world.

A pivotal finding that determined the future of fracture risk assessment was that BMD, the diagnostic focus for osteoporosis, had relatively poor performance characteristics. It was evident that BMD alone was a poor screening tool in that the majority of fractures in the community occurred in individuals without BMD-defined osteoporosis (Kanis et al 2000b). For example, if it were wished to select for treatment the 15% of the female population at highest risk at the menopause, the use of hip BMD would have a specificity of 85% but a sensitivity of only 45% (Kanis et al 2000a). The low sensitivity was one of the major reasons why many health care payers were reluctant to recommend population screening on the basis of BMD testing (WHO 1994). However, our models indicated that BMD had a different prognostic significance at different ages (Kanis et al 2000b). Thus, age contributed significantly to fracture risk

independently of BMD. The implication was that diagnostic thresholds are not equivalent to intervention thresholds since the range of risk varied so markedly for any given BMD. This raised the question whether there were other risk indicators that could improve still further the sensitivity of a risk assessment algorithm (Kanis et al 2002a). The expected improvements in sensitivity were modelled (De Laet et al 2005) and prototype models developed (Kanis et al 2005a, Johansson et al 2004).

The hunt for clinical risk factors began.

HEALTH ECONOMIC PERSPECTIVE

From the late 1990s, treatments were becoming available that were based on high quality randomised placebo controlled trials. Since health economics in this field was in its infancy, it became important to determine the information base necessary to populate health economic models and identify important drivers of cost-effectiveness. This was made possible by the work undertaken in the development of the risk assessment tool (Kanis et al 2001a) and in particular by the development of methodology to integrate the multiple fracture outcomes in osteoporosis (Kanis et al 2001a, Zethraeus et al 2002). A focus was to determine the fracture probability at which hypothetical interventions became cost-effective (Kanis and Jönsson 2002, Kanis et al 2002d). This work, led by Bengt, provided the basis for the development of a reference model for osteoporosis in 2007 (Zethraeus et al 2007), adopted by the International Osteoporosis Foundation and remains so today.

As might be expected, subsequent work focussed on intervention thresholds (Borgström et al 2006b, Kanis et al 2005c, 2005d): the hip fracture probability at which interventions became cost-effective. As treatments became available, specific analyses were undertaken for alendronate (Borgström et al 2004a, Johnell et al 2003, Kanis et al 2008a), risedronate (Borgström et al 2006a, Kanis et al 2004a), raloxifene (Borgström et al 2004b, Kanis et al 2005b), hormone replacement treatment (Zethraeus et al 2005), strontium ranelate (Borgström et al 2006c), denosumab (Ström et al 2013, Jönsson et al 2011, 2012). In addition to assessing these treatment modalities for osteoporosis, it was possible to compare cost-effectiveness with interventions in other chronic non-communicable diseases such as hypertension and hyperlipidaemia (Zethraeus et al 2008). With the advent of FRAX, it was possible to integrate the FRAX algorithms into health economic models so that intervention thresholds could be expressed in terms of 10-year probabilities of a major fracture (Ström et al 2013, Kanis et al 2008b, Kanis et al 2005c). An important later development was, for the first time, to integrate FRAX-based models with relevant parameters of adherence (Jönsson et al 2012, Ström et al 2009).

These studies were used to validate FRAX-based intervention thresholds in several countries including the UK, US, Switzerland and Sweden (Tosteson et al 2008, Lippuner et al 2010, Kanis et al 2008b, Socialstyrelsen 2010).

BURDEN OF DISEASE

During the course of our collaboration it became apparent that major drivers of cost-utility were the costs and disutility assumed to be a consequence of different fracture outcomes. With the exception of hip fracture and forearm fracture, the disutility assumed was based on expert opinion (Zethraeus et al 2002). Even for hip and forearm fractures, the empirical database was small and confined to a few countries. The data available on resource use and cost were not available in any standardised way across counties. This led Bengt in 2006 to set up the International Costs and Utilities Related to Osteoporotic fractures Study (ICUROS) which is an ongoing 18 months prospective observational study with the objective of estimating resource use and health related quality of life related to osteoporotic fractures. At present, 11 countries are recruiting or have completed recruitment in Australia, Austria, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain, UK and the US with a total of about 6,600 patients. The programme is supervised by the International Osteoporosis Foundation and the first manuscript was published early in 2013 (Borgström et al 2013). It is expected to be an enormous resource in the years to come.

A parallel activity initiated by Bengt has been to document the economic burden of osteoporosis in Europe. This was a joint project of IOF and EFPIA which in the first instance focussed on the major EU countries of France, Germany, Italy, Spain and the UK with the addition of Sweden for obvious reasons (Ström et al 2011). The project has now been extended to the entire 27 EU countries to estimate the clinical and economic burden of osteoporotic fractures in 2010.

It is estimated that 22 million women and 5.5 million men have osteoporosis; and 3.5 million new fragility fractures were sustained in 2010, comprising 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures (i.e. fractures of the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures). The economic burden of incident and prior fragility fractures was estimated at € 37 billion. Incident fractures represented 66% of this cost, long-term fracture care 29% and pharmacological prevention 5%. Previous and incident fractures also accounted for 1,180,000 quality-adjusted life years lost during 2010. The costs are expected to increase by 25% in 2025. The majority of individuals who have sustained an osteoporosis-related fracture or who are at high risk of fracture are untreated and the number of patients on treatment is declining. The report

together with a compendium of country-specific reports is in press at the time of writing and is expected to be a landmark achievement at an EU level in terms of informing policy (Hernlund et al 2013, Svedbom et al 2013). Indeed, it has formed the basis for the development of an EU scorecard also recently published (Kanis et al 2013).

CONCLUSION

Bengt Jönsson has played a crucial role in the understanding of osteoporosis – in its assessment, the development of intervention thresholds and characterising the international burden of disease. This in no small measure is due to his skills in teaching us economics but perhaps also our skills in teaching him osteoporosis. Above all, we have enjoyed the experience.

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QALYs, Tariffs and ICERs

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INTRODUCTION

Over the past two decades, a number of countries have passed legislation regarding the use of cost-effectiveness studies in decisions about funding of medical treatments on the public budget. In each of these countries, guidelines have been elaborated to define the methodology to be used for reimbursement submissions. In Europe alone, over twenty methodological recommendations and mandatory study and submission guidelines have been published (http://www.ispor.org/peguidelines/index). As might be expected, these documents present more similarities than differences in their content, although they vary greatly in the amount of details they provide. The document from NICE (NICE 2013) in the UK has over ninety pages, the TLV guidelines in Sweden have merely three (TLV/LFNAR 2003:2). The most important difference relates to the perspective recommended for the treatment of costs: societal or that of the public payer. The most important similarity is the preferred outcome measure, the QALY, which is also the recommended outcome measure in the core-model for cost-effectiveness analyses proposed by EUnetHTA (European network of Health Technology Assessment agencies (https://meka.thl.fi/htacore/viewhandbook).

Most people agree, however, that the QALY is not a perfect measure of health-related quality of life, though most would probably agree that currently there is no better alternative. To quote Alan Williams (1994, p 10): “When Maurice Chevalier was getting quite old he was asked by a reporter how he viewed the ageing process. ‘Well’ he said ‘there is quite a lot I don t like about it, but it is not so bad when you consider the alternative.’ Perhaps the same is true for the QALY approach to collective priority setting in health care. If so, we should

beware of rejecting potential improvements simply because they fall short of perfection."

There has been a vast literature over the past thirty years discussing the QALY as a health measure for social resource allocation, from which three main (interdependent) topics emerge:

- Should there be thresholds for willingness to pay for a QALY? (see e.g. Eichler et al 2004; Jönsson 2009)
- What methodology should be used to assess preferences? (see e.g. Kind 2008; NICE guidelines 2004/2008/2013; Swedish guidelines TLV 2003)
- Whose preferences should count? (see e.g. Sackett and Torrance 1978; Williams A 1985; Dolan 1999; Culyer 2001)

My purpose is not to discuss this literature. Rather I would like to contribute to the methodological debate with some data. My empirical question is: are measured outcomes sensitive to the identity of those whose preferences are being elicited?

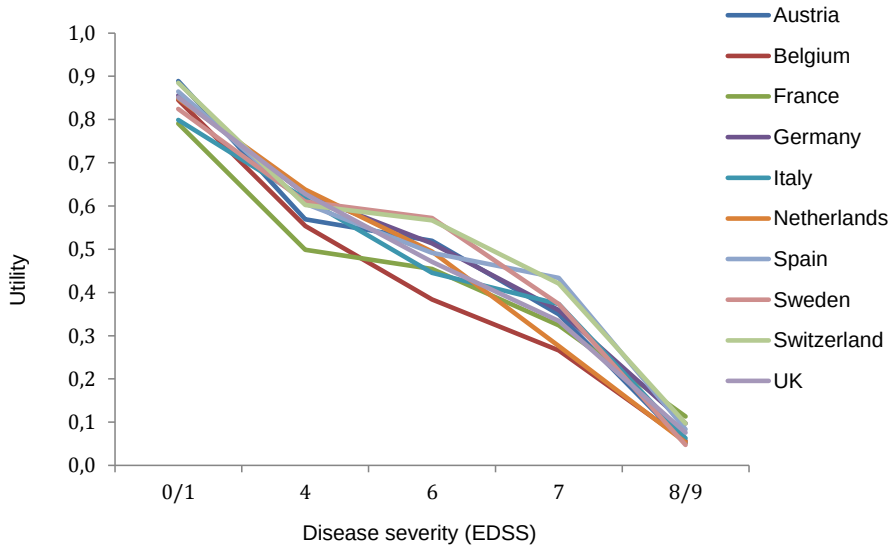
A UNIVERSAL "TARIFF"?

The debate about whose preferences should be used when measuring and valuing heath related quality of life is usually in terms of whether the values of patients or the general public, or of some proxies, are the most appropriate.

The question has arisen in particular with respect to the EQ-5D (EuroQol). The original proposal was to value health states with the general public and relate patients' answers on the instrument to this value set or "tariff" (Dolan et al 1995). For many years, most researchers adopted this approach and, in the absence of any other value set, used the original tariff from the UK population in cost-effectiveness studies. One advantage of this has been that studies produce comparable results, as can be seen in Figure 1 (Kobelt et al 2006).

A survey in 10 European countries with 16'000 multiple sclerosis (MS) patients using the EQ-5D and the UK tariff showed almost perfectly overlapping utilities for different levels of severity of MS. The fact that the utility curve is not perfectly linear is in this case an expression of non-linearity of the scale measuring disease severity (EDSS) rather than of intervals on the utility scale. The burden of MS, and subsequently the benefit of treatment estimated, was thus the same for patient in all countries, differences in the ICERs resulting only from differences in costs.

FIGURE 1 – UTILITIES RELATED TO DISEASE SEVERITY IN MS: A SURVEY IN 10 COUNTRIES



Source: adapted from Kobelt et al 2006

More recently, a considerable number of country specific value sets have been produced, most often based on answers from the general population. Feng and colleagues (2014) performed a systematic review of value sets and identified 31 studies. They concluded that the valuation studies varied widely in their design and in the resulting algorithms. Indeed, the developers of the Dutch guidelines stated that the valuation of health states in their study differed considerably from the value set used so far in Dutch cost-effectiveness analyses (Lamers et al 2005). Similarly, the results from the first Canadian validation study (Bansback et al 2012) showed that, while there was a high correlation between predictive values for the US (Shaw et al 2005) and UK values, the Canadian values were systematically different from both the US and UK values, placing lower values on severe health states in comparison to the US, and higher values on these states in comparison to the UK.

The question is, does it matter?

Oppong and colleagues (2013) collected data on health outcomes from patients with acute cough/lower respiratory tract infections over a four-week period in seven countries, applying in each country three different value sets (local, UK and European). They found that, although baseline EQ-5D scores were similar for all three sets in all countries, the local value sets resulted in a smaller

improvement after 4 weeks in most countries, while the UK tariff showed the largest improvements in every country. They concluded, however, that using different tariffs would not have made a difference to a decision based on the results of cost-utility analysis.

Karlsson and colleagues (2011) compared utilities derived with the Danish (Wittrup-Jensen et al 2009), UK and US tariffs in a one-year study comparing mono therapy with biologics to combination therapy with methotrexate in patients with rheumatoid arthritis (RA) in Sweden. While baseline differences were not significantly different, the incremental QALY gain with combination therapy was estimated at 0.09 with the UK tariff and 0.06 with the Danish and US value sets. The authors came to no conclusions regarding consequences, which would depend on local incremental costs. If we were to assume an incremental cost of € 4,000, combination therapy would be considered acceptable in Sweden using the UK tariff (ICER € 45,000) but not when using the Danish or US tariffs (ICER € 67,000). In reality, methotrexate is inexpensive, and the incremental cost for combination versus mono therapy is negligible or even negative (Kobelt 2005). Thus, the decision would be the same, regardless of the tariff.

A slightly more general question was addressed by Chapman and colleagues (2004). They investigated whether quality-adjustment of life-years gained would change the cost-effectiveness in a set of 228 cost-utility analyses. Using QALYs instead of survival increased 8% of the ICERs beyond USD 50,000, 6% beyond USD 100,000. The authors concluded that the collection of preferences should be undertaken only if the value of this information was likely to be greater than the cost of obtaining it. In general, this “likeliness” is difficult to foresee, as small increments on either side of the equation may change results that are in the proximity of the threshold of willingness to pay.

THE SWEDISH “EXCEPTION”

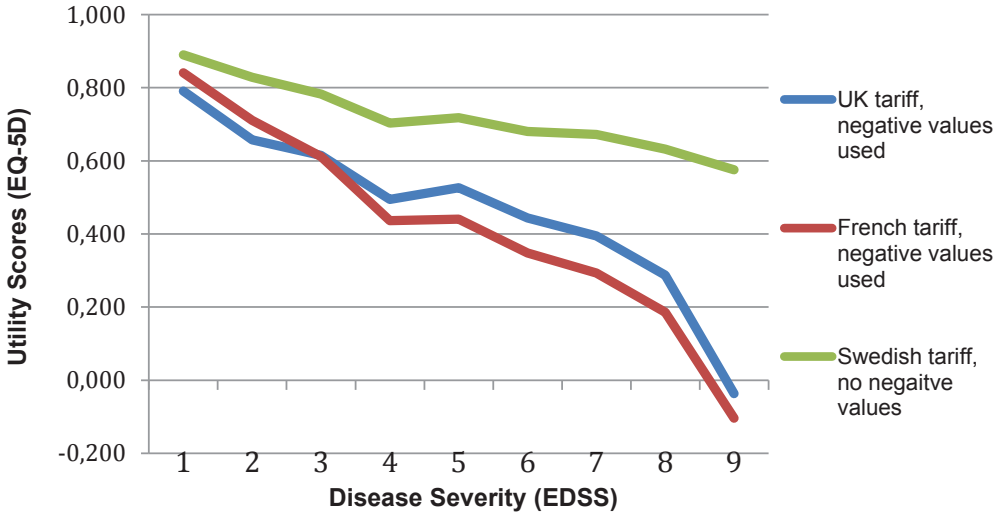
National guidelines for economic evaluation are often a reflection of the health economics research and peer influence in the country concerned. In particular, the Swedish guidelines reflect the research and thinking of Bengt Jönsson and his colleagues. Major examples include the principle that analyses are to be done from the societal perspective (Jönsson 1976; Jönsson 2009); that costs in added years of life should be included (Johannesson and Meltzer 1998); and that the QALY is the outcome measure of choice (Johannesson and Jönsson 1993). Bengt’s position on how QALYs should be measured is not known. The Swedish guidelines state that QALYs can be based either on direct or indirect measurements, using any of the accepted methods, but “weightings based on the appraisal of persons in the health condition in question are preferred from an

average of a population estimating a condition depicted for it" (TLV/LFNAR 2003:2, p 2).

As a consequence, a tariff for Sweden was developed using patients' preferences rather than those of the general population (Burström et al 2013), which makes it an exception among currently available tariffs. Not surprisingly, it also gives significantly different values: scores in the UK tariff range from -0.59 to 1, the Swedish scores range from 0.34 to 0.97.

We have used a French dataset of 1200 MS patients to calculate utilities by disease severity to compare the Swedish patient values to the French (Chevalier and Pouvourville 2011) and UK population tariffs. The difference is striking, particularly in the more severe disease states. The Swedish values are significantly higher than those derived with the French and UK tariffs, the curve is much flatter and the burden of MS thus appears to be lower.

FIGURE 2 COMPARISON OF UTILITIES BY DISEASE SEVERITY IN A FRENCH MS PATIENT SAMPLE (N=1202) USING THE UK, FRENCH AND SWEDISH EQ-5D TARIFFS



MS is diagnosed in young adulthood and patients live many years with the disease and its associated progressive disability. The aim of current treatment is to slow progression. Cost-effectiveness studies thus model the progression of

the disease over many years, and the health gain is that which results from delaying the most severe states combining both low quality of life and high dependency. Considering the slopes of the three curves in Figure 2, and regardless of the modelling technique, one can hypothesize that the ICER for a new treatment will be lowest in France as the health gain will be largest. The "flatness" of the Swedish utility curve will make any treatment less cost-effective.

To test this, a published cost-effectiveness model for MS was used with all three utility sets (Kobelt et al 2008).[3] Simulations were run over ten years, using the societal perspective.

- With the UK values, the cost per QALY gained with a new treatment compared to current therapy was estimated at € 31,000, with an incremental cost of € 5,200 and a QALY gain of 0.17.
- When the UK values are replaced with the French values, the ICER is lower (€ 23,000), due to the slightly steeper decline of utilities with advancing disease which produces a larger health gain with treatment (0,23 QALYs). The decision would remain the same.
- Contrary to this, when the Swedish values are used, the new treatment becomes cost-ineffective at € 61,000, due to a reduced health gain of 0.086 QALYs.

As all economic evaluations for MS treatments have used a similar modelling approach, it must be concluded that most of the previous treatments would also not have been acceptable, assuming a threshold of € 50,000.

We thus find that the value set can matter, depending on the case. And it can matter quite a lot!

CONCLUSION

The Swedish authorities (TLV) prefer health state valuations by people who are experiencing the condition rather than valuations by the general population. It is well known that patients with a particular condition will assign higher scores than those assigned by people without it. The question is whether we should take into account that people adapt to poor health states (coping), or base our judgment on such states not being desirable in the first place. Ultimately, the decision is a political one: "The issue as to whose values shall count is not a scientific, but a political one. A QALY may be derived by any one of several different valuation

[3] Help with the simulations by Jenny Berg (Stockholm) is gratefully acknowledged.

processes and that choice is essentially a socio-political judgement requiring socio-political justification...” (Williams 1985/2012 p 426).

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THE STATIN STORY

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There is really no avoiding 4S. This is true irrespective of whether you are talking about health economics and its use in the cardiovascular field, or you are discussing the scientific contributions of Bengt Jönsson in general. The Scandinavian Simvastatin Survival Study (4S) was a landmark study in the field of cardiovascular prevention, randomising 4,444 patients with a history of cardiovascular disease to receive either simvastatin or placebo and showing that simvastatin use led to a reduction in both mortality and morbidity. Although several studies had previously shown that the use of a statin was associated with lower LDL-cholesterol levels, to this point no-one had demonstrated that this led to the expected effects in terms of a reduction of cardiovascular events.

As important as the trial was to clinicians, equally important was the health economic work emanating from the study so closely associated with Bengt Jönsson and his team to those concerned about the impact of resource allocation within the health care sector, and for similar reasons.

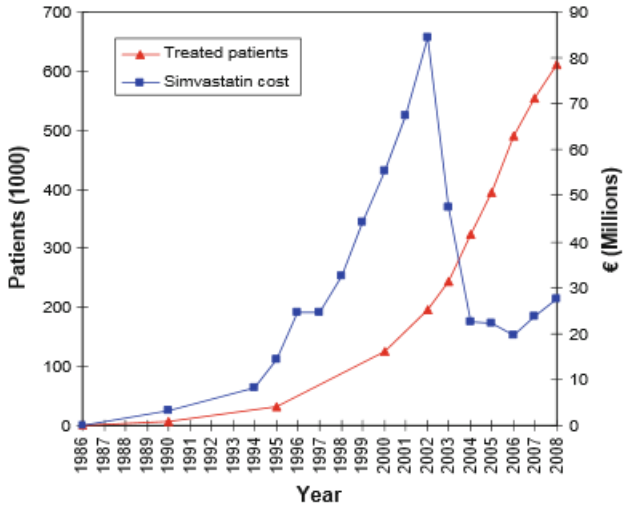
There had of course been several economic evaluations of the use of statins published prior to the publication of the work based on 4S. These studies were modelling studies based on risk functions estimated from epidemiological data. In other words, the estimation of future costs for an individual or population of the risk of cardiovascular events was based on the profile of risk factors, e.g. LDL cholesterol and the assumptions that these were associated with new events to the same degree as had been observed in previous studies. Since statins were known to reduce the levels of LDL, it was assumed that the risk of events in patients treated with statins in the model would be the same as for

individuals who had lower LDL-levels in the first place. There were concerns about the validity of both these fundamental assumptions in the models. What if the external validity of the risk functions was not high enough? This would mean that the baseline risk of patients was either too high or (more problematic in the eyes of those concerned with scarce resources) too low. The latter would mean that the estimated cost-effectiveness ratios would be underestimated and therefore, potential overuse of a drug perceived as pricey. (Somehow, less than optimal use of an effective drug never seems to cause as much consternation.) What if reduced LDL with a statin did not reduce risk of future events to the assumed degree? Once again, cost-effectiveness ratios would be too favourable.

So what did Bengt and colleagues show? The first analyses reported from the trial utilised data collected during the trial to measure resource consumption in patients with or without simvastatin treatment, contrasting this to the cost of the study drug: There were cost offsets but the net costs were still positive due to the cost of the drug. The study did show reduced mortality in the simvastatin arm: extrapolating this the resulting cost per life-year gained was indeed quite low and the conclusion therefore that the therapy was cost-effective in the studied population (Jönsson et al 1996). More extensive modelling work based on the trial including indirect costs showed that these conclusions held true across age groups (for patients aged 35 to 70), across gender and for patients with different cholesterol levels at the initiation of therapy in the trial (Johannesson et al 1997). The latter study represents a rare case of the New England Journal of Medicine publishing an economic evaluation – based on Swedish data to boot. This gives a clear measure of the importance given to these findings at the time. A separate analysis of patients with diabetes indicated that cost-effectiveness ratios were even more favourable in this group of patients (Jönsson et al 1999). It is very likely that the results from these economic evaluations helped ease the concerns about the economic consequences of a wide uptake of the drug, and contributed to the subsequent wide use of the drug.

Figure 1 shows how the use of simvastatin has increased with a marked increase after the data from 4S became available – the sharp decrease in costs observed in later years is due the loss of exclusivity of the drug which together with a system of generic substitution being used in Sweden which caused large and rapid reduction in the price of the drug.

FIGURE 1. SIMVASTATIN USE IN SWEDEN OVER TIME (TREATED PATIENTS AND COSTS).



Source: Lindgren and Jönsson 2012. Reprinted with permission from the European Journal of Health Economics.

To use a movie metaphor, there have been several sequels to the original statin story by the same director: In the IDEAL trial, the use of a high-dose statin (atorvastatin in this case) was compared to regular-dose simvastatin (Lindgren et al 2007). Analyses of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) looked at the use of a low-dose statin in patients with cardiovascular risk factors and being treated for hypertension but otherwise not normally targeted with lipid lowering therapy (Lindgren et al 2005, Lindgren et al 2009). In the wider cardiovascular field, there were also studies of hypertension, such as the LIFE, HOT studies and the blood pressure lowering arm of ASCOT (Jönsson et al 2003, Jönsson et al 2005, Lindgren et al 2008). Other studies included heart failure and anticoagulation (Ekman et al 2001, Lamy et al 2004). It is probably fair to say that they all drew upon the experiences from the work on 4S.

An interesting twist to the statin story is this: The results of the large end-point driven cardiovascular trials of the statins has led to more faith in early modelling work where the long-term effects of a drug are extrapolated based on intermediate endpoints. Together with data indicating that a very large share of the social surplus generated by simvastatin has been generated as consumer surplus, this has led us to argue that reimbursement policy should allow for early acceptance of new drugs paired with coverage with evidence development (Lindgren and Jönsson 2012).

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RELATIVE EFFECTIVENESS ASSESSMENT AND ECONOMIC EVALUATION: RECENT DEVELOPMENTS IN SPAIN

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The financial crisis will, we have to assume, come to an end and the tax policies of the Member States of the European Union or, at least, of the Eurozone will start to be coordinated. This extension of the scope of the European Union, which is critical for its own survival, will open the path to a greater coordination of health policies and a harmonisation of the public health insurance systems to the west of the continent. As a result, the single European medicines market, which is very limited today, is likely to experience new advances. These will probably not be limited to safety, effectiveness and quality assessments and the free circulation of products. In the long term, and following the fiscal redeployment of the European Union, they are likely also to include an alignment of pricing and reimbursement policies.

With such a forecast, we might reflect on the path travelled by the European Medicines Agency (EMA), national agencies and health systems with regard to the criteria and procedures for marketing authorization and their relation to economic evaluation studies, nowadays common in some Member States to support rational pricing and reimbursement decisions.

The European efficacy and safety evaluation has traditionally focused on the risk/benefit balance of the specific drug without making comparisons to define the added value (positioning) of the new drug relative to existing treatments. A drug that does not offer advantages over those already available may still be approved. The authorization and supporting documents thus do not include recommendations for clinical use. This state of affairs is changing and EMA and the national agencies are taking steps towards the introduction of comparative or relative efficacy or effectiveness assessments, as part of the authorization

criteria. Relative efficacy can be defined as the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions. Relative effectiveness can be defined as the extent to which an intervention does more good than harm compared to one or more alternative interventions for achieving the desired results when provided under the usual circumstances of health care practice (Working definitions adopted by the European Union High Level Pharmaceutical Forum 2008, p.58).

Furthermore the risk-benefit balance is now assessed, not just when authorizing a drug but throughout its lifetime. European legislation increasingly requires the constant monitoring of the benefit-risk ratio of authorized drugs. Assessments of comparative effectiveness and safety profile against established standards have been taking shape as decision criteria. Now it is considered essential to ponder not only the risks but also the benefits compared to the alternatives when assessing a drug. Therefore, risk management plans required from companies as part of the authorization package are becoming relative risk-benefit relationship management plans.

According to European Union regulations, when assessing the balance between benefit and risks of a new product, comparative efficacy evaluation "should not be conducted in the context of the marketing authorization, for which it is agreed that the fundamental criteria should be retained" (Regulation EC Nº 726/2004. Introduction paragraph 34). But the same paragraph recognizes that "Member States have developed an evaluation of the comparative efficacy of medicinal products aimed at positioning a new medicinal product with respect to those that already exist in the same therapeutic class. Similarly, the Council, in its 'Conclusions on medicinal products and public health', adopted on 29 June 2000, emphasized the importance of identifying medicinal products that presented an added therapeutic value"… "It is useful in this respect to allow for the possibility of gathering information on the methods used by the Member States to determine the therapeutic benefit obtained by each new medicinal product."

Although superiority versus existing drugs or treatments in the European Union is not a requirement, relative efficacy or effectiveness is a part of the evaluation. When established medicines are already available, the normal or even mandatory design for clinical trials is to use controlled trials (or arms in a trial) enabling comparison against an active comparator, on a case by case basis (EMA 2004). Therefore, if the new product seems to compare unfavourably with an established medicinal product, comparative trials or indirect comparisons should be provided by the applicant (Avendaño 2011).

The EMA Roadmap 2015 points to the different approaches of the licensing process (performed by regulators as EMA itself and national agencies) and the

relative-effectiveness and cost/benefit assessment processes (carried out by Health Technology Assessment - HTA - bodies). It also emphasizes the need for closer interaction and collaboration between both parties, as demanded by the High Level Pharmaceutical Forum. This is to be accomplished by increasing transparency of European Public Assessment Reports and engaging with HTA bodies in the early stages of development of a medicine and throughout the medicinal product's lifecycle in order to align regulators' and HTA bodies' evidence requirements (p.22).

Of particular interest in this respect is the work already undertaken within the framework of the European Network for HTA Joint Action by a specific working party on the subject. It has developed guidelines for conducting a rapid relative effectiveness assessment as part of the Methodology for HTA Core Model Application for Pharmaceuticals (European Network for HTA Joint Action 2012).

All these developments are related to cost-effectiveness analysis, because its very essence is to compare between alternative treatments and to consider opportunity costs, which may vary over time as the characteristics of the comparators change. From these premises, one could deduce that a comprehensive approach may arise in the future since "the development of methods and data collection for relative-effectiveness assessment and cost-effectiveness assessments can be done within a coherent HTA framework" (Jönsson 2011, p.98).

In Spain the central government and seventeen regional health authorities ("comunidades autónomas") are responsible for public health, health services and drugs to different extents. Sometimes responsibilities are shared, implying a certain degree of coordination and cooperation. Over time problems have arisen with regard to how the assessment of the relative effectiveness and the added therapeutic value of drugs should guide clinical practice.

On the one hand, the Spanish Medicines and Healthcare Products Agency (AEMPS), part of the EMA system, evaluates the safety, efficacy and quality of drugs in the context of marketing authorization procedures. In 2011 and 2012 two laws[4] laid the foundations for introducing economic evaluation into pricing and reimbursement decisions. However, the laws were broad with very general provisions that were not developed in detail and therefore not enforced. For the moment economic evaluation in Spain is not required for pricing or reimbursement decisions, at least not systematically and within the framework of a legally established procedure.

[4] Real Decreto-Ley 9/2011 and Real Decreto-Ley 16/2012.

On the other hand, the regions responsible for the management of health services – in this vacuum where economic evaluation is not legally established - have to decide upon the effective inclusion of drugs into clinical practice, set priorities and make recommendations for use. These decisions require a comparative assessment between existing therapeutic options. Thus, in recent years, the regions have been considering the clinical impact and budget implications of new drugs and established specific regulations for their utilisation. This has sometimes resulted in different regional assessments and conflicting results concerning the therapeutic value of drugs, and consequently different recommendations for clinical use. The process has generated confusion and distrust by professionals and patients, as well as equity issues, since access to medicines may be different among regions[5].

More recently there have been important steps to solve this issue and achieve a unified drug efficacy or effectiveness assessment within the National Health System. In May 2013 the Commission of Pharmacy of the Interregional Council of the National Health System (CISNS) approved in an agreement including a regulation and a procedure for the new **Therapeutic Positioning Reports** (IPT is the acronym in Spanish). As for the method, it is intended to engage the relevant health authorities[6], base the positioning judgments on scientific evidence, avoid duplication, maintain consistency and share resources. The result will be a single assessment report accepted by the entire National Health System (Ministerio de Sanidad, Servicios Sociales e Igualdad 2013) regarding the positioning of the new drug in therapy.

Although IPTs are primarily intended to provide guidance to clinicians, the economic consequences are many. This is because "relative effectiveness is thus a key concept for the assessment of value and thus for pricing and reimbursement" (Jönsson 2011, p.98). The Ministry of Health has highlighted this point: the reports will be used "as one of the bases for selective reimbursement and the pricing of medicines and also as a reference for any action related to the acquisition and promotion of the rational use of the drugs" (Ministerio de Sanidad, Servicios Sociales e Igualdad 2013, p .5)[7]. "The

[5] The Deputy Director of the DGF explained the problem clearly: "The high prices asked by the holders of marketing authorizations for these medicines require that their introduction is accompanied by restrictive measures in order to lessen to some extent their economic impact. The result is often a delay in price and financing decisions, and many times the repetition of these assessments at regional and hospital level, subsequently resulting in delays in the availability of these drugs for patients who could benefit from them" (Lens 2013).

[6] It could be argued whether the participation of the regions in these efficiency and efficacy assessments was legally mandated and appropriate, or if they should concentrate on their health services management duties.

[7] This sentence could surely have been written more respectfully of public health priorities. Information on relative effectiveness is key for clinical decisions and rational use. Economics comes later.

immediate practical use of IPTs is to guide cost-effectiveness analysis and budget impact calculations, which are deciding elements for pricing and reimbursement ... "(Lens 2013).

There is no doubt that IPTs are a step forward that will facilitate implementation of cost-effectiveness analysis as a legal requirement in Spain and, in general, the development of economic evaluation. Firstly, "assessments of cost-effectiveness are, in a majority of cases, driven by the evidence on relative effectiveness rather than differences in costs" (Jönsson 2011, p.98). Secondly, therapeutic positioning to identify the relevant comparators shows the strategy to be followed by cost-effectiveness or cost-utility assessments. Pharmaceutical firms will also benefit from reduced uncertainty, as IPTs allow companies to know what are the values most preferred by authorities. Furthermore, as the reports are sufficiently detailed they identify the more relevant clinical trials and health outcomes to be used in cost-effectiveness analyses. Lastly, in a foreseeable future, methodological development and data collection for relative-effectiveness and cost-effectiveness assessments can indeed be done within the HTA framework (Jönsson 2011).

However, it is clear that IPTs are not complete economic evaluation exercises in themselves. They are based on clinical studies and data that allow reaching judgments about efficacy and effectiveness from which "recommendations of use" and "common criteria for drug utilisation in the entire National Health System" are derived. However, for outcome data from clinical trials to be usable in cost-effectiveness or cost-utility assessments, they have to be planned at the outset and developed accordingly. Also, costs are not considered at all by the EMA or the National Agencies in authorisation procedures and thus not considered in IPTs either. Indeed European regulations require that market authorisation decisions do not consider economic constraints. Thus the path from an IPT to an economic evaluation is still long.

The relationship between IPTs and economic evaluation appears somewhat confusing in the texts of the Ministry. In its own words economic assessment is to take place after pricing and reimbursement decisions[8]. It seems that the focus

[8] . "Reports will contain in the first phase the compared effectiveness and safety assessment as well as use and monitoring criteria. Optionally, they may include an economic assessment if GCTT decides so. In a second phase, following the pricing and financing procedures, they shall always incorporate economic valuation and budget impact." (Ministry of Health 2013, p. 6). "The report will be forwarded to the DGF prior to the pricing and financing decision. Following these decisions the report will be finalized, including aspects of comparative economic assessments and budgetary impact. This comprehensive report will be submitted to GCTT for approval and proposal for publication by the Commission of Pharmacy"(Ministry of Health 2013, p. 12).

is on direct costs deriving from drug treatments. But, needless to say, these are not the only costs to be considered. In addition, non-pharmacological types of costs may vary when the medication changes. It also seems that the main focus is on budget impact studies. Yet, we must remember that these are limited in scope and that the general perspective of society as a whole, which may differ from that of the payer, is always relevant in economic evaluation, though avoidable for practical purposes. Even though in times of crisis budget constraints seem to be ubiquitous, the distinction between the two approaches must never be forgotten.

The agreement of the Commission of Pharmacy of CISNS, approved in May 2013, establishes a Therapeutic Positioning Coordination Group of drugs for human use composed by AEMPS (which provides the secretariat), the Pharmacy Directorate General of the Ministry, and one representative from each region. The IPT for each drug will be drafted by an evaluation team composed of the AEMPS and two regions designated in rotation. The agreement also provides a well-defined procedure with a reasonable schedule that includes a hearing process for pharmaceutical firms to present their views. The reports have started to be published in mid-2013. The transparency with which the process has begun is remarkable, since the relevant documents are posted on the website of the Ministry of Health.

Finally, IPTs now have a legally binding status. According to Law 10/2013: “The actions aimed at establishing the position of a drug in the pharmaceutical benefits scheme and its comparison with other therapeutic alternatives shall have a common technical and scientific basis for the entire National Healthcare System and will be developed within the framework of the positioning reports issued by the Spanish Agency for Medicines and Health Products. These reports will be legally binding.”

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A TRIBUTE TO BENGT JÖNSSON AND "FIRST-GENERATION" HEALTH ECONOMISTS

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INTRODUCTION

In the old days, before ICERs and league tables and cost-effectiveness acceptability curves, and well before the creation of ISPOR, HTAi, IHEA, NICE and SBU, Bengt Jönsson was already toiling as a productive health economist. In those days, health economists were simply "plain vanilla" economists who happened to be focusing on health care topics. Bengt was and is a key member of the first generation of health economists who were developing the methods and applications for the field of economic evaluation in health care, and building the academic programs to foster the research and train the next generation of practitioners. A full list of Bengt's early compatriots is too numerous to include here, and naming anyone risks offense to worthy candidates omitted, but most lists of notables would almost certainly include individuals such as Ron Akehurst, Martin Buxton, Tony Culyer, Mike Drummond, Frans Rutten, Milt Weinstein, and Alan Williams.

In honouring Bengt's achievements and longevity, it seems only appropriate to tip one's hat at the outset to his cohort of "greats" and to reflect on larger trends in economic evaluation in health care. Suitably, Bengt's career tracks the major

developments in the field. One might group his contributions in any number of ways, but somewhat idiosyncratically, I will highlight four categories.

APPLIED ECONOMIC EVALUATION

Economic evaluation in health care has grown rapidly since Bengt began his work. As one indication, the Tufts Cost-Effectiveness Analysis Registry now lists some 3500 cost-utility analyses (CUAs) published in peer reviewed journals. Between 2000 and 2009, over 2,000 CUAs were published, compared with 340 during the 1990s and only 20 or so in the 1980s. The analyses pertain to a diverse array of interventions and diseases. We now take this vast inventory for granted, but it rests on the shoulders of those first generation health economists who set the foundation.

A perusal of the literature shows Bengt to have been an early and active contributor. A paper from the late 1970s examined the cost of diabetes and diabetes control in Sweden (Jönsson 1983). Another from the era evaluated the value of prevention (Jönsson 1985). As the years progress, his work applied broadly, covering economic evaluations of interventions for diseases from arthritis to multiple sclerosis to osteoporosis.

Perhaps his most noteworthy contribution in this regard pertains to an economic evaluation in the mid-1990s of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. The Scandinavian Simvastatin Survival Study (4S) had recently shown that simvastatin reduced coronary events and overall mortality in patients with preexisting coronary heart disease (Scandinavian Simvastatin Survival Study Group 1994). However, an important question remained about whether its use was cost-effective, given the large populations and potentially high costs involved.

In a series of papers, Bengt and colleagues estimated the cost-effectiveness of lowering cholesterol with simvastatin -- overall and for subgroups defined by age, gender, and pretreatment cholesterol levels (Jönsson et al 1996; Johannesson et al 1997). Using the clinical data produced by the 4S study, they concluded that the cost per life-year saved of simvastatin in the treatment of post-myocardial infarction and angina patients was well within the range typically considered cost-effective. Their cost-effectiveness analysis published in the *New England Journal of Medicine* concluded that simvastatin was cost-effective for treating patients with coronary heart disease in both men and women at the various ages and cholesterol levels studied.

While these papers did not represent the earliest cost-effectiveness analysis or the only ones published at the time, they were important on several levels. They

confirmed that statins were cost-effective for secondary prevention of coronary heart disease. While earlier studies had *modeled* the impacts of statins in secondary prevention using extrapolations from epidemiological data (Goldman et al 1991), the Swedish group's CEA was based on the costs and effects of treatment obtained directly from the randomized clinical trial. Thus, it served to validate earlier models and to demonstrate the practicality and usefulness of trial-based cost-effectiveness analyses. Moreover, the papers were exemplary in their careful analysis and conservative assumptions. They made no assumptions about the impact of treatment on cerebrovascular events, for example, because such effects were only suggested by post-hoc analysis. They estimated the reduction in risk only for the first coronary event and not for subsequent events, because the group lacked sufficient data to permit a stable estimation of the risk of subsequent events. As an indication of its importance and meticulousness, the group's *NEJM* paper remains one of the few cost-effectiveness analyses published in that journal, and the rare one published there that was funded by a pharmaceutical manufacturer.

COST-BENEFIT ANALYSIS AND CONTINGENT VALUATION

Cost-benefit analysis (CBA) has never gained the foothold in health policy anticipated by its early promise. For many years, published CEAs in health care have far outpaced CBAs, presumably because CEAs allow analysts to quantify health benefits in "health" rather than in monetary terms and thus confer some practical and political advantages in that they sidestep some of CBA's measurement difficulties and ethical dilemmas (Neumann 2005). However, CBAs offer advantages because they are more firmly grounded in principles of welfare economics and they remain an important implement in the health economist toolkit.

Again, the literature reveals Bengt as a contributor on some early cost-benefit analyses with applications to hepatitis B vaccination and dental implants, in additional to his Ph.D thesis in 1976 on the subject (Jönsson et al 1987; Jönsson et al 1990; Jönsson 1976). He was also – along with Magnus Johannesson -- a co-author on a key methods/review paper on cost-benefit analysis in health economics (Johannesson and Jönsson 1991). This paper described the contingent valuation (CV) approach and argued for its application, while acknowledging and critiquing issues concerning the reliability and validity of the method. While not the first paper to recognize the CV method and its potential, the paper stands as a landmark review and analysis, and likely helped spur a boomlet in CV applications over the ensuing decade, including some by Bengt and colleagues (Johannesson et al 1991).

HEALTH TECHNOLOGY ASSESSMENT

Beyond his applied economic work, Bengt has had an outsized impact on the development of health technology assessment, within Sweden and in the European Union and beyond. His papers on the topic span a wide range from the role of economic evaluation in the pricing and reimbursement of medicines (Drummond et al 1997) to health technology assessment for new oncology drugs (Jönsson 2013).

A brief recitation of some organizations he served in various advisory or other capacities hints at his influence: the Swedish Council for Medical Technology Assessment (SBU); the Swedish Social Insurance Agency; the Committee on Funding and Organisation of Health Services and Medical Care in Sweden; Karolinska University Hospital; and the National Board of Health and Welfare, Sweden. To this list, one should add countless advisory boards for pharmaceutical companies to help guide their clinical and economic research programs.

"ACADEMIC ENTREPRENEUR"

A final area pertains to Bengt's role as "academic entrepreneur," an oxymoronic-sounding phrase that nonetheless underscores the important responsibility that certain scholars assume as builders of research programs. The academic entrepreneur is a specialized breed that is essential for the sustenance and growth of healthy research ecosystems. He or she is a jack-of-many-trades that combines academic ability with a diverse set of functions: fundraiser, manager, administrator, politician, diplomat, visionary, and arm twister. In Bengt's case, that meant playing this role to construct health economics research groups in no fewer than three sites in Sweden: Lund, Linköping, and Stockholm.

He was also the founder and director of the Swedish Institute for Health Economics (IHE) in Lund and longtime member of the IHE Board, as well as founding director of the Centre for Health Technology Assessment (CMT) at Linköping University and president of the International Health Economics Association.

CONCLUSION

In a paper published almost twenty-five years ago, Bengt Jönsson asked, "What can Americans learn from Europeans?" (Jönsson 1989). He meant it in the way of what Americans can learn about health policy. But reflecting on the matter in

a tribute such as this -- especially one offered by an American -- the question seems imbued with larger meaning.

Many of those first-generation economists who developed the methods of economic evaluation were, in fact, European. We Americans have learned a lot from them. They provided the methodological framework, developed the applications, constructed and shaped the academic programs and professional societies, and advised the relevant government institutions. Those individuals, of a certain time and place, forged the new discipline, carved the emerging landscape and contributed to an intellectual shift in the field with important policy consequences. Bengt Jönsson's place among them is firmly established. To an American's eye, he seems even more European and of the Old World than the rest. A tribute to him and his colleagues is an opportunity to recognize their achievements and contributions and one that seems long overdue.

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BENGT JÖNSSON AND THE COST OF BRAIN DISEASES

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It has always been intuitively clear to me that health economic data are of paramount importance in the struggle to improve healthcare services. As president of the International Headache Society and in my then capacity as vice president and later president of the European Federation of Neurological Societies, I started looking around for a health economist with whom we could collaborate. At the time most health economists did not believe in indirect costs. They were only willing to calculate and take into consideration direct health care costs. Even direct non-medical costs were not often accounted for. This struck me as highly unreasonable because one type of cost seemed to me as important as the other. Money would just come from different sources. On this basis I met and discarded several health economists. In association with the introduction of beta interferon treatment of multiple sclerosis in Denmark I had the good luck to meet Bengt Jönsson. He presented data about the cost of multiple sclerosis and here I met a much more open attitude which meant including all relevant costs of a disorder. I followed up on this acquaintance by inviting him to give an overview talk about health economics in relation to headache disorders and again I was struck by the clarity and vision in his presentation.

A few years later I had started and was the first president of a new organisation called European Brain Council where all different specialties with an interest in the brain as well as patient organisations, basic scientists and research oriented

industry worked together to promote brain research and the care of patients with a brain disorder. Brain research in Brussels had been seriously overlooked and the European Brain Council started a long drive to improve the situation. People in the commission, notably the commissioner Philippe Busquin, were attentive to our views but it was clear that simple arguments were not enough. I therefore conceived the idea of a huge Pan-European study of the cost of all brain disorders. Most people considered this a totally crazy idea as it had never been done before with such a large group of disorders. I was adamant, however, that such a study must be done and I managed to secure financial support from the Danish drug company Lundbeck. I furthermore had at my disposal a large number of neurologists and psychiatrists with expertise in epidemiology who were willing to work voluntarily.

I contacted Bengt and he immediately caught on to the idea. I think he, like myself, feels attracted to seemingly impossible tasks. It triggers his intellect because it requires thinking out of the box. His company at that time, Stockholm Health Economics, was engaged to do a large part of the work together with the voluntary epidemiologists. More than 100 people worked on this project for a couple of years and the project would have been completely impossible without the enthusiastic leadership of Bengt. Difficulties were innumerable. We had to work with a number of doctors who were high calibre scientists and who therefore found it very difficult to work with the limited available data. Data were missing from most countries of Europe – for some countries in one disease and for other countries in another disease. Bengt developed a health economic model where available data were summarised for each disease. Then values both for the epidemiology and for the costs of each patient per year were imputed for all of Europe taking in consideration a number of health economic factors. In this way it was possible to obtain the costs of one disorder and the same procedure was repeated for all disorders where data were deemed sufficient although, in most cases, very far from being optimal.

Together Bengt and I made the whole orchestra play together and we managed to publish the Cost of Disorders of the Brain in Europe as a whole issue of the European Journal of Neurology in 2005. This was just in time before the program for the 7th Framework Program of research of the European Union was being finalised. The data were presented in Brussels and elsewhere and had tremendous impact. These data were probably the single most important of many factors leading to a huge increase in the funding of brain research at the European level. It actually increased from 260 million Euros in the years 2003-2006 to 1.47 billion in the years 2007 to 2013. The study was followed up by national papers about the cost of brain disorders in each single country and also by disease specific papers describing e.g. the cost of headache disorders in

Europe. All in all more than 40 publications resulted from this study with a budget of only 600,000 Euros.

During the course of this study Bengt and I became very close friends. We also did a study of the funding of brain research in Europe called “Resource Allocation to Brain Research in Europe” which was published in 2006. It showed how poorly brain research was funded compared to several other fields of biomedical research. Also this study has had big impact on research policies in Europe.

The tradition in the European Commission has been to rotate interests from one framework program to another. It was therefore likely that the next framework program called Horizon 2020 would greatly reduce the funding of brain research. In order to avoid that and because better data were available, we decided to repeat our pioneering study of the cost of disorders of the brain. In the meantime new cost and epidemiological data had become available for many of the disorders included in the first study and data were now sufficient to include six new disorders. We used the same approach and worked very closely together, ably assisted by Bengt’s former company, now part of a major American company but still located in Stockholm. The results were astounding. The cost of disorders of the brain doubled to a staggering 800 billion Euros per year making brain disorders by far the most costly group of disorders. The cost equalled cancer, heart diseases and diabetes combined. Again we managed to get this publication out before the decisive moment of the program for Horizon 2020. It was our impression that these enormous costs had great impact in the commission but we cannot say for sure. It seems, however, that brain disorders will still have big attention in Horizon 2020. We immodestly claim that this is not least due to the Cost of Disorders of the Brain in Europe in 2010 study.

It seems clear from the above that the basic neuroscientists, clinicians caring for patients with neurological or psychiatric disorders, patients with a brain disorder and the pharmaceutical industry working in the CNS field all owe a great thanks to Bengt for his pioneering work on the health economics of these disorders.

A PAYER PERSPECTIVE

Sören Olofsson

Former Head of Stockholm and Skåne County Councils

Health Economics has been instrumental in the development of health care organizations, enabling decision-makers to balance their financial responsibility and scarce resources with the need for better and more equitable publicly funded health.

My payer experience is limited to Sweden where I have been part of a rather dramatic development of how health care is organized and managed. Many of these development steps have been inspired by the introduction of health economics into the public debate and the presence of health economic scientists in that process.

The importance of Bengt Jönsson in this development can scarcely be underestimated. He has not only been a strong driving force for developing the discipline in three universities, including training a lot of young researchers who have been quickly absorbed by various stakeholders like the pharmaceutical industry, government agencies and health care organizations, but he has also to a very high degree been part of, and inspiration to, a public debate on health care policy.

In the last three decades we have experienced a rapid development in the organization and management of health care. Change has been driven by many forces.

One of these forces is the discussion about the role of politics in health care, emphasizing the duty of representing the population and/or patients and therefore expressing needs and formulating demands leading to health policies that go beyond responsibility only for service delivery. Bengt was elected to the Board of Directors of the Karolinska University Hospital in 2004. The hospital had just merged with Huddinge University Hospital. The Board had two to three years of intensive work to make the merger successful both in organizational and financial terms, and not the least in creating even stronger position in research and development. Besides the difficult task of merging two organizational cultures, the Board had to guide the hospital management team in the negotiations with The Stockholm County Council over annual production

contracts and their related fee structures as well as short and long term investment plans. They also had to work very closely with the Karolinska Institute in creating a working environment and daily integration between the two organisations that combined clinical effectiveness with extensive and high profile research and education. Bengt's research background and knowledge was of great importance in this process.

Another driving force was the rapid development in technology, enabling us to do so much more to cure or help patients, often at the expense of accelerating cost, not only because of expensive technology but also because it enables longer survival and consequent greater consumption of health care resources. In times of very rapid technology and skills development this calls for a parallel development of analytical tools to predict needs and calculate investments in the infrastructure of health care. The issues of affordability and cost-effectiveness had to be resolved through the mutual collaboration of the medical profession, health economic scientists and the political decision-makers.

In a fragmented health care decision-making system, assessment of technology is difficult to organize and even more difficult to implement. From the late 1980s onwards this was further complicated by the very important development of patient empowerment. Freedom of choice of provider has gradually developed from a local or regional level to a national and even European level. As politicians focused more on population needs and demands they also made room for greater diversity in the production of health care. The development of independent producers working on contract with the political purchasing organization in turn led to a need for sophisticated contracts with providers. It also increased the need to control the expansion of costs by deciding on priorities and assessing new medical technologies Productivity improvements and cost–effectiveness were both stimulated via payment systems and public procurement, although some of the incentives created were counterproductive and led to a focus on quantity rather than quality.

Accessibility has become a strong political priority, which of course has led to an increased interest in developing incentives to balance the demand for accessibility with the need for measuring process quality and outcomes. With an increased focus on documentation and information structure the coverage of quality registries grew and new registries were started. These registries gave tremendous opportunities for epidemiologic and health economic research. This will further improve the possibilities for payers to obtain health technology assessments of innovative technologies and provide an opportunity to sort out how best to handle non evidence-based treatments. It also offers an opportunity to combine clinical research and clinical practice follow-up, which I foresee will be very important especially in early and controlled introduction of new drugs.

Personalized medicine will further call for national coordination with the possibility of government agencies and payers following-up regulatory decisions, reimbursement and clinical use, and revising them.

Bengt has been very influential in creating methods and suggesting processes that would enable decision makers to base their decisions on evidence, while simultaneously generating real live clinical data to allow scientifically based conclusions to improve outcomes and cost-effectiveness in health care. He has early on formulated the need to create evidence bases that reduce uncertainties and inequalities in the introduction of innovations, recognizing that the value of an innovation might be different in a clinical setting compared to the more limited base in the innovation process. With his societal insight he has been instrumental in introducing value based pricing of drugs, recognizing the budgetary aspects of a health care system with 21 regional political organizations each with their own taxation rights.

Bengt's important role in the ongoing debate on the development of health care has been accompanied by very successful initiatives for executive training programs for professional managers in health care. Throughout his career he has been most willing to advise and generate expertise to all stakeholders.

I would like to conclude by quoting from two slides that express the very valuable combination of scientific knowledge and societal understanding that makes him such an important and influential person. These quotes are from Bengt's presentation at the Oncopolicy Forum 2012.

WHAT ARE HEALTH CARE SYSTEMS LOOKING FOR?

- Improvements in outcome (population health)
  - including equity aspects
- Evidence of cost-effectiveness
  - which patients will benefit most
- Well constructed evidence base
  - clear definitions of which patients that would be treated

THE KEY POLICY ISSUES FOR HEALTH TECHNOLOGIES

- Innovation, reimbursement and optimal use
  - The major challenge is the move of the evidence base from clinical trials to clinical practice
  - from efficacy to relative effectiveness and cost-effectiveness"

DEMOGRAPHY, SUSTAINABILITY AND GROWTH
NOTES ON THE SUSTAINABILITY OF HEALTH AND PENSION SYSTEMS IN EUROPE

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"*The net present value of future increases in health care and pension spending is more than ten times larger than the increase in public debt due to the crisis. Any fiscal consolidation strategy must involve reforms in both these areas. Given the magnitude of the spending increases involved, early action in these areas will be much more conducive to increased credibility than fiscal front-loading […]. Altogether, in the G-7 economies, the key policy challenge over the coming decades will be to make health care systems sustainable by containing costs as well as creating fiscal space in other areas so as to adapt to societal preferences and needs for a greater share of ageing-related spending [...]*"

(IMF, Ten Commandments for Fiscal Adjustment in Advanced Economies, Commandment V).

INTRODUCTION

Population ageing is one of the most important challenges that Western countries have been facing in recent decades, and its effects are expected to hit economies even harder in the near future. The impact on health expenditure growth on the other hand is still a debated empirical issue, with mixed evidence in favour and against the "healthy ageing" hypothesis or the "expansion of morbidity" one. In their seminal paper, Gerdtham and Jönsson (2000) attribute a secondary role to ageing in explaining the observed and expected increase in acute health care expenditure growth as a percentage of GDP, identifying income elasticity and technology as the primary drivers of health expenditure growth (see also Pammolli, Magazzini and Riccaboni 2012; De La Maisonneuve and Oliveira Martins 2013).

* The Authors acknowledge funding from the SwitchProject, Crisis Lab; IMT Institute for Advanced Studies;Cerm Foundation.

Nonetheless, while structural reforms have partly contained the growth of pension costs, health expenditures (both acute and long-term care related) have grown rapidly in the last decades and are projected to increase as a proportion of state budgets according to all sources, such as the OECD and the European commission.

Demographic changes and the current negative economic outlook are putting welfare systems under pressure, questioning the sustainability of current levels of health and pension services for (near) future cohorts of beneficiaries. On the hand, lower fertility rates and higher life expectancy are not compensated by immigration flows. This induces population ageing, which increases the ratio of beneficiaries of welfare systems with respect to contributors. On the other hand, the decrease in the share of active population and, within this, the population of workers due to rising unemployment, is increasing the fiscal pressure on income and growth within PayGo budget rules, which are largely adopted by European Union Member States. As PayGo systems are based on the principle that benefits are paid by current workers, higher entitlements for pensions and health must be paid for by tax increases or cuts in other mandatory spending programs if either the number of dependents increases and the number of contributors decreases, or both.

In view of these challenges and predictions, and along with the many different architectural possibilities for government financing of welfare (mix of public and private, income vs. general revenue taxation, for instance, see Jönsson and Musgrove, 1997), it seems crucial to explore the budgetary mechanisms that may improve sustainability without reducing “universality” and equity of the welfare state. Current welfare systems were largely born in times of demographic and economic boom, in which both fertility and growth rates were constantly increasing. Nowadays, in a profoundly different environment, financing alternatives to PayGo with reduced sensitivity to demographic changes need to be considered.

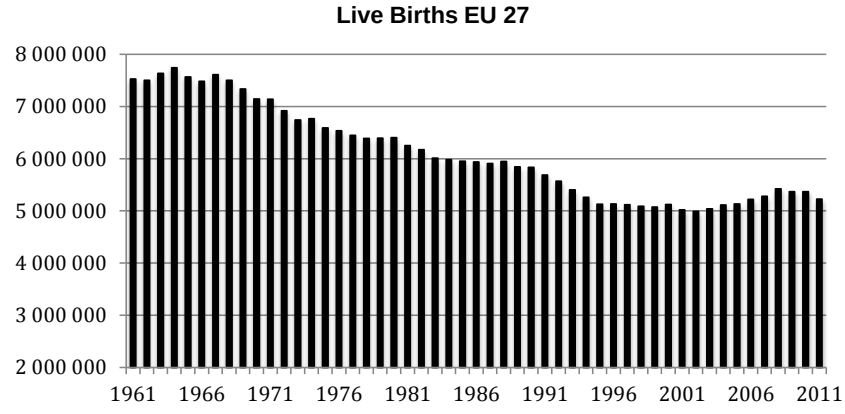
In this paper, we analyse the possible benefits of combining PayGo and Funding to finance health and pension costs to improve the sustainability of European welfare systems.

DEMOGRAPHIC CHANGES IN EUROPE AND THE WELFARE SYSTEM

The current and upcoming retirement of the “baby boom” generation born in the Fifties and Sixties exposes EU pension and health care systems to unprecedented challenges.

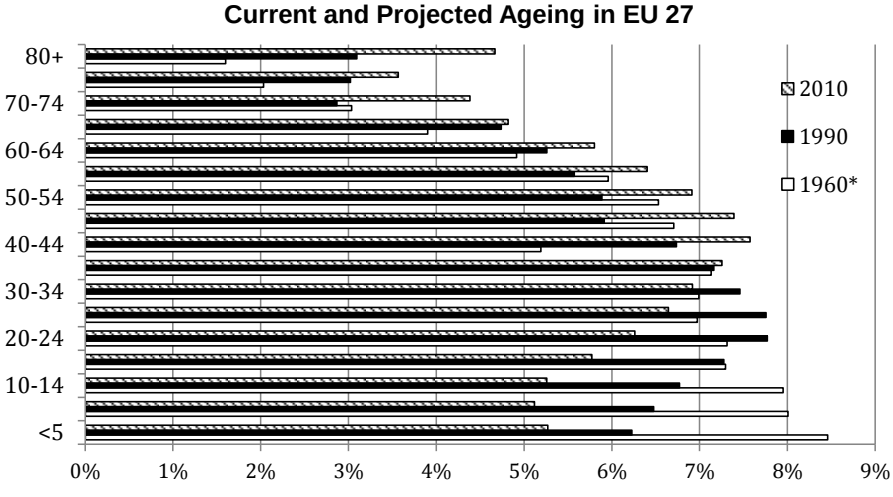
Figures 1 and 2 capture the dramatic demographic change that occurred in the last 50 years. Fertility decreased steadily (Figure 1), while life expectancy increased due to better economic and health conditions. These two phenomena together have determined the profound change in the age structure of the population (Figure 2).

FIGURE 1: NUMBER OF NEWBORNS IN EU27 FROM 1960 TO 2011



Source: Eurostat

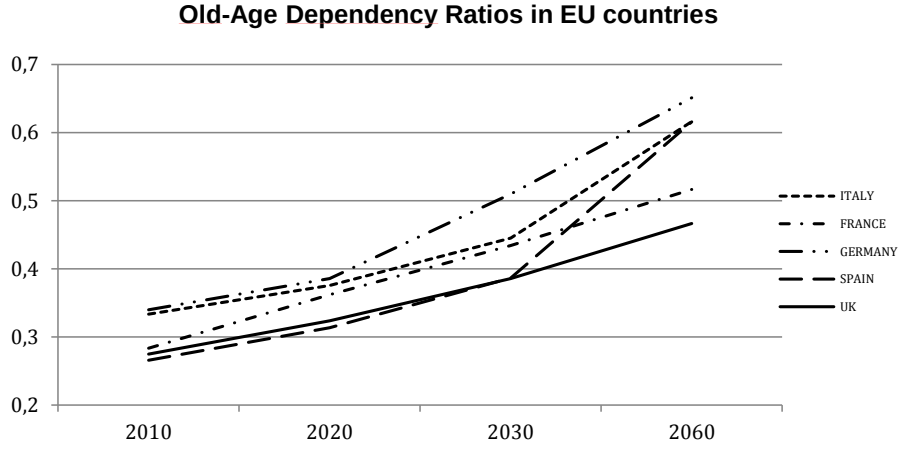
FIGURE 2: AGE-STRUCTURE OF EU 27 POPULATION (1960 FIGURES REFER TO EU15)



Source: Eurostat and Europop2010 Projections. 1960 figures are EU 15 ones.

While in 1960 the largest age cohort was the youngest, actual (2010) figures show that the number of individuals aged 80 or older has almost reached the number of children aged 5 or less. This ageing process does not seem to have slowed its pace in recent years and demographic projections foresee further improvements in longevity. In particular, old-age dependency ratios, which measure the proportion of people beyond working age compared to the percentage of active people are expected to rise sharply in the next decades, as the demographic projections for the 5 most important European countries in Figure 3 highlight. Without adjustments, the direct consequence of this trend is an imbalance between contributions and benefits of PayGo systems prevalent in Western Europe.

FIGURE 3: CURRENT (2010) AND PROJECTED OLD-AGE DEPENDENCY RATIOS FOR FRANCE, GERMANY ITALY, SPAIN AND UK.



Source: elaborations from Europop2010 projections by Eurostat.

Building on Samuelson's (1958) seminal paper, Aaron's "social insurance paradox" (1966) stated that efficiency in PayGo schemes occurs if, and only if, the sum of output and population growth rates is greater than real interest rate. While this condition was fulfilled during the thirty years following the end of the Second World War, today most OECD economies relying on PayGo are far from the conditions that would justify its optimality (See Abel et al. 1989, for instance). In addition, important enough, Aaron's original argument on the optimality of PayGo or funded system was derived under a set of simplifying assumptions and in particular under a constant age-structure of the population.

Today, an almost exclusive reliance on PayGo rules for pensions and health cannot be justified by efficiency arguments. Reasons different from mere efficiency such as equity considerations might, however, justify PayGo financing. Being financed mostly through payroll or personal income taxes, PayGo systems contribute to intra-generational redistribution. In addition, PayGo creates an inter-generational redistributive channel, which takes the form of a direct transfer of resources, and generates a risk-sharing mechanism between generations (Gordon and Varian, 1988). The recent projections contained in the EU Stability and Convergence programs highlight the fact that maintaining the current PayGo-based financing of pensions and health requires a very high burden on contributors, which might have distortive effects.

In this environment, Member States might soon be faced with a dilemma between reducing benefits and coverage and increasing taxes/retirement age. Although some countries have adopted measures to improve sustainability of their public finances, a general common increasing trend in the burden on workers can be detected. In addition, the recent economic crisis has accentuated the combined effects of low fertility rates and longer life expectancy, reducing further the number of active people due to rising unemployment and slowing output growth.

As a consequence, the EU is facing a *welfare reform trap*, since there does not seem to be room for a further increase of taxes and social contributions, in a context in which the great debate is how to create employment. A difficult balance must be pursued, in which reforms that aim at maintaining the core distinctive features of the European Social Market Economy do not depress investment and production nor discourage employment. In this context, the effects of alternative funding models deserve to be assessed, in order to explore whether they might prevent the seemingly inevitable cuts in services.

PAYGO AND FULLY FUNDED SYSTEMS

In this changing demographic context, a partial shift to funding welfare can be considered an option to reduce the actual and projected excessive PayGo burden. In funded systems, benefits are paid from individual funds built over time by the very same individuals who receive the benefits, rather than from payroll or personal taxes as in PayGo systems. In fully funded programs, the capital accumulated during the working life and the future benefits are influenced by market fluctuations. In PayGo systems, future benefits are influenced by demographics and macroeconomic developments.

Some authors have supported funded programs as alternative to PayGo, on the basis that contributions produce fewer distortions in the labour market and on growth, and that stock markets produce higher returns than PayGo schemes.[9] Sinn (2000) provides a critical analysis of these arguments, highlighting however that, in light of demographic changes, a shift to a greater level of funding vis-à-vis PayGo financing is desirable to reduce the exposure to the variability of demographic conditions. Overall, a partial transition to a funded system can reduce uncertainty of future benefits, contain the impact of demographic trends, and limit the threat of ex post redefinition of the rules of the system due to budgetary "emergencies".

Recent literature has highlighted the serious threats to the sustainability of PayGo schemes not only from longevity improvements per se, but also from the uncertainty surrounding the estimates of its intensity. The possibility of unforeseen changes in longevity (longevity risk) is now considered one of the most important risks for the solvency of pension schemes. Such changes affect both the likelihood of becoming a beneficiary and the time spent being a beneficiary of the welfare system.

Mixing PayGo and funding can indeed minimise the exposure to the uncertainty surrounding the net flows in a pension system, resulting from the variability of the balance between the cohorts of contributors and beneficiaries due to macro-economic and demographic factors in PayGo schemes, and the tendency of financial markets to fluctuate in fully - funded systems. Longevity risk affects both funding arrangements to some extent.

Some studies analysed the features of these two different forms of financing separately. In particular, in the context of ageing societies, the literature has focused on PayGo efficiency costs and its tendency to induce distortions on labour and on capital accumulation. Feldstein (1996) showed that an excessive reliance on payroll taxes can induce a deadweight loss, distorting demand and supply on the labour market, retirement decisions, occupational choices, and effort. Moreover, an excessive reliance on PayGo tends to depress savings and capital accumulation. This, in turn, affects investment and, ultimately, growth.

While a transition from PayGo to fully funded schemes can produce a positive impact on the labour market and on economic growth in the medium or long run, welfare losses in the short and medium term for the "transition generation"

[9] For example, Feldstein and Samwick, 1997 and Lindbeck and Persson 2003, highlight the most relevant features of funded systems: a) lower uncertainty on future earnings and benefits at an individual level; b) lower dependence of sustainability level on future demographic structure, at the cost of a higher vulnerability to capital market fluctuations; c) lower distortions in the labor market and dependence on domestic labor market; d) enhanced capital accumulation, increased capital stock available through funds.

(which finds itself in the unpleasant position of "paying twice") have been studied extensively [10]. Until the transition is completed, current benefits of the elderly can be financed only through a reduction of public expenditure in other parts of the budget, or, less credibly, through higher taxation or additional government borrowing. In any case, a Pareto-improving transition requires a compensation for the generations working immediately after the reform. This is difficult, but not impossible, since the transition can be smoothed through the adoption of "hybrid schemes", with both funded and PayGo-financed benefits.

Recently, McGrattan and Prescott (2013) have argued that for the US economy it is possible to design a transition path obtained by progressively shifting contributions to a fully funded system, which can produce welfare gains to all cohorts, "transition" ones included. Medium term effects on growth will also likely occur because a balanced funding architecture can contribute to capital accumulation and generate positive incentives for labor supply and demand.

CONCLUDING REMARKS

In the light of the above trends and scenarios, a necessity towards a reconsideration of the funding mechanisms of welfare is emerging. The exclusive reliance on PayGo to fund health care and pensions seems to conduct to long-term challenges in fiscal sustainability, with consequent depressing effects on economic growth.

In this Chapter we have proposed some reasons why a combination between PayGo and fully funded schemes might improve sustainability of pension and health systems in Europe. Such a coexistence of a PayGo and a funded component should fit into a common multi-pillar system for pensions and health care, a possible option entailing a PayGo universalistic pillar, a second, funded, mandatory tier, and a third private, voluntary pillar.

However, even a correct balance between PayGo and funding might be insufficient to prevent other interventions on current welfare schemes such as revisions of benefit rules. Nonetheless, we claim that a broad convergence of solutions to finance health and pensions systems can be effective in lowering

[10] Some authors have analysed theoretically the implementation and the effects of a transition. For instance, Raffelhüschen's (1993) analysis shows that a modest efficiency gain is possible for Germany's transition to a fully funded system by financing the old pensioner and compensating loser with borrowing and taxation. Kotlikoff (1996, 1998) analyzed the case of United States, concluding that a shift to a fully funded system can be Pareto-improving under certain conditions.

the uncertainty regarding future sustainability of welfare systems and can carry over positive effects on growth as well as on capital and labor mobility.

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COST-BENEFIT ANALYSIS AND THE USE OF INDIVIDUAL'S WILLINGNESS-TO-PAY FOR HEALTH IMPROVEMENT IN THE HEALTH CARE

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INTRODUCTION

The purpose of Bengt Jönsson's thesis (1976) was to demonstrate the way in which economic theory and method can be used to clarify the resource problems of the medical sector. It should be noted that Bengt's economic problem formulations and estimations were intended to improve the political and administrative decision process, not the medical decision process itself. Economic theory in health economics has mainly been represented by what is called welfare theory, and as Bengt points out, welfare theory starts from individual's evaluation and choices. When welfare theory is used for allocation decisions in particular situations we call it cost-benefit analysis, "sometimes in its attenuated form cost-effectiveness analysis" (Williams 1976, p.2).

When Bengt wrote his theses, there was apparently a tendency in health economics "to concentrate too heavily on narrow economic variables such as treatment costs and production loss" (Jönsson 1976, p.11). Already in the introduction of his thesis Bengt said "to conduct a cost-benefit analysis, we have instead to determine and evaluate the resultant gain in welfare and to compare this with the value of the corresponding resource sacrifice" (Jönsson 1976, p.11). It is obvious that he was not satisfied with the applications of health economic appraisals conducted so far and he thought that the researchers' formulation of the problem was too often inadequate. One example was that those formulated the problem used a too narrow perspective. Another was that the decision problem is hardly ever "all or nothing" but usually "how much more" or "how much less", as was pointed out by Alan Williams (1976, p.6), the

discussant at Bengt's dissertation. In Bengt's language we read "It is not the absolute size of the social costs (of a disease) that is interesting; it is how far these can be reduced" (Jönsson 196, p.125).

An economist's contribution to decision making in health care is, however, not limited to problem formulation, but also includes guidance on valuation problems generally. Bengt starts from the basic premise that cost-benefit analysis is ideally based on consumers' own valuations of health as it would be revealed in a perfect insurance market, if we had one.

Two of the economist's major contributions to resource allocation analysis in health care are making the formulation of the problem clear and providing methods for valuing health. Bengt's contributions to the development of health economics in these two aspects are significant. The purpose of this paper is to provide some example from Sweden, where problem formulation and valuation method is of the utmost importance for the outcome of the analysis. The examples are based on the authors' own experience and involvements and are therefore not limited only to the health care sector but also include economic appraisals in the transport sector.

COST BENEFIT ANALYSIS OF ROAD TRAFFIC SAFETY

Allocation of public resources for safety, e.g. investment in new or safer roads, requires knowledge of people's valuation of improved safety. In Sweden, the Swedish Transport Administration (STA, Trafikverket) is responsible for road maintenance and road construction and for the execution of cost-effective road construction projects. Since the second half of the 1960's, the STA has included cost-benefit analysis in their framework for investment appraisal. The STA is the only Swedish authority that performs such cost-benefit analyses on a routine basis, and these are made by order of the Swedish Parliament and Government.

Within this framework, prospective safety improvements are given explicit monetary values. These values are then considered together with other costs and benefits, such as the value of changed traveling time and changes in vehicle operating costs. In developing a method of investment appraisal that would withstand close economic cross- examination, STA consulted economists on several occasions, which has led to several major revisions of STA's way of valuing safety.

The *value of safety per se* is usually estimated using the individual willingness-to-pay (WTP) approach (Jones-Lee 1989). Individual valuations reflect what people would be willing to pay (or sacrifice) to obtain benefits or to avoid costs. Assuming that an individual prefers a low probability of death or injury to a high

probability, we can then assume that the individual would be willing to sacrifice some of his present income or wealth in order to reduce the probability of death or injury. The WTP approach assumes that individuals are willing to pay for small improvements in their own and others' safety. Therefore, an aggregation of these amounts across all individuals affected reflects the overall value of the safety improvement in question.

STA uses the concept of the *value of a statistical life*. To illustrate, suppose that 100,000 people enjoy a safety improvement that reduces individual probability of death by 1/100,000. The expected number of deaths within that group (during a defined period) is then reduced by one. Thus, the safety improvement can be described as involving the avoidance of one statistical death (or the gain of one statistical life). Now suppose that the affected individuals are each willing to pay approximately SEK220 for the 1/100,000 reduction in the probability of death. The total willingness-to-pay for the safety improvement would then be SEK 22 million. It should be observed that this is equal to the average willingness to pay, SEK220 divided by the individual risk reduction of 1/100,000. This ratio is defined as the individual's *marginal rate of substitution,* of wealth for risk. Under the willingness-to-pay approach, the value of a statistical life is given by the mean marginal rate of substitution of wealth for risk, calculated over the affected population of individuals

Several Swedish WTP studies have been conducted on the value of safety in transport in Sweden (Hultkrants & Svensson, 2012). I will use one of the studies to illustrate some of the strengths and weaknesses in methodologies (Persson and Cedervall 1991). This was the first Swedish WTP study to investigate the relationship between individuals' WTP for reductions in the risk of fatal and non-fatal injuries, including factors like initial risk level, size of the risk reduction, income and age, in a nationwide sample of 1000 individuals aged 18 – 74, living in Sweden. Data for the study were collected using a postal questionnaire that included background questions, risk perception questions and valuation questions. The study used an open-ended WTP format.

The respondents were also asked about their own subjective annual risk of death due to traffic accidents. Based on their own subjective risk estimates, the subjects were then asked about their WTP for sizes of risk reductions, e.g. 50, 25 and 10 per cent risk reductions, respectively.

As with many other empirical investigations, the three surveys produced a variety of estimates of the value of safety and the value of statistical life. However, the analyses indicated some important properties of the marginal rate of substitution. One is that the marginal WTP is a decreasing function of the size of risk reduction. Consider, for instance, individuals at the baseline risk level of 20/100,000; they were willing to pay SEK 279 for a 10 per cent risk reduction. At

the same baseline risk level, the WTP amount was SEK 583 for a 25 per cent risk reduction and SEK 908 for a 50 per cent risk reduction.

For 10, 25 and 50 per cent risk reductions, thus, the ratios of the WTP amount and the risk reduction (WTP/risk reduction) at the initial risk level of 20 in 100,000 are SEK 13.9 million, SEK 11.7 million and SEK 9.1 million, respectively. Incremental risk reductions from 10 to 25 per cent and from 25 to 50 per cent would be valued at SEK 9.7 million and SEK 5.3 million, respectively. Furthermore, our empirical findings indicate that the marginal rate of substitution is an increasing function of the size of the risk reduction.

The STA estimated the size of the risk reduction when building new roads to be 30 percent. Results from the WTP study for an average risk reduction in the magnitude of 30 % with baseline risk of about 10 in 100 000 would yield a value of about SEK 12 to 13 million in 1990 prices (Persson 2004).

This valuation resulted in an increased value of a VSL in transport from SEK7.4 million to SEK 12-13 million. This re-evaluation had practical implications. For example, with a value of a fatal casualty of SEK 7.4 million, it was profitable to build motorways when traffic flows exceed 10,000 vehicles per day. With an increased value of a fatal casualty up to SEK12 to SEK13 million, it became profitable to build motorways when traffic flows exceed 7,400 vehicles per day (Persson 2004).

THE USE OF COST-EFFECTIVENESS ANALYSIS IN THE VALUE BASED PRICING OF PHARMACEUTICALS IN SWEDEN

In October 2002, a new Swedish public authority was created, the LFN (Läkemedelsförmånsnämnden). Later on it changed name and is now called TLV (Tandvårds- och läkemedelsförmånsverket), The Swedish Dental and Pharmaceutical Benefits board. The TLV's role is to decide about the reimbursement and settle the price of drugs in the outpatient settings in Sweden. A Value Based Pricing (VBP) system for pharmaceuticals was born. VBP is a method of setting prices based on expected value to the customer (the payer). The manufacturer must avoid setting prices that are either too high for the consumers (payer) or lower than they would be willing to pay if they knew what kind of benefits they could get by using the product. Cost-effectiveness evaluation is the method used to provide TVL's board with information about the costs and benefits of different health interventions. The analysis aims to demonstrate how much it costs to produce a unit of "value", i.e. a quality-adjusted life-year (QALY) with one treatment compared to another. From the

beginning TLVs role was not defined in detail. The intension was that TLV would develop gradually as a consequence of the TLV Committee's decisions.

In their reimbursement decisions the TLV board uses multi-criteria analysis. That means that in addition to the criterion of cost-effectiveness, it also applies equity and severity criteria.

The pharmaceutical VBP system is built on three cornerstones of. These are:

- Reimbursement decisions of pharmaceuticals are based on cost-effectiveness analyses with a broad socio-economic perspective on costs in order to consider cost offset in other sectors/budgets than the health care, with effect measured in terms of QALYs;

- A threshold value, based on individuals' maximum willingness-to-pay for a QALY gained; in order to discern whether or not a treatment is cost-effective.

- Marginal decreasing utility of treatment, i.e. the benefit (and hence the reimbursement decision) varies by indication or by degree of severity.

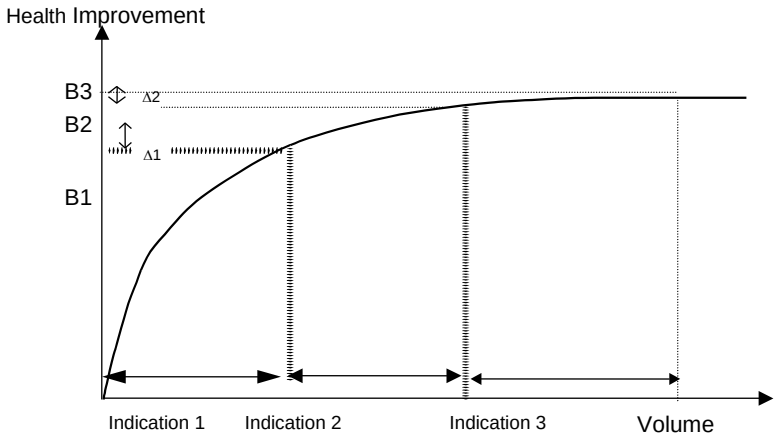
The VBP system is product-orientated. This means that TLV has to decide about one single price for a product even if the cost-effectiveness of the product varies with the usage of the product in different indications. However, TLV can decide that a drug is to be reimbursed only for certain indications and/or sub-groups of patients. This means that the TLV may decide to reimburse a drug for a narrower indication than the one for which the drug has been licensed for marketing.

The VBP system requires a threshold value, i.e. a maximal willingness-to-pay for health benefits (QALY). TLV has nether been very explicit about the threshold value they use. However, TLV have some references when deciding on price and reimbursement. One reference is the value of safety in the transport sector. Persson & Hjelmgren (1993) have used modelling technique based on a value of statistical life (VSL) accepted by the Swedish Government for use in traffic safety planning to calculate the corresponding value of a QALY. With a VSL of SEK 22 million in 2012 prices (approximately €2.4 million), this approach resulted in a cost per QALY of approximately SEK 1.0 million (€ 110,000). Another survey (pilot study only comprising 133 Swedish respondents) that elicited individual's willingness to pay for a QALY gain estimated a value of a QALY in the region of SEK 400,000 (€45,000) in 2004 prices (Persson et al 2008).

The third cornerstone (diminishing marginal utility of treatment) may need some clarification. Because the benefits of drug treatment often vary considerably across different indications (if more than one) and patient-sub-groups, TLV can

choose to grant reimbursement only for particular uses that are cost-effective. The diminishing 'marginal utility' of drug treatment is depicted in Figure 1, where the numbers of patients are arrayed by indication (in order of responsiveness to treatment) on the horizontal axis and total health improvement is depicted on the vertical axis.

FIGURE 1. DIMINISHING MARGINAL UTILITY OF DRUG TREATMENT

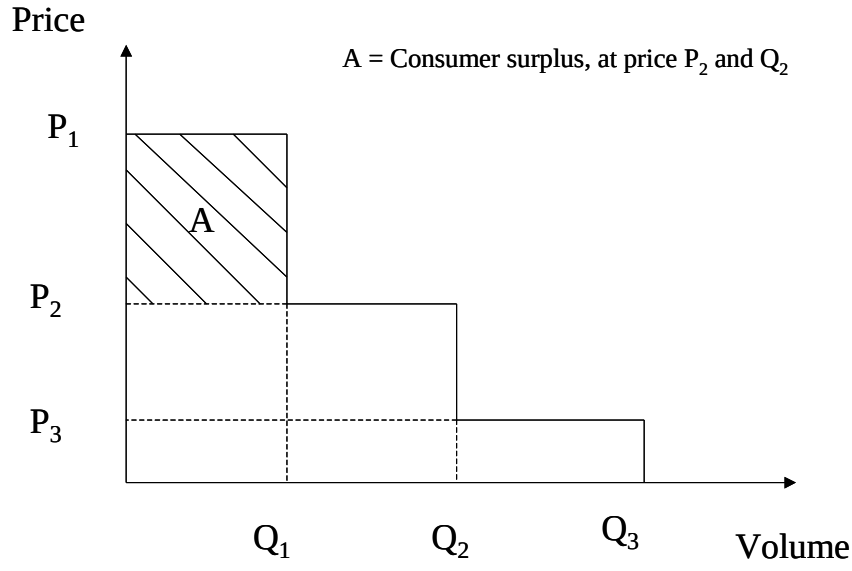


Treating all of the patients in indication 1, perhaps at serious disease severity, will produce a total improvement in health of B1. Expanding treatment to include patients with indication 2, perhaps a less serious disease severity will produce a marginal health improvement of Δ_1 (B2 – B1), which as depicted is smaller than the health gains from treating patients with the first indication despite the larger number of patients. Given proportional drug acquisition costs, treatment for patients with indication 2 will necessarily be less cost-effective than treatment for patients with indication 1. Expanding treatment in this example to include even patients with indication 3 produces even smaller incremental benefits per patient (Δ_2 / # of patients with indication 3). TLVs decision-making takes into account the cost-effectiveness of these different indications separately rather than in entirety.

Corresponding to Figure 1 are different prices that can be justified according to different subgroups. For example, the three subgroups (Q_1, Q_2, and Q_3) the medical technology is most cost-effective for Q_1 and least cost-effective for Q_3. A manufacturer on this market could choose P_1, but will be reimbursed only for use in Q_1, can choose P_2 and sell Q_2, or P_3 and sell Q_3. On a regulated market there

are incentives for the manufacturer to provide information only about the average cost-effectiveness ratio and at the same time claim reimbursement for the entire indication including all three subgroups. However, according to this, reimbursement, price and granted coverage would result in only small consumer surplus, area A, a loss of consumer surplus of an area (P_2 - P_3) * (Q_3 - Q_2) resulting in a small net consumer surplus if any to the health care sector.

FIGURE 2. VALUE, BASED PRICING (VBP), COST-EFFECTIVENESS AND CONSUMER SURPLUS FOR MARGINAL SUBGROUP



The Swedish guidelines for cost-effectiveness require subgroup analysis, and this is a consequence of explicit criteria for price and reimbursement, set by the Swedish government, accounting for the concept of *marginal utility* (i.e., an explicit recognition of the diminishing cost-effectiveness across indications or patient groups). The reason for the marginal utility criteria can be explained in Figure 2. It is obvious that pricing and reimbursement at the margin, i.e. at the least cost-effective subgroup within the claimed coverage, is the only way for the health care system to get a net health benefit, i.e. a net consumer surplus for technological innovations.

TLVs approach for running a VBP system for pharmaceuticals in outpatient care is built on the principles of a broad societal perspective, individual's WTP for the benefits and an incremental analysis incorporating decreasing marginal utility

and reimbursement for subgroups of patients if not cost-effective for all indications. Once again we have identified importance of the economist's contribution to decision-making in the health care sector. A broad societal perspective and the incremental analysis are both examples of problem formulation that were identified as crucial points by Jönsson (1976). The individuals WTP for the benefits is an example of the importance of the valuation method used where the economists could contribute.

DISCUSSION

In Sweden a broad societal perspective is used in both the health care sector and in the transport sector when TLV and TRA are evaluating pharmaceuticals and in the construction of new roads, respectively. The transport sector had used cost-benefit analysis in their framework for investment appraisal since the second half of 1960's. However, it took until the 1990's until the individual WTP approach was fully established as the acceptable method to estimate the value of safety. In the health care sector the cost-effectiveness approach, with QALY as outcome measure, was fully accepted when TLV started running the value based pricing approach for pharmaceuticals in 2002. Because of the reference to the value of a statistical life when setting the threshold value for a QALY, we can say that both sectors are using an individual WTP perspective when valuing the health benefits.

NICE does not apply a broad societal perspective in its appraisal of medical technology used in the National Health Service (NHS) in the UK. NICE's threshold value is much lower then TLVs'. The NICE threshold value is often referred to as £30,000 per QALY. It is not based on individual WTP estimations as the Swedish figures for the value of a QALY. The NICE threshold is currently under discussion and lowering it to about £18,000 to £20,000 has recently been suggested, based on opportunity cost calculations conducted by Claxton et al (2013).

The Department of transport in the UK uses a similar approach for cost benefit analysis and also similar methods for estimating the value of safety as the STA in Sweden. In the transport sector a broad societal perspective and VSL based on individual WTP estimates are accepted both in the UK and in Sweden.

Bengt Jönsson, in his dissertation, identified some of the crucial topics for the outcome of the economic analysis, i.e. the problem formulation and the valuation method. It is also obvious that almost 40 years later there are still several remaining research questions to consider, including learning how to implement the result into real world decision making in the health care sector.

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MEDICAL INNOVATION AS REAL "HEALTH INSURANCE"

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Bengt Jönsson has devoted much of his life helping the rest of us better understand the value of new medical innovations. On this side of the Atlantic, he is widely recognized as one of the European pioneers in the methods and applications of economic evaluation of new medical technologies. Invariably when I tell people that I was born and raised in Sweden, the first question is directly "do you know Bengt?". When I tell them that I do not only know him professionally, but also that my parents know him socially, people will always have some fun story about Bengt to relate.

In honouring Bengt, in this chapter I wanted to discuss what I perceive to be an important extension of the valuation of new medical technologies that Bengt's work centered around. The discussion of this issue is based on Philipson and Zanjani (2013) who provide a more quantitative discussion. In short, my argument is that medical technologies are more valuable than traditionally perceived, because they complete previously incomplete markets for risks due to health shocks.

Dealing with uncertainties of health shocks in the future has generated much economic and government activity, as well as intense policy debates. Many markets and government institutions exist to attempt to reduce the risks of such health shocks including life insurance, annuities, workers' compensation, health care insurance, long-term care insurance, and disability insurance, to name a few. A central feature of many insurance arrangements is the pooling of financial risks, whether in the private or public sector, such that those who are

lucky enough to avoid sickness or death pay for the losses of the unlucky ones who do not.

However, existing economic research is focused on consumption insurance against financial shocks and thus does not adequately address a more central and fundamental concern in dealing with health shocks --- the restoration and insurance of *health itself.* To illustrate, when an incurable disease such as pancreatic cancer hits, consumption of all goods including health care may be fully insured, but what is not insured is the loss in health --- and this is the real risk that may impose the largest loss. Unlike consumption risk, risk to one's health is not as easily insured. This is because human capital cannot be traded, and risk pooling arrangements in health itself, whether through private or public insurance, are often infeasible. For example, if Alzheimer's disease strikes an individual, he or she cannot be made "whole" or fully healthy by getting health reallocated from someone else. A rare exception is when transplantation is feasible, but market mechanisms for such health transfers have been deemed unethical and are outlawed in many countries. In the extreme case of death, there is no amount of financial insurance that can make a purely self-interested person whole again as the reward cannot be consumed.

Thus, methods other than risk-pooling must be used to reduce risks to health itself. Given that medical innovation is the primary method by which the real price of health is reduced over time, an unrecognized value of such innovation is the role of insuring future health. For example, innovation in treatments for breast cancer and HIV has lowered the price of health after diagnosis, which in turn has smoothed health across such uncertain future disease states. Medical innovation is to health what health care insurance is to health care. A certain payment for medical R&D may lower the price of future health, while a certain health insurance premium may lower the price of future health care. Thus, medical R&D is "health insurance" in the literal sense of the phrase, as opposed to the colloquial usage where it refers to insurance of health care expenditures. Thus, medical innovation acts like a financial innovation that completes a previously incomplete market for health itself by enabling a previously uninsurable shock to be insurable through traditional health care insurance.

It seems that the value of improvements in smoothing of health through new medical technology may often be much larger than the value of consumption smoothing. To illustrate this, consider the extreme case of an incurable disease for which the current medical technology is completely ineffective or equivalently not invented yet. In this extreme case nothing is spent on care as it is unproductive, so expected utility before being diagnosed would just be that from experiencing the health shock ithout being able to mitigate it. Even though there may be perfect consumption smoothing while alive there is of course a loss in

health induced by this health shock. Note that the value of traditional health care insurance is zero in this case since there is no productive care to insure, as was often the case historically. Thus, even if insurance were free, it would have no value. Gains in welfare in this scenario can come only from reducing the price of health through medical innovation.

Now consider the other extreme case in which medical innovation progresses in a way that makes it costless to restore health once diagnosed with a bad disease.. In this case, expected utility before diagnosis converges to the case where there is no health shock as health is repaired without any cost in the limit. With this most extreme form of perfect medical productivity, it is as if no health shock occurred in the first place. There will therefore be little value of consumption smoothing related to medical expenditure as medical technology is very cheap. Put differently, there is no need for insuring consumption when faced with cheap care. Insurance for cheap vaccines have this high productivity nature and could potentially be paid out of pocket without insurance. In sum, for both forms of extreme medical productivity, an infinite versus zero price of restoring health, consumption insurance had little value but progress in medical technology did.

Economists have not fully appreciated this ex-ante insurance value of medical innovation, which suggests that there are several avenues for future research. One is in assessing the relative value of public subsidies for medical innovation affecting smoothing in health versus health insurance reforms affecting consumption smoothing. Much legislation concerning health reforms has been under the rationale of reducing market inefficiencies in health-induced shocks to consumption. One may conjecture that given the potentially large value of smoothing health itself rather than consumption, more explicit analysis is needed on the relative value of public programs stimulating medical innovation rather than health reforms aimed at enabling consumption smoothing. Recent evidence by economists such as Kevin Murphy and Robert Topel suggests that the value of longevity improvements in the last century were on par with the value of growth in measured GDP per capita. Therefore, the current preoccupation with policies aimed at consumption smoothing across disease states may have lower marginal returns than policies aimed at smoothing health itself across those same disease states.

A second area of research concerns a more comprehensive analysis of the role of rare disease R&D that eliminates small risks with severe health effects. Public subsidies of rare disease R&D are common, such as the Orphan Drug Act enacted in the 1980s in the United States. However, according to traditional analysis R&D for small markets is inefficient given that the surplus generated in such markets may not be able to support the fixed costs in R&D as well as

surpluses in larger markets can. However, the discussion above suggests that small disease R&D may be efficient when it is interpreted as an insurance mechanism for a low probability event with severe health effects. For the same reasons that life insurance is valuable to the vast majority of people with coverage who do not die, small disease R&D is valuable for the vast majority of people who never get the rare disease. More generally, the value of new medical innovations for a given disease for individuals who never are diagnosed with the disease need to be better understood, particularly so for rare disease R&D.

A third area research area concerns the exact ex-ante risk properties of medical treatments and how FDA regulations affect their market access. In particular, clinical trials only estimate mean effectiveness or side effects levels, and not the covariance between them. However, the net benefit of a treatment - the value of health it generates net of side effects and price - has very different risk properties depending on whether side effects are positively or negatively correlated with effectiveness. If a side effect only occurs when a treatment is successful, it is a more tolerable treatment than if it only occurs when the treatment is unsuccessful.

In summary, research building upon Bengt Jönsson's important contributions in assessing the ex-post value of medical innovations once marketed may usefully consider the quantitative importance of their ex-ante value as a means of "health insurance". It would naturally extend his work on the ex-post impacts on health and costs of new medical innovation, to consider the ex-ante value that innovation generates by providing a piece of mind not fearing future disease states.

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EUROPEAN HEALTHCARE DECIDERS FORUMS

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INTRODUCTION

The *European Healthcare Deciders Forums* have since 2007 been a major meeting point for academics, public healthcare decision makers, healthcare professionals and representatives of the industry, under the inspiring European leadership of Bengt Jönsson.

Bengt's reputation was known to me long before I ever met him in person and joined him in many diverse activities. As a latecomer to health technology assessment, the cost-effectiveness analysis associated with the famous 4S interventional study was one of the outstanding references that helped me get into the field (Jönsson et al 1996). Over the years, we met many times in committees and advisory boards and it was obvious that Bengt has a profound understanding of issues that are not only of Swedish concern but also European. His messages go beyond national boundaries.

The most important project with which I have been associated was his initiative in establishing the Healthcare Deciders Forums. The Forums were built on clear principles. First, it was the responsibility of an academic scientific committee (of which I was a member) to set the agenda, define the issues to be addressed and select speakers. Second, the Forum was to focus on key questions common to all stakeholders, with the aim of providing well-founded policy recommendations. Third, the Forums also provided an opportunity to exchange national experiences, discuss best practice examples and facilitate their diffusion. This article focuses on the main outcomes of the five events that were organized under the leadership of Bengt. To stress his influence on the events, it is notable that three out of five meetings took place in Sweden, following the

inaugural Forum in November 2007, the two others being held in Paris and London.

THE FORUMS

Discussions in any forum naturally reflect the diversity of speakers and their various perspectives, so it may sound presumptuous to give one person the credit for their outcomes. It was particularly to Bengt's credit that the careful selection of subjects for each Forum addressed issues that were by common consent both topical and on the political agendas of many countries.

Two permanent threads ran through the five events. Not surprisingly, the first arose from Bengt's insistence on our taking a broad perspective in HTA, which should indeed use cost-effectiveness as one of its central tools but also take a broad societal perspective on costs and consequences (Drummond et al 2008). The second, which is closely related, is the importance that the Forum has always given to representatives of patient associations. Each time, and for different diseases, the main message, which has sometimes been quite complex, has been on the necessity to include specific patient reported outcomes in HTA. Not all patient groups have reached the same level of sophistication in formalising outcomes and the feasibility of their valuation. With the possible exception of orphan drugs, there is still a long way to go in getting effective involvement of patients in formal decision making processes. Health economists should be good advocates for patients, since our common goal is to maximise the surplus to citizens through an efficient allocation of resources. However, the institutionalisation of QALYs as a primary outcome measure may hinder progress in this domain, despite its being recommended in every session of the Forum.

Another issue raised early in the first forum has led to important developments in both academic research and decision making processes. This relates to the question of how HTA reports should deal with major residual but important uncertainties both at the time of launch and during their life cycle. In 2007, risk-sharing agreements were only an emergent idea but again they have been a continuing theme throughout successive Forums. HTA bodies and public authorities have been increasingly insistent on post-launch studies, with the aim of managing and sharing over time the costs of uncertainty on effectiveness, safety and efficiency. This development is consistent with the claim made by Bengt and co-authors that HTA should be a continuing process, not one-off and not restricted only to decisions on coverage (Drummond et al 2008).

A European aspect of the Forums was also visible in two other major issues. Systematic data on the differences in access to innovations in the European

Community were frequently presented, most notably in the field of cancer, but also for autoimmune diseases (Jönsson and Wilking 2007; Lundqvist et al 2008; Kobelt and Kasteng 2010). Such data illustrated the role of the different market access processes in the European countries. More importantly, they also showed how far we in Europe still are from having equal access for all European citizens. Obviously, such differences in access are strongly determined by the relative wealth of each country as well as prices but the Forums also included many discussions on the influence of external reference pricing and the potential negative impact of European regulations allowing for parallel trade, driving companies to adopt a "corridor price" strategy.

Another key policy challenge addressed by the successive Forums was the difficulty of matching countries' public health priorities with therapeutic innovations. The difficulty here is to articulate two partly independent processes: one concerning the setting of healthcare priorities at the national level, taking into consideration the observed demographics and illness distribution and the treatment gaps; the other concerning the dynamics of R&D. Although pharmaceutical companies will obviously define their research agenda according to observed prevalence of diseases and existing treatment gaps, R&D also relies on the existing stock of scientific knowledge and on serendipity. Investing in one area with large unmet needs, like Alzheimer's disease, does not lead to a hundred percent chances of success, and delivers only incremental progress, which will not meet the full expectations of payers.

Finally, the Forums have not escaped discussion of the issue of harmonising HTA processes in Europe. Industry has strong expectations on this issue. In this respect, the Forums have been a place where the modality of possible convergence has been much discussed and contributed positively to the convergence on methods and principles of HTA at the European level.

CONCLUDING REMARKS

Bengt Jönsson is known for his many achievements in research and teaching as well as for his activity as a member of the board of the prestigious Karolinska Hospital. I have presented here another facet of his talent, his capacity to communicate and organise debates on major policy issues in healthcare. Through five editions of the European Healthcare Deciders Forum, he has allowed major stakeholders from all over Europe to confront their experiences and perspectives, focussing on efficient resource allocation and transparent decision making processes. This has been done in a strongly principled way, ensuring the independence of the scientific committee, the openness of debates, and with recognition of and respect for the diverse interests of stakeholders.

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"VALUE" IN HEALTH CARE: WHAT DOES IT MEAN?

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It is rare nowadays that a respectable conference on health care – certainly one in the United States – fails to have several sessions containing the word "value" in their title.

There are presentations on "value pricing" (i.e., extracting the maximum revenue from patients and insurers through price discrimination), "value purchasing" (i.e., no longer paying for useless or only marginally beneficial treatments), "value-based health insurance", "innovation for value", the "value-chain in health care" and, last but not least "value maximization." One should not be surprised to find soon a conference session on "value valuing," which sounds like something to be wished for.

Remarkably, few if any of the speakers who talk about "value" in health care ever stop to ponder precisely what is meant by that word, let alone how it is to be measured. The closest that management consultants of the real world come to a defining the term is the ratio:

[1] Value = Quality/Cost

or, alternatively,

[2] Outcome/Cost,

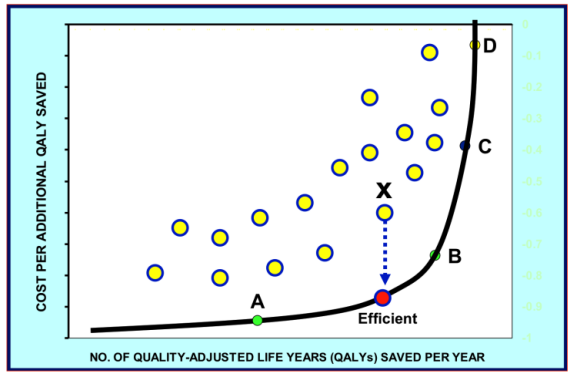
The second definition, for example, serves as the foundation of Harvard Business School professor Michael E. Porter's and the University of Virginia's Darden Graduate School of Business professor Elizabeth Olmsted Teisberg's by now famous tome *Redefining Health Care: Creating Value-Based Competition on Results* (2006). Early on in their book the authors note that "value in health care is the health care outcome per dollar of cost expended" (p.4). That

definition is then repeated throughout the 505 page book, without much attention to the challenging task of defining "outcome" for purposes of measurement or coping with its multi-dimensionality, other than to note that "patient value (sic) in health care delivery can only be understood at the level of medical condition."

The question I seek to explore in this essay is whether economists have done better than have real-world management consultants in defining "value" in health care. My conclusion will be an unambiguous "maybe." Brilliant thinkers have wrested with the concept of value through the millennia. Modern economic theory does include a theory of value, but its usefulness in particular, concrete applications to health care policy remains controversial and hence limited, even among economists with divergent ideological predilections.

A discussion on value in health care can be focused with the aid of the following construct. Suppose we set aside the still lingering controversies over the metric QALY (Nord *et al*, 1999) and accept it as a valid distillate of some multi-dimensional "outcome" from a medical intervention. In the graph below, we imagine all possible medical interventions produced by a nation's health system capable of producing added QALYs for the population, *ceteris paribus*. These interventions are arrayed, from left to right, in terms of the rising associated marginal cost of producing the QALYs. The solid line in the graph represents the minimally required marginal cost per QALY, attainable with the most efficient treatment method under the current state of the art. Points above the solid line – e.g., point X in the graph – are inefficient in the sense that the associated QALY could be produced at lower marginal cost with an alternative treatment process. The solid curve in the chart can then be viewed as the QALY-supply curve that a country's health-care system presents to society, at constant levels of all other non-medical determinants of QALYs, including life styles, with the price per QALY on the vertical axis.

FIGURE 1 -- THE SUPPLY CURVE FOR QUALITY-ADJUSTED LIFE YEARS WRESTLED FROM NATURE BY A HEALTH SYSTEM



Economists are superbly trained to help the health system move from inefficient health-care delivery above the QALY supply curve towards the least-cost supply curve. But the question is what they can contribute to answering questions on the merits of different points on that efficient supply curve, among them:

1. Is there a maximum price (marginal cost per added QALY) beyond which society no longer wishes to purchase added QALYs through added spending on health care? If so, how is that price determined?
2. If there is a maximum price, should it be the same for all members of society, or should it be allowed to vary with willingness of individuals to pay the prices of added QALYs, which naturally will be linked to the individual's ability to pay these prices? (This question may seem far-fetched to Europeans, but it definitely is now on the agenda in the debate on U.S. health policy.[11])
3. Should a health system be so configured and operated as to maximize the number of QALYs that can be purchased, so to speak, with a given budget? It would imply exhausting the budgets by purchasing added QALYs in the order of their marginal cost of production, until the entire budget is spent and the maximum allowable price per QALY is thus determined.

Ultimately, at the practical level of health-policy design and implementation, the answers to these questions force one to put a monetary value on the QALY. Do economists have any clue as to what that value should be, and is there a consensus even within the profession on how that value should be determined?

THE THEORY OF VALUE IN ECONOMICS

Given the central importance of "value" in economic analysis, it is surprising how many introductory textbooks in microeconomics pay scant attention to defining the term[12], let alone reviewing the fascinating history of thought on "value." Some texts do not even include a definition of "value" in their subject index. More's the pity, because Western thought alone on defining "value" goes back to Plato and Aristotle and, in health care, even to the Code of Hammurabi of 1780 B.C., which included a monetary fee schedule for physician services along with damages for medical malpractice (Paul; Halsall, 1998; Codes 215-223).

More attention to the term "value" in modern teaching would be helpful, to show how brilliant thinkers of the past have wrestled with the term. Furthermore, most

[11] One need only peruse right of center blogs such as this one http://healthblog.ncpa.org/

[12] A rare exception is Walter Nicholson and Christopher Snyder (2008) who devote 3 pages to the "Development of the Economic Theory of Value."

non-economists today have only a fuzzy idea what "value" may mean in general, let alone in health care, or they hold the incomplete cost-of-production theories that date back to the early nineteenth century. In debates on prices of pharmaceutical products, for example, a common ploy to prove alleged avarice is to contrast the production-cost of a pill with its price.

In his *The Wealth of Nations* Adam Smith makes a distinction between "value in use" and "value in exchange" (Book I, Chapter IV), a dichotomy that actually goes back to the medieval scholastics and through them to Aristotle and Plato. "The things which have the greatest value in use," Smith writes, "have frequently little or no value in exchange; and, on the contrary, those which have the greatest value in exchange have frequently little or no value in use." He dramatized this proposition with the famous diamond-water paradox, whose resolution long bedevilled and eluded the classical economists of the first half of the nineteenth century.

In the main, Smith concentrated the analysis in his book on "value in exchange," that is, on the price at which commodities were traded in the market (Book I, Chapter VII). Here he distinguished between the "natural price" of a commodity and the "market price" at which it actually traded. He theorized that the natural price was the cost of the land, labor and capital to produce the commodity and bring it to market. The "market price" at which it actually is traded at a point in time might be above or below its natural price, depending on whether the demand for the commodity at the natural price is above or below the quantity being offered in the market at the natural price. But he viewed these as temporary imbalances and argued that "the natural price, therefore, is the central price, to which the prices of all commodities are continually gravitating."

We may note in passing that the production-cost of value theory accepted by economists in the early part of the nineteenth century find a fascinating echo in today's U.S. health care. The fee schedule used by the U.S. federal government to pay physicians for care rendered to elderly Americans covered by the federal Medicare program, and widely copied by private American health insurers, is based on what is known by the oxymoron "Resource-Based Relative Value scale" (RBRVS). That scale, however, is based solely on estimated production costs and has nothing whatsoever to do with the value of the services covered by the schedule to anyone. A lower price may be paid for a high-value service that costs little to produce than for a low-value service that costs much to produce.[13] Likewise, the diagnosis-related grouping (DRG) payment system for

[13] I recall once illustrating this oddity to the Massachusetts Medical Society, owner of The New England Journal of Medicine, by doctoring a page from that august journal to make it appears as a comparison of a transurethral with a trans-oral tonsillectomy, the former being much more generously "reimbursed" than the latter.

inpatient care in hospitals is based strictly on relative historical costs, not value. One must wonder whether even classical economists really would have thought this valuation reasonable.

Only in the latter part of the nineteenth century – in what is now known as the "marginalist revolution" -- did economists rediscover the ancient Roman dictum *"res tantum valet quantum vendi potest"* (a thing is worth what you can sell it for).

Marginalists (*alias* neo-classicists) such as Stanley Jevons, Leon Walras, and Alfred Marshall realized that the value of a good or service is not determined objectively by its intrinsic qualities, nor by its production costs, but instead subjectively by the importance that a particular potential buyer puts on it. Although, in principle, that subjective value can be measured only ordinally, and not cardinally, for practical purposes economists have adopted the convention – legerdemain, really -- of measuring it cardinally anyhow, by the maximum money price the individual in question would offer for an additional unit of the good or service subject to trade. This practical and somewhat dubious compromise of conceptual theory is the foundation of modern welfare economics, as it is practiced in the sphere of public policy and, in particular, of the willingness-to-pay principle that guides welfare economics in general.

Under this construct, the objectively observable "value in exchange" of a commodity then is the subjective value that the last buyer willing to trade in the market puts on the good or service in question. As Alfred Marshall elegantly showed in his *Principles of Economics* (1890), in a perfectly competitive market that value, the equilibrium value in exchange (or equilibrium market price) also happens to equal the marginal production cost of the last unit some seller is willing to offer in the market for the commodity. It is this circumstance, vaguely remembered by educated lay persons from freshman economics, which seduces so many into believing that the value of a good or service – or even of an entire office tower -- depends on its cost of production.

Evidently, the neo-classical synthesis, as it is widely called, put to rest the long search for the resolution of the water-diamond paradox, as every modern freshman in economics now understands. The synthesis shows that critics of the economics profession, who, paraphrasing Oscar Wilde's definition of a cynic, depict economists as people who know the price of everything and the value of nothing are wrong. Economists arguably rank among the few disciplines, along with philosophers, who do understand the distinction between price and value.

"VALUE" IN HEALTH ECONOMICS

Now it can be asked what light the elegant neoclassical synthesis of diverse theories of value can shed on the three questions raised earlier in connection with Figure 1. Even at the purely conceptual level, for example, what value would modern value theory in economics impute to a QALY? At the practical level, what monetary value should be put upon it?

There is a huge international literature on putting monetary values on life, life years or QALYs, based either explicitly or implicitly on the willingness-to-pay principle of modern value theory. These studies use either a revealed-preference approach or a stated-preference approach (e.g., contingent valuation).

Under the revealed-preference approach, viewed as more objective and reliable than the hypothetical, state-preference approaches, values of a statistical life or life-year or QALY are inferred from actual decisions made by individuals or legislators involving risks to life - for example, willingness to pay to reduce risk of mortality from environmental hazard, or reductions of risk associated with certain consumer goods (e.g., automobiles), or willingness to accept a higher risk of mortality in a job for higher pay. Unfortunately, as a recent survey various estimates in the literature of the value of a statistical life in the U.S. by Maureen Cropper, James Hammit and Lisa Robinson (2011) shows, the estimates span a wide range, from a low $3.2 million per statistical life under a stated-preference approach to a high $11.1 million under a revealed preference approach. This great variance should not come as a surprise, because there is no reason to assume that actual decision makers or respondents to stated-preference surveys even understand how to think about the (often very low) probabilities that confront them in particular contexts, or even that these probabilities are an accurate description of the risk actually faced.

In his study of the contribution of health-care to U.S. living standards William Nordhaus (2003) uses a value of $3 million per statistical life and, using a life-cycle model with variable life time, converts that number to $75,000 per statistical life year. In their more recent study of the value of medical spending in the U. S., David Cutler, Allison Rosen and Sandeep Vijan (2006) use a value of $100,000 per life year, which had earlier been recommended by other economists (for example, George Tolley, Donald Kenkel and Robert Fabian, 1994).

Although it is difficult in many political forums – certainly in the U.S. – to persuade public policy makers that a statistical human life year has a finite value that can be estimated by economists, these estimates can serve a very useful purpose when used to inform public decision makers explicitly of the value of life

or life years they implicitly bake into their decisions – for example, sending soldiers into battle without flak jackets. Sometimes it may goad these policymakers to reexamine their decisions.

By their very nature, however, the studies referenced above are implicitly egalitarian, in the sense that they assume the same value of a life year or QALY regardless of who is its recipient. At their best, then, these studies could help inform an answer to the first question raised above, namely, should there be a maximum price at which a health-care sector purchases added life-years or QALYs through added spending on health care. One should think that, if policy makers are comfortable baking finite values of life-years into many of their decisions in other spheres, they could be made to accept it in health policy, too.

But these studies cannot answer the second and third questions raised above, because the answer to these questions involves the distribution of economic and other privileges among members of society. As such they are inherently political and beyond the proper scope of economic analysis, even though some economists may be tempted to offer a view on them just the same. Leaning on the Benthamite utilitarianism that inspires modern welfare economics, for example, it may seem natural for economists to recommend that a health system allocate fixed annual budgets so as to maximize the number of QALYs that can be had with those budgets, regardless of who receives these QALYs. Is that so obvious? As Nord et al. (1999) have argued rather persuasively, it is not how the general public wishes to see those budgets for health care spent.

Many economists believe to have discovered in welfare economics an objective algorithm that can redistribute among individuals in society economic and other privileges – including life-years or QALYs – in a way that maximizes a mystical something called "social value" or "social welfare."[14] Although economists may pretend that their advice respects individual preferences, in effect that pretense is a collectivist impertinence (Reinhardt, 2001). No one has authorized the profession to view "society" as the analogue of a cattle farm to be operated so as to maximize the herd's aggregate weight of meat on the hoof.

[14] In this regard, readers may find interesting a lengthy exchange on "efficiency" and "social welfare" on a blog run by University of Rochester, N.Y. economist Steven E. Landsburg. In comment 67, I had asked Landsburg: "So, to round this off, let me ask you this final question: If, as a result of implementing Policy A, Jack gains $10 and Jill loses $5, does Policy A yield a "social welfare gain" of $5? " His response, in comment 69: "Yes. This is a direct consequence of the definition and I am extremely puzzled as to why you have to ask." How many non-economists whose "welfare" is thus being rearranged would agree with this dictum? See http://www.thebigquestions.com/2010/08/30/efficiency-experts/.

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TOWARDS A COST-EFFECTIVE BENEFIT PACKAGE

SOME THOUGHTS FROM A HEALTH ECONOMIC PERSPECTIVE

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INTRODUCTION

European countries all struggle with the issue of how sharply to define their insurance benefit package and get rid of ineffective and too costly diagnostic and therapeutic activities. This is especially true for medicines, where each country has its own specific process for deciding on reimbursement and its own demands regarding the evidence that is needed as an input to such process (Busse and Schreyögg 2005).

Examples of countries where these processes are more sophisticated are the UK, Sweden and the Netherlands. It is no coincidence that health economics has been very strong in these countries since the early seventies. Clearly, health economists in these three countries have been influential in advising their governments about which inputs are needed for defining the benefit package and how decisions are to be made.

Bengt Jönsson was the founding father of health economics in Sweden and has significantly contributed to shaping decision making on health benefits. He also has an excellent track record in educating Swedish economists in different places like Lund, Linköping and Stockholm. So he has ensured that there is enough expertise in health economics in Sweden to supply the appropriate knowledge to operate health technology assessment and decision making bodies like the 'Statens Beredning för medicinsk Utvärdering' (SBU) and 'Tandvård- och Läkemedelsförmånsverket' (TLV).

Therefore it seems appropriate to contribute to this *Festschrift* by providing some thoughts on how defining benefit packages may evolve in Europe and what role health economic evidence can play. I will consider the role of real

world evidence, some aspects of the process of decision making, the role of guidelines and I conclude with a suggestion for a risk-based approach to defining the benefit package.

REAL WORLD EVIDENCE

Because of the restricted value of evidence from controlled experiments (e.g. strict patient selection, forced compliance, specific dosing, intense follow-up) and the emergence of personalised medicine, real world evidence is increasingly in demand as an input in reimbursement decisions. This is often combined with conditional reimbursement of some kind. In the Netherlands expensive hospital medicines are reimbursed conditionally on real world cost-effectiveness as can be established after 4 years of experience with such medicine. For this reimbursement scheme a large number of studies are currently carried out using real life data and many new patient registries facilitate these. In most studies comparator information is lacking, often due to treatment heterogeneity or missing baseline prognostic variables. Though the scientific challenges are larger than in a straightforward piggy back study, knowledge about how to get reliable real world evidence is growing. In observational studies confounding by indication can be tackled by statistical adjustment, often using propensity scores (van Gils et al. 2013a). The trend is to use multiple data sources and use sophisticated techniques to extract the evidence (van Gils et al. 2013b).

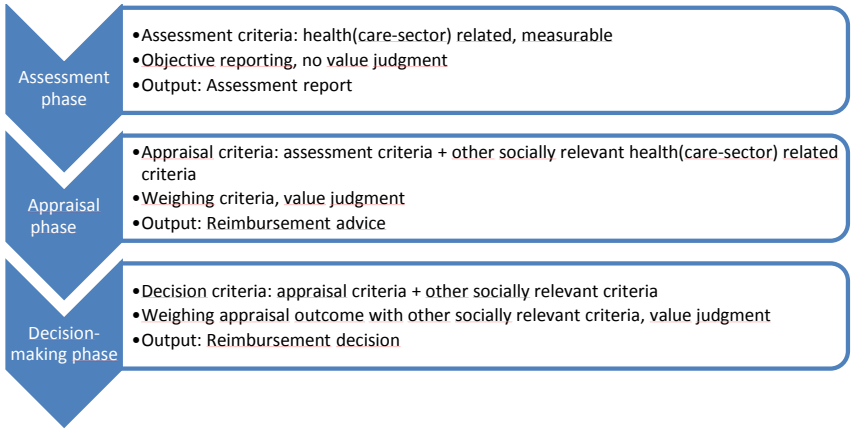
'ASSESSMENT' OR 'DELIBERATION' DRIVEN?

Another trend in decision processes on the benefit package is to involve more stakeholders. Several countries (e.g. Belgium and Austria) have formed committees of representatives of different stakeholders, who advise on reimbursement (KCE 2010). Other countries have mixed committees with scientific experts and stakeholders combined (e.g. the Netherlands) or rely predominantly on experts (e.g. the UK). These committees play a role in the appraisal phase just before decisions are taken (see table 1).

One may ask whether a more 'deliberation driven' system is to be preferred. Daniels and Sabin (1997) were mentioned in the KCE report (2010) as having defined the conditions for legitimate and fair coverage decisions: transparency (about rationales behind a decision), relevance (to all stakeholders), revisability (in light of new evidence) and enforcement (of the three other conditions). As long as there is no consensus about exactly which criteria should be used to define the package, a deliberation driven system carries a risk. But the organisation of the process involving stakeholders is also crucial: the committee

advising on the benefit package in the Netherlands found it difficult to reach a conclusion on the reimbursement of very expensive medicines for Pompe's disease in the presence of actual patients sharing their experience, since draft recommendations as derived in the assessment phase caused much public unrest. As health economist I would prefer to shift the focus to the appraisal phase with the observation that consensus is needed over the criteria to be used for decisions, how they are to be measured and combined in a decision making framework.

TABLE 1. ASSESSMENT, APPRAISAL AND DECISION-MAKING



Source: KCE 2010, table 2

A NEW DECISION MAKING FRAMEWORK

From an economic perspective a new medical service should be incorporated in the health basket when the associated cost-effectiveness is lower than a threshold representing the monetary value of health gains. Such a threshold represents what society is willing to sacrifice in order to obtain one additional unit of health. Little work is actually done to establish this monetary value of health gains empirically, but some studies have used methods that mimic the insurance character of the health care market and ask individuals about their willingness to contribute in order to allow a person in society to gain one QALY (Bobinac 2012). This particular study came up with a range of €52,000 - €83,000 (for one QALY), which looks reasonable in the light of figures quoted in the literature.

But cost-effectiveness alone cannot fully guide societal decision making (see phase 3, table 1). The implicit assumption underlying cost-utility analysis that 'a QALY is a QALY no matter who gets it', appears to be at variance with societal

preferences for a fair distribution of health and health care. People tend not to consider erectile dysfunction or heart failure to be similar in terms of 'necessity' and 'therefore' attach different weights or values to the gains in both contexts. In the Netherlands, rather than working with weights, a flexible threshold was proposed. This threshold would increase (easier access) when the intervention was deemed more 'necessary'. The latter concept was proposed to be measured as the burden of the disease for the patient in question (operationalised as proportional shortfall). The underlying principle here is that those patients who lose the greatest proportion of their remaining health expectancy due to some illness should receive priority for treatment.

But other characteristics of the patient may also be input to the decision about who gets priority. Can an elderly patient get less priority because he already experienced many healthy years (fair innings), or because the high expenditure in the last year of life (often marginally effective) has to be reduced? And looking at the intervention itself, should we consider at all new treatments or medicines for reimbursement if the health gain is below a certain threshold, e.g. 0.02 QALY? Light and Lexchin (2012) observe the large number of new medicines below this threshold. And finally the innovative character of a new intervention (potential for greater future benefits) may also be a relevant criterion, but one that is difficult to operationalise (Refoios Camejo 2010).

My colleague Werner Brouwer is developing a research programme at Erasmus University Rotterdam to deal with those and other questions in order to arrive at a scientifically based decision making framework. More scientific inputs from others would be required to make this a sound basis for decision making in Europe. Furthermore, more cooperation in Europe would be needed to organise the expertise to perform studies and judge the evidence. Recently a study was done to elicit preferences for different scenarios for such cooperation ranging from developing and maintaining an ICT platform for HTA to a situation where coordinated/joint assessments would be performed (Ecorys 2013). Most interviewees from HTA agencies in Europe doubted whether the latter would be realistic in the short run (though perhaps preferable in the long run). Most thought that it would be best now to concentrate on the development of common generic guidelines for HTA studies and to realise a coordinating secretariat (shared ICT platform, common generic guidelines, future joint assessments) preferably within the existing network of HTA agencies. Given that there are a few very large and renowned scientific institutes in Europe (Rotterdam, Sheffield, York) an alternative may be to have a secretariat under the auspices of these institutes. The current cooperation between these institutes for NICE-assessments may provide an example.

MORE EMPHASIS ON GUIDELINES

Maybe even more important than putting the right benefits into the basket is to make sure that these benefits end up with the right patients. Such appropriate use of services should be timely, targeted to the needs of a specific patient, and should meet quality standards. The use of practice guidelines may support this and can function in a complementary fashion to defining the benefit package. Indeed if a similar framework as mentioned above guides the development of such guidelines, and if health economic expertise is systematically involved such practice guidelines (with efficiency enhancing start and stopping rules), these may help to increase efficiency in the health care system. NICE's guideline program is an example to be followed elsewhere. In the Netherlands a program to develop guidelines for cost-effective health care has run some 10 years ago (Niessen et al 2007) and now the new Dutch Institute for Care (previously CVZ) will start with a guideline program somewhat similar to that of NICE. In insurance based systems it can be foreseen that compliance to such guidelines will be an issue in contracting between health insurers and health care providers and hospitals.

A RISK-BASED APPROACH

As health economic expertise and resources are scarce one may predict that a risk- based approach toward defining the health care basket may evolve, which distinguishes 4 steps:

Estimation of the risk of a wrong decision of admission or rejection of a new health service, looking at the consequences in terms of both costs and health benefits.

If the risk is small one may just include the service in the package (open system) and focus on control through practice guidelines.

If the risk is high and info on costs and effects is available one may decide on the basis of a framework as suggested above. In case of high risk of inappropriate use practice guidelines using such info may contribute as well.

If the risk is high and info on costs and/or effects is lacking one may start a CED-process (coverage with evidence development) to get real world evidence on cost-effectiveness, on the basis of which a final decision may be taken and also practice guidelines may be developed.

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DO WE HAVE TO WORRY ABOUT REGIONAL DIFFERENCES IN THE PHYSICIAN-POPULATION RATIO?

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INTRODUCTION

In most countries there are regional differences in the physician-population ratio. (Brooks et al., 2002). This phenomenon is considered as a consequence of market failure: because physicians are able to induce demand for their services, they have the freedom to settle where it is pleasant to live and not necessarily where the demand is for their services. As a reaction, politicians and health care specialists propose giving incentives to physicians to move to so-called underserved areas.

However, regional differences in physician density could also be a result of demand differences. For instance, if we were to the spatial distribution of gas stations, would we claim that a large concentration of stations is because owners of the gas stations love to live in regions with a large number of gas stations?

It is surprising that the regions with low physician density are mostly rural areas and that regions with high physician density are urban areas. Could it be that the demand per capita for physician services is lower in rural areas than in urban ones? If that is true, there would be no need for governmental intervention or incentive programs that physicians move to “underserved” areas.

In this paper, we will show in a simple microeconomic model that differences in physician population density can be explained either by physicians’ preferences

for certain regions with or without the ability of physicians to induce demand ("supply push differences") or demand differences ("demand pull differences").

THE MODEL

The model has four parts. The first part presents the demand-side. The second part introduces the time costs for the consumer when consulting a physician. The third part models the physician's choice of where to locate. In the fourth and final part we compute the regional equilibrium to determine the physician-population ratio in urban and rural areas.

For simplicity we assume two regions, urban (u) and rural (r). Both have the same population (n=nu=nr), but differ in their area. The area of the rural region is mr and of the urban area mu (mu<mr). Thus the population density n/m is higher in u than in r.

Needless to say, we assume in this simple model no regional difference in morbidity, demographics, preferences or quality of the services.

1. DEMAND FOR PHYSICIANS' SERVICES

An individual has a fixed income of y, which is spent for services of general practitioners A and specialists S or other consumption Y. p is the price for those services and α is the co-insurance rate:

(1) $y = Y + \alpha\, p_A\, A + \alpha\, p_S\, S$

The consumer has a time budget of l, which is divided between consumption (time L) and consulting a doctor (t). t is the time needed to see a physician, including travel time, wait time and consultation time:

(2) $l = L + t_A\, A + t_S\, S$

The resources used for other consumption are expressed by

(3) $Z = Y + \varrho L$

where ϱ denotes the individual's shadow price for time. In this simple model ϱ is exogenous. But it can be determined endogenous if we would add a labor supply model to this model.

The individual has a Cobb-Douglas type utility function:

(4) $U = A^a S^s Z^z, \;\; s > a$

This type of function has plausible properties: $s > a$ means that specialists' activities are preferred over GPs' activities, but GPs' activities cannot be fully substituted by specialists' activities and vice versa.

(1) to (4) allows us to formulate the problem of the individual:

(5) $max\ Q = A^a S^s Z^z + \lambda\ [Z - y + \alpha\ p_A\ A + \alpha\ p_S\ S - \varrho\ l + \varrho\ t_A\ A + \varrho\ t_S\ S]$

Differentiating (5) with respect to A, S, Z and λ lead to the first order conditions for an optimal consumption plan:

(6) $\frac{S}{A} = \frac{(\alpha p_A + \varrho\ t_A)}{(\alpha p_S + \varrho\ t_S)}\ \frac{s}{a}$

(7) $\frac{Z}{S} = (\alpha p_S + \varrho t_S)\ \frac{z}{s}$

(8) $\frac{Z}{A} = (\alpha p_A + \varrho t_A)\frac{z}{a}$

It is not surprising that the relative demand for services of general practitioners, specialists and other consumption depends on the insurance coverage, the price of other consumption, the time needed to consume physician services and other goods and the preferences expressed by the coefficients in the utility function.

Inserting (6), (7) and (8) in the budget constraint (5), we obtain

(9) $(\alpha p_A + \varrho t_A)\ \frac{z}{a}\ A - y - l + (\alpha p_A + \varrho t_A)A + (\alpha p_S S + \varrho t_S)\ \frac{(\alpha p_A + \varrho t_A)}{(\alpha p_S + \varrho t_S)}\ \frac{s}{a}\ A = 0$

which yields to

(10) $A = \frac{a\ (y + \varrho l)}{(\alpha p_A + \varrho t_A)(a + z + s)}$, and

(11) $S = \frac{s\ (y + \varrho l)}{(\alpha p_S + \varrho t_S)(a + z + s)}$.

By multiplying the number of inhabitants in each region with the demand for physician services, we receive the demand for the whole region, i.e. nAu, nAr, nSu and nSr.

2. TIME COSTS

The time cost of consulting a physician includes travel time, wait time and time of consultation. Time cost decreases with the average regional distance between physicians' practices. Whereas in urban areas the nearest doctor's office can be reached in just a few minutes, travel time in rural areas is more important. Following this argument, we assume the following time cost function

(12) $t_{A_i} = (\frac{GP_i}{m_i})^{-q_A}$ with i = {u,r}; $0 < q_j < 1$; $q_S > q_A$

(13) $t_{S_i} = (\frac{SP_i}{m_i})^{-q_S}$

where GP stands for the number of general practitioners, SP for the number of specialist and i for the region. q is the time cost coefficient. The time cost is dependent on the regional physician density. q is assumed to be lower one, so that the time-cost-physician elasticity is lower one. This means that the demand for physician services does not grow faster than the number of physicians.

It is plausible to assume that it takes more time to find an appropriate specialist than a GP, due to the heterogeneity of specialists i.e. qA<qS.

3. Physician's Regional Preferences

For simplicity, we assume that physicians have some regional preferences. They seek also to income. The income of a general practitioner (GP) and a specialist (SP) in a rural or urban region is given by:

(14) $Y_{j_i} = (p_j - c_j)\ D_i n / j_i$ with j={GP,SP}, D={A,S}, i={r,u}

If physicians are free to choose where to open their practice, in a state of equilibrium physicians' incomes are the same in both regions:

(15) $Y_{j_r} = w\, Y_{j_u}$ with j={GP,SP}, $w \geq 1$

w expresses the regional preference. If w is 1, physicians have no regional preferences. If it is lower than 1, they prefer rural areas. We assume, that it one or greater than 1. Greater one means, that they prefer urban areas, i.e. they are willing to sacrifice part of their income to live in a preferred region. The model does not assume that physicians are able to induce demand for their own services.

4. Regional equilibrium

Inserting (10) to (14) in (15) yields the following if $\alpha = 0$:

(16) $\frac{GP_u}{GP_r} = (\frac{m_r}{m_u})^{\frac{q_A}{1-q_A}}\, w^{\frac{1}{1-q_A}}$

(17) $\frac{SP_u}{SP_r} = (\frac{m_r}{m_u})^{\frac{q_S}{1-q_S}}\, w^{\frac{1}{1-q_S}}$

(16) and (17) show that the number of physicians and hence the physician density is larger in urban than in rural areas, because the right hand side is

greater 1. The urban-rural-discrepancy increases if the regional preference for urban areas increases.

Dividing (17) by (16) yields

$$(18) \quad \frac{SP_u}{GP_u} = \frac{SP_r}{GP_r} \left(\frac{m_r}{m_u}\right)^{\frac{q_S - q_A}{(1-q_A)(1-q_S)}}$$

Obviously the specialist-general practitioner relationship is higher in urban than in rural areas if qA<qs.

DISCUSSION

Our model leads to four propositions:

1. Regional preferences of physicians lead to differences in regional physician-population ratio (no surprise).
2. If physicians have no regional preference, in our model the physician population ratio for each specialist group is higher in regions with a high population density than in rural areas.
3. Not only the absolute number of specialists but also the specialist-general practitioner ratio is higher in urban than in rural areas, if search and travel time cost are higher for specialists.
4. The higher the level of insurance coverage or the lower co-payments, the higher the regional inequality of outpatient care.

Proposition 4 can be derived directly from the model if, for instance, α is set equal to 1. If the monetary cost increase, the relative importance of the time cost decrease.

The first two proposition show that it is an empirical question whether differences in physician population ratio are really a sign of market failure that means a supply push or a demand pull phenomenon. Like every simple model, this one has strong and obvious limitations.

As it is an empirical question whether the variation in physician population density is supply side or demand driven, empirical research is needed to resolve it. Schulenburg (1987a and 1987b) has shown with Swiss data, that the differences of physician population ratio are very much influenced by the demand side. The same was shown by Schulenburg (1989) in a study on German data. Scholz, Greiner and Schulenburg (2013), who employ a similar model, show in a very comprehensive empirical study employing German data, that the demand factors dominate the supply factors.

Günther et al. (2010) conducted among 14,939 German non-postgraduate physicians a discrete-choice experiment to weight the attributes of hypothetical locations for practices. The study concludes that income was weighted with the highest utility weight. However, other parameters play a role too in the decision where to open the physician office. The study by Roick et al. (2012) result in an opposite conclusion: Financial incentives are less important for physicians for their regional decision than a positive environment for the family and occupational duties.

Kazanjian and Pagliccia (1996) used a very similar methodological framework as Roick et al. They analysed Canadian physicians' location choice in 1989. According to this study, the highest influence on the location have the physicians' spouses, the desire to grow a family in an environment similar to the own childhood, and peers and friends. Nevertheless, income and other location factors are important for the satisfaction with the current location, but no factor is dominating the others.

Other studies by Breyer, Mühlenkamp and Adam (1986) and Kistemann and Schröer (2007) have shown, using German data, that many different factors influence the regional distribution of physicians. It would be interesting to run an international study using the same methodological approach in each country and to compare the results for the various countries. This would also allow some inferences about how much the health care system and monetary incentives influence the regional distribution of physicians.

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FROM BENEFIT-RISK TO BENEFIT-COST (A REGULATOR´S VIEW)

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My acquaintance with Bengt Jönsson goes back a very long time. I cannot pinpoint exactly when we first met but it was most likely in a conference on pharmacotherapy recommendations for clinical practice. My career had taken a turn because I had accepted the joint position as Head of the Pharmacotherapeutic Division of the Swedish Drug Regulatory Agency (DRA), and Head of the Clinical Pharmacology Unit at the Uppsala University Hospital.

A unique feature of the DRA was the publication of comparative evaluations of the clinical value of newly approved medicines (the comparators being products already on the market). Some regulatory colleagues argued that the approval process should not be contaminated with later appraisals concluding that the new drug did not bring any real advantages to the health care system. The answer was clear: the legislation did not call for superiority for a new product and the evaluations were performed by staff not involved in the approval process. Another unique service provided to the prescribers was the production of guidelines on drug treatment of specific diseases. The guidelines were put together by invited experts, who during two-day workshops produced draft guidelines that were sent to all participants for consultation and then finalized The guidelines were not to take the place of textbooks but were to be practically oriented and reader-friendly.

In this period costs, pricing and reimbursement were seldom an issue. The legislation for authorization of new pharmaceutical products made a strong point about the absolute need to exclude costs as a factor in the decision process for

a new product. The decision was to be based solely on whether the product in question met the regulatory criteria for quality, safety and efficacy. A positive benefit-risk relationship had to be demonstrated. All prescription drugs were automatically accepted for reimbursement. Pricing was a matter between the pharmaceutical company and the state-owned monopoly pharmacy group covering all Sweden. In the few cases where an agreement was not reached the case was handed over to the DRA for decision.

This was in the period 1970-1990. Bengt participated in a number of the above workshops. The focus of his presentations was not pricing and reimbursement but the health economic gains that could result from introduction of new therapies. Nobody will forget the classic comparative studies of surgery versus treatment with H2-blockers or omeprazole in patients with gastro/duodenal ulcers. His analyses predicted lower costs due to lower surgical rates. These savings were indeed achieved, although they were initially off-set by higher drug costs, as many more patients received medical treatments than would ever need surgery. Thus more patients benefitted. Inclusion of sick leave and early retirement costs associated with surgical interventions in the analysis showed, however, clear savings, while providing relief to a much larger patient population. The discovery of the role of H-pilori resulting in a cure provided the true savings (Jönsson et al 1991, 1996, 1996).

Bengt was the first in Sweden to introduce the value of conducting health economic analyses into the health care system. Suddenly “everybody” in the system went to classes and conferences in health economics organized by Bengt and staff at the Institute for Health Economics in Lund. The pharmaceutical industry increasingly employed these services and commissioned studies, in particular studies aimed at showing comparative advantages at the expense of standard therapies.

Beginning in 1995 the European regulatory system became more harmonized with the creation of a common EU legislation and the establishment of the European Medicines Agency (EMA). The operational work is performed by the pooled staff resources of the 28 Member States and Iceland and Norway, and is coordinated by the EMA. A positive opinion issued by the Committee on Human Medicinal Products (CHMP) on a Marketing Authorization Application (MAA) is transferred to the EU Commission for a formal decision allowing market entry for the product in all Member States and the named EFTA countries. Bringing about this formidable task is one of the EU´s major success stories from both a public health and business perspective. A positive outcome in the EU regulatory process today results in a faster access to the entire EU/EFTA market comprising more than 500 million persons. But does it translate to improved and

equal access to new medicines for EU inhabitants, i.e. an over-riding objective of the EU pharmaceutical legislation?

The short answer is “No”. There are many reasons for this but they all converge into the challenge of meeting the increasing costs for new medicines. This issue was infrequently on the agenda before. Focusing on development of medicines alone - putting the many other factors aside - it is important to note that discovery and development of well-tested medicines is a very young discipline. In essence, it started during the Second World War period and took off exponentially after the end of the war. In a sense, there was virgin country to be exploited when drug development started to take advantage of the rapid advances in basic science disciplines, e.g. chemistry, physiology and pharmacology, which offered great potential to address the many un-met needs in clinical medicine.

This was an era when medicines started to be developed using a strategic approach: compounds were synthesized to act on specific biological functions compared to prior approach to investigate the pharmacological profile of a new compound and then conclude in which biological system it might be effective. The development of receptor pharmacology was a key component in the new research model.

In the ”golden period” an abundance of new more effective drugs for treatment of common serious diseases were developed, e,g. asthma, hypertension, diabetes, infectious diseases and psychiatric and neurological diseases. This was done at low cost and the regulatory requirements were not particularly demanding. Hence the payers were put in a situation they could easily cope with. The health economic gains were obvious.

The medicines developed then are nick-named “low hanging fruits” to contrast the realities of drug development today. Now pharmaceutical companies are researching therapeutic areas where the diseases are much more complex and the regulatory requirements more extensive. For chronic diseases long term data on efficacy as well as safety are required, and strict proofs of clinical relevance of efficacy data are needed. In reality superiority or added value needs to be shown tin comparison with standard therapy. Increasingly, companies aim for limited indications in order to gain market access and, building on this, embark on studies to add more indications to the product license. In addition, companies try to explore new territories for their products thereby prone to encounter earlier unknown obstacles/risks that may limit the chances for successful outcomes. The introduction of new types of biological products has added new dimensions to regulatory science with regard to both proofs of efficacy and risks for compromising patients´ immune system etc.

From this follows that the development costs and now also the costs for follow up of efficacy and safety post-approval have escalated dramatically making the risk-taking in industry a prime concern with likely consequences of stopping many treatments from climbing the development ladder

Moreover, health technology assessments (HTA) of new treatments have been introduced to obtain an improved basis for decisions on pricing and reimbursement as well as clinical value. Thus for true market access, i.e. the product being actually used in clinical practice, a positive benefit-risk for a new medicinal product does no longer suffice, compelling data on “value for money” have to be presented. Freedom of prescription is long gone for physicians working in the European health care systems.

Over recent years several new pharmaceutical products, though approved following positive CHMP opinions, have been judged by one of the influential HTA organizations, the British National Institute for Health and Care Excellence (NICE), not to meet the requirements for a recommendation supporting their introduction in the National Health System. A positive EU regulatory decision now constitutes no assurance that market access will be gained. A fourth hurdle, “Benefit-Cost”, has to be jumped.

This situation is naturally difficult to grasp for patients aware of the arrival of new treatments. It begs the question whether other data than those used in the regulatory process are required in the HTA process, or whether the “value for money” principle should be taken into account also in the regulatory decision.

After my two terms as a regulator at the Medical Products Agency, I worked with a Swedish consultancy firm to establish an expert group of ten high-level ex-regulators who could give strategic advice to industry on the development of new products. Considering the development of joint scientific advice given by national regulatory and pricing/reimbursement authorities, e.g. in Sweden, and most importantly also by EMA and NICE, we decided to add an HTA expert group, which would provide an appropriate structure for joint reviews of the adequacy of development programmes for new pharmaceutical products, from a regulatory as well as a HTA perspective.

I could think of no better chair for this new HTA advisory board than Bengt. He was interested in getting involved in this pioneering consultancy project and accepted the role. He set out to recruit board members making use of his network of experienced experts and managed to bring renowned colleagues from the major markets on board. The initiative was launched in 2012 and so far 18 projects have been completed.

It took much too long to harmonize the EU regulatory requirements and to achieve a one stop process for obtaining marketing authorizations of new medicinal products in the EU. Embarrassingly enough, co-operation between regulators had to be driven by legislation.

I am confident that Bengt will be an outstanding leader in the EU HTA harmonization and co-operation process. He has the necessary knowledge and experience in the field as well as the social competence that is so often needed to bring negotiations to a successful conclusion.

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COMPARATIVE AND RELATIVE EFFECTIVENESS: A CHALLENGE FOR HEALTH SYSTEMS, REGULATORS, OR PHARMACEUTICAL COMPANIES?

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Looking at how well drugs work in routine clinical practice (as opposed to in experimental RCTs) is increasingly seen as essential for a proper assessment of both net benefit (health gains minus harms [15]) and of value (net benefit minus net cost). Establishing net benefit involves estimating effects in routine clinical practice, termed comparative effectiveness research (CER) in the USA and relative effectiveness (RE) research in the European Union (EU) [16]. Yet, assessments for both market authorisation by drug regulatory authorities (DRAs) such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) and "at launch" appraisals by Health Technology Assessment (HTA) bodies acting on behalf of payers (such as HAS and IQWiG) typically use efficacy and relative efficacy data [17].

[15] We should note whilst HTA bodies regard effectiveness as health gains minus any health losses from side effects or adverse reactions, Drug Regulatory Authorities (DRAs) regard most health losses as safety effects, to be assessed separately.

[16] We henceforth use the terms comparative effectiveness research (CER) and relative effectiveness (RE) research interchangeably. Comparative effectiveness is defined as "comparing health outcomes and the clinical effectiveness, risks, and benefits of two or more medical treatments, services and items" (PPACA, 2010) which means "real world settings" (Garber and Sox, 2010). Relative effectiveness can be defined as "the extent to which an intervention does more good than harm compared to one or more alternative interventions under the usual circumstances of health care practice" (HLPF, 2008). For a discussion by Bengt of the relationships of EBM, HTA, CER and CEA see Luce et al. (2010).

[17] For a discussion of the scientific issues that give rise to tensions between DRAs and HTA bodies around relative efficacy data see Eichler et al., 2011).

Bengt Jönsson (Jönsson, 2011) identifies three reasons why RE may differ across (and within) health system, reasons that may not be captured in relative efficacy studies:

- Differences in population. Even if we assume relative effectiveness is the same, differences in base line population risks will produce different *absolute* gains in health for a given incremental cost. Relative efficacy studies use entry criteria to ensure the population in the RCT is the same and so will not pick this up;
- Different comparators. Existing practice varies as both small area variation studies and studies of the extent of variations in the use of new medicines tell us (Wilking et al., 2009) hence so will the impact of switching to the use of a new treatment. Relative efficacy studies can also use different comparators, but part of the variation may come from how the comparators are used in practice. Controversy about the relative effectiveness of SSRIs versus tricyclic's for depression reflected the lower doses of the latter used in clinical practice to avoid the greater side effects of tricyclics, reducing tolerability and therefore effectiveness (Anderson, 2000). More recently, sustained release risperidone for psychosis has been found to be more effective than repeat dosing because it increases compliance (Lambert et al., 2011). Most comparator issues can be dealt with through the use of active comparators in RCTs, or the use of indirect comparisons using efficacy data. On some occasions, however, real world data will be needed;
- Differences in the efficiency of health systems. This is a key issue for Bengt, and one that is often not picked up by policy makers. Efficiency will be partly caught in the choice of comparator, yet as we have noted, for any given use of a comparator, health systems may differ in the health gain they achieve. RCT based studies of relative efficacy will usually eliminate these differences through use of the same clinical protocol, with very occasional exceptions. One exception was a multi-country RCT of NOACs against warfarin, which found large differences in the outcomes achieved for patients on warfarin (and therefore in the relative efficacy gain from use of the NOACs) because of differences in the effectiveness of warfarin management between countries within the trial (Wallentin et al., 2010). National system differences had not been eliminated by the trial protocol.

Bengt points out that the single European market for pharmaceuticals could be seen as being built on the concept of *relative efficacy*. The EMA licenses on the basis of RCTs of efficacy and relative efficacy [18], HTA bodies use the same RCT

[18] We do not use an acronym for relative efficacy. One of the problems in the debate about the merits of evidence of relative efficacy versus evidence of relative effectiveness in Europe has been that both have been given the acronym RE which means that it is often not clear which concept is being talked about!

evidence in “at launch” assessments to determine use and/or reimbursement price, the EU Directive giving patients rights to cross-border health also assumes that a drug has the same effect wherever given [19], and the R&D-based industry puts its efforts into RCT-based clinical development. On this model, there is unnecessary duplication between the EMA and HTA bodies and across HTA bodies themselves – all analysing the same data. Bengt points out there is a strong scientific case for the EMA to look at relative efficacy (including analysis of indirect comparisons) on behalf of HTA bodies. Such an option was rejected by the HTA bodies who do, and want to do, this themselves[20]. A European Network for Health Technology Assessment (EUnetHTA) initiative (EUnetHTA, 2014) involves undertaking 10 pilot Rapid Reviews of Relative Effectiveness with two lead HTA bodies sharing the review process as a prototype pan-EU process. Given these are “at launch” reviews they will inevitably focus on relative efficacy. However, they will provide a basis for avoiding duplication and provide building blocks for both those systems that look at cost-effectiveness using RE (including the Netherlands, England, Scotland and Sweden) as well as those that focus on relative efficacy to assess therapeutic added value (notably France and Germany) (Towse and Barnsley, 2013).

Yet, as Bengt argues (Jönsson, 2011), the challenge for both EU and the US is realising value in practice. I would interpret the challenge Bengt gives us as a simple one:

> *Can we create an EU (and US) environment in which the focus is on relative effectiveness (RE) and cost effectiveness with an optimal amount of RE evidence generated and used efficiently?*

Efficiency, I would argue, in this context requires (i) static efficiency in maximising the use of cost-effective new drugs and other technologies [21] (ii) sending the correct signals to companies about research priorities – to achieve dynamic efficiency - and (iii) health care systems put under pressure to move towards their efficiency frontiers to (a) get optimal health from their use of any given set of technologies, and that, in turn, they (b) choose the most effective

[19] It could be argued that the cross border Directive is designed to increase competition in services and so to enable patient choice across member state boundaries to improve effectiveness and cost-effectiveness. It is, however, widely seen as a mechanism to drive a uniform approach to coverage, i.e. what is provided to patients, on the assumption that effectiveness is the same wherever it is provided.

[20] Strictly no formal proposals were made or rejected. The EMA took informal soundings. HTA bodies were opposed to the EMA entering “their” terrain. The progressive part of the pharmaceutical industry saw that without buy-in from HTA bodies it would introduce another hurdle not eliminate one. The conservative part of the industry has always opposed any extension of the EMA’s remit into HTA.

[21] Strictly, this is second best static efficiency, i.e. maximising use subject to prices being above marginal cost during the patent period.

set of technologies given income constraints and enrollee preferences for health over other goods and services.

We seek to address this challenge in two parts.

Firstly, where are we starting from in the EU? The relative efficacy approach is increasingly seen as not enough. Payers, HTA bodies and regulators are asking for post-launch studies. Pharmaceutical companies are investing in "real world data" collection in anticipation of further growth. Yet collecting and using such evidence can be resource intensive. There is, as Bengt has pointed out, a great risk of:

(a) Duplication and lack of synergy, with: companies expected to undertake similar but different post-launch studies for DRAs and multiple HTA bodies in different jurisdictions; these bodies in turn each separately assessing and appraising this evidence; these studies being additional to current pre-launch RCTs; and companies making multiple sequential and duplicative ad hoc investments in research capability in both pragmatic trials and observational studies;
(b) A mismatch of expectations as to what these studies will reveal. Companies are looking for higher prices and revenues, payers for more targetted use and lower expenditure;
(c) Such results being seen only as informing drug pricing or approved use, and not being used to improve health system performance. For Bengt this would be a missed opportunity.

Secondly, what needs to happen to create a better environment? Looking first at RE information and then at cost-effectiveness. Three things are needed for a system built around RE to lead to improvements in efficiency:

1. A *new drug development paradigm* in which companies can generate RE evidence in either (i) pre-launch pragmatic trials whilst meeting DRA requirements or (ii) post-launch as part of adaptive licensing [22] combined with coverage with evidence development or some other form of performance-based risk sharing arrangement. This requires, inter alia, two major changes to the parallel scientific advice given by DRAs and by HTA bodies acting on behalf of payers. Firstly, there needs to be a conscious effort to achieve a consensus as between both the DRA and HTA bodies and as between the various HTA bodies about end points and study design. Secondly, this should not only cover pre-launch evidence collection, but also post-launch evidence collection with a potential trade off between them. In

[22] Adaptive licensing has been defined as "a prospectively planned, flexible approach to the regulation of drugs and biologics…iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation." (Eichler et al., 2012)

other words, the DRA and HTA bodies might be willing to accept more uncertainty around at-launch evidence if this uncertainty is to be addressed post-launch and, conversely, they may accept that no substantial post-launch studies are required if particular plans for extensive pre-launch data collection are put in place. Such a mechanism would make a reality of the need for manufacturers to trade pre- and post- launch studies to keep development costs under control.

2. A *major elimination of the duplication of infrastructure and assessment effort* to drive costs out of the system. This requires:
   a. Health systems to introduce information systems which track patients , in particular electronic health records (EHRs), so enabling them to improve the efficiency of their health systems, but which then offer the by-product of the opportunity for companies (at a fee) to "piggy back" on top of them to conduct observational studies of the RE of drugs, to identify patients for RCT or pragmatic trial recruitment and to conduct pragmatic clinical trials at low cost by tracking patients through routine data sources (i.e. their EHRs) after the intital randomisation;
   b. Health systems and governments to put in place research infrastructure for pragmatic clinical trials including Large Simple Trials [23], which companies would have to pay to use, but would not have to replicate on each occasion that they wished to (or were asked to) conduct a study;
   c. EUnetHTA to achieve the goal of a single pan-EU HTA submission for at-launch rapid assessment of RE, with mutually recognition of rapid-RE assessments of that submission (i.e. as with the EMA rapporteur system, only two agencies conduct the review), reducing HTA/payer and manufacturer duplication of effort. Effective use of the EMA's assessment of the RCTs as part of its licensing role should be part of this, whether through a further revised EPAR or other means. Other means could include HTA bodies paying the EMA for additional analysis or reporting, if that is a more efficient way of achieving the goal of a high quality RE assessment, rather than HTA bodies conducting their own reviews. Such an RE assessment would then be used by all national / regional HTA bodies and payers in the EU as input to their appraisal and reimbursement decisions.
3. An *understanding of the efficiency of health systems* into which new drugs are to be delivered (or not as the case may be). This requires the use of techniques such as Data Envelope Analysis, including the calculation of Malmquist indices, and Stochastic Frontier Analysis to understand how well health systems are using particular technologies or performing more

[23] A Large Simple Trial is a prospective, pragmatic controlled trial that combines randomisation with large numbers of patients, broad inclusion criteria, multiple study sites, minimal data requirements, and electronic registries.

generally in the transformation of inputs to achieve health gain outputs. Such analysis can then be put to two uses:

a. Firstly, it provides a basis for understanding whether post launch studies of drugs are likely to produce different answers in different health systems. Whilst Eichler et al. (2011) in their analysis of efficacy – effectiveness differences argued that population differences were likely to be minimal within the EU, they did acknowledge other health system differences might exist – a key aspect of Bengt's approach. The use of analytical techniques offer a route to identify where efficiency differences may require separate studies;
b. Second, it provides a basis for identifying poorly performing health systems, i.e. those that appear to be delivering health care treatments and health outcomes well within their potential given the resources they choose to deploy.

These factors governing the generation and use of RE will move us towards an EU-wide model for efficient health systems, achieving elements (i) and (iii)(a) of our efficiency requirements.

Achieving all the elements of efficiency will require adding *cost effectiveness* to the use of RE evidence. Pharmaceutical prices, whether set by companies or negotiated in some way, need to be linked to use in each health system according to the value (net benefit minus cost) they deliver. Bengt has long argued (Drummond et al. 1997) that reference pricing is inefficient and prices should reflect local incremental value. This will be essential to achieving elements (ii) and (iii)(b) of our efficiency requirements. The EU has no political responsibility for pharmaceutical pricing [24]. However, it can support efficient local value assessment and use through its support for the pan-EU RE process and for adaptive licensing [25]. It is also, importantly, supporting comparisons of health system efficiency and the IMI initiative to promote more efficiency drug development. I referred above to the dangers of a mismatch of expectations as to what RE studies will reveal. Companies are looking for higher prices and

[24] We can note that the European Commission currently seems to think that efficiency in pharmaceutical use will be encouraged by having a single price for drugs throughout the EU and encouraging pricing disclosure and transparency in order to achieve this. As a report for the Belgian Presidency of the EU (Annermans et al., 2010) pointed out such a policy will lead to substantial unnecessary inequality in access to drugs within the EU as patients in poorer countries area are denied access to new medicines because their governments cannot afford to pay the European price. It fails element (i) of our efficiency criteria in a rather spectacular way. Not unsurprisingly low income countries and manufacturers are opposed to the policy, whilst some richer countries support it as a mechanism to get lower prices for their health systems.

[25] The European Commission seems to be reluctant to actively support adaptive licensing – presumably because of fears that it may lead to more product withdrawals. However, it is supporting pan-EU discussions on coverage with evidence development by payers and HTA bodies acting on their behalf, and commissioned research. This is a necessary corollary to adaptive licensing – payers will need tools to help them deal with greater uncertainty at launch.

revenues, payers for more targetted use and therefore lower expenditure. Appraisal of RE evidence should edge both parties towards efficient pricing and use of a new drug. It assumes that pricing and use will reflect value and as evidence of value changes, so will price and use. In some cases, study results will mean that companies will end up with lower prices and/or less use than they had expected, in other cases payers may end with higher prices and/or greater volume generated expenditure than they had expected.

Member state health systems decisions about the effiency use and pricing of medicines will continue to differ as between them because of variations in: (a) clinical practice (b) willingness to pay for health care treatments (c) health system efficiency and (d) patient demographics. Some or all of these should converge over time, and achieving the efficiency objective we have ascribed to Bengt does require movement on (a) and (c).

Finally, it is important to ask "how might Bengt's approach be translated into a US setting?" not least because drug development is a global activity and duplication of evidence generation, gathering and review as between the US and the EU is not efficient, unless there are genuine differences in RE on each side of the Atlantic such that separate evidence is required.

Looking first at the US alone, it has hitherto been built on the efficacy approach. The FDA issues market authorisation. Payers manage drug budgets by a combination of high copayments (via tiers) and seeking discounts from suppliers of competing therapies – often linked to tier placement. There is a huge variation in outcomes. Increasingly, the focus is on achieving health outcomes, and achieving them more efficiently. There is an interest in real data. Payers and manufacturers are already using observational data generated within claims databases. Investments in EHRs are taking place. Payers are looking for RCT evidence from pragmatic trials. If the Accountable Care Organisations (ACOs), now being established under the Patient Protection and Affordable Care Act, take on capitation based contracts placing them at risk for patient outcomes, they will have a strong incentive to understand how they can cost-effectively manage patients over time. As a consequence, the importance of collecting routine outcome data will increase substantially. Whilst it is very unlikely that the FDA would introduce adaptive licensing, its use of Accelerated Approval is achieving the same effect. PCORI and NIH are making investments in pragmatic cliical trial research infrastructure capability. All of this offers the potential for the US to move towards a model based on generating and using CER evidence.

Could we improve trans-Atlantic efficiency? It is possible that PCTs and observational studies carried out in the US or EU would provide relevant evidence on the other continent, albeit with some adjustments. This is a scientific issue to be explored. Could there be mutual recognition by the FDA

and EMA of each others assessment reports – recognising that decision criteria differ – and a shared view of relevant trial design, and so of the nature of scientific advice offered? That may be more difficult to achieve. It would be ironic if trans-Atlantic convergence on efficient approaches to assessing CER/RE evidence, together with local use of cost-effectiveness analysis (achieving Bengt's efficiency objectives) occurred before convergence of FDA and EMA approaches to efficacy and relative efficacy assessment. I think that would make Bengt smile.

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COST PER QALY IN THE U.S. AND EUROPE: WHEN HEALTH ECONOMICS MEETS POLITICS

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Policies regarding, and public attitudes toward, the use of cost-effectiveness analysis in the U.S. and Sweden are very different. Indeed, the notions of "health economics" are very different in these two counties, owing in part to their divergent views of the role of the public sector in health care. Since the readers of this paper know more about Swedish health care – or, for that matter, health care in other countries – than I, my remarks will mostly concern the situation in the United States. I leave it to readers to draw out the contrasts, although I will conclude with some observations about the differences between the practice of cost-effectiveness analysis in the U.S. and Sweden and other European countries.

In the market-driven U.S., health economics is concerned mostly with the functioning of private health care markets, identifying the causes and consequences of market failure, and studying the effects of remedies for market failure. Government does play a major role as the health care insurer for retired, disabled, and indigent persons, and most federal employees, but politics has precluded meaningful intervention to remediate the consequences of moral hazard and information asymmetry between physician and patient, even under public health insurance plans. Incentives are mostly aligned with maximization of profit and/or personal income, and not directly with maximization of health. Since no central authority is charged with allocating health resources nationally, there is no direct role for economic evaluation in the U.S. Even the public health insurance programs do not use cost-effectiveness analysis, at least not explicitly. Although some government agencies do pay attention to cost-effectiveness analyses to guide decisions about programs and policy recommendations, such as for immunizations through the Advisory Committee

on Immunization Practices administered by the Centers for Disease Control and Prevention, these are the exceptions to the rule.

The watershed legislation that mandated nearly universal health insurance coverage in the U.S. – the Affordable Care Act of 2011 – seeks to accomplish this goal mostly through creation of private "health insurance exchanges", rather than by expansion of public insurance. So-called "Accountable Care Organizations", charged with being the stewards of financial resources on behalf of providers and their patients, may or may not choose to use cost-effectiveness as a criterion for resource allocation. While creating a quasi-public organization – the Patient-Centered Outcomes Research Institute (PCORI) – to conduct studies of the comparative effectiveness of health care interventions from a patient-centered perspective, the legislative mandate under which it operates is silent on the role of cost in this research. While PCORI could arguably undertake cost or cost-effectiveness studies on its own, it has not done so. Indeed, the same legislation that created PCORI explicitly proscribes the use of cost-per-QALY thresholds in coverage and pricing decisions by public payers:

> "The Patient-Centered Outcomes Research Institute (PCORI) …shall not develop or employ a dollars per quality-adjusted life year (or similar measure that discounts the value of life because of an individual's disability) as a threshold to determine what type of health care is cost effective or recommended. The Secretary [of Health and Human Services] shall not utilize such an adjusted life year (or such a similar measure) as a threshold to determine coverage, reimbursement, or incentive programs under [Medicare]." Source: The Patient Protection and Affordable Care Act. PL 111-148. 3-23-2010.

In the political discourse surrounding the passage of this contentious legislation, decision making based on value was equated with "death panels":

> "The Democrats promise that a government health care system will reduce the cost of health care, but … government health care will not reduce the cost; it will simply refuse to pay the cost. And who will suffer the most when they ration care? The sick, the elderly, and the disabled, of course. The America I know and love is not one in which my parents or my baby with Down Syndrome will have to stand in front of Obama's "death panel" ... Such a system is downright evil." Source: Sarah Palin, on Facebook, August 7, 2009.

Even well-meaning scholars and observers of American health care have conjured up a number of mythical reasons why cost-effectiveness analysis is unnecessary, if not harmful, in order to contain health care costs in the U.S.,

which are far and away the largest in the world, now exceeding 18 percent of gross domestic product.

REASON #1. THERE IS NO RELATION BETWEEN HEALTH CARE EXPENDITURES AND HEALTH OUTCOMES ACROSS HOSPITALS AND GEOGRAPHIC AREAS.

This fact is confirmed by numerous cross-sectional studies of health expenditures and health outcomes across geographic areas. Some of these studies even show that places (states, cities, hospitals) that spend more per capita get worse outcomes or lower health care quality (Baicker and Chandra 2004). This inverse relationship between expenditures and health care quality has been widely misinterpreted. The naive, but mostly incorrect, explanation is that the extra spending in high-cost, poor outcome areas is wasteful or, worse, harmful. If that were true, then the painless remedy would be to cut out wasteful spending and useless services, with no need to confront the tradeoff between lower cost and better outcomes implied by cost-effectiveness analysis. This interpretation may be wrong, however, because there is another possible explanation of the inverse or null relationship between spending and outcome observed in cross-sectional studies. The alternative explanation is that the high-spending areas are spending too much on low-value health services (high cost per QALY) and not enough on low-value services (low cost per QALY) (Weinstein and Skinner, 2010). Several empirical studies support this alternative hypothesis. One such study shows that the inverse relation between spending during the first year after a myocardial infarction and 12-month survival, which was observed across U.S. hospitals during the period from 1980 and 1990, was due to differences in the rate of adoption of highly effective – and cost-effective – technologies such as post-MI aspirin use, beta-blockage, and thrombolysis (Skinner and Staiger, 2009). After controlling for this rate of adoption, the relation between expenditures and survival became positive, suggesting that cutting the budgets of high-cost hospitals would have cost lives, not saved them. On the other hand, the pathway toward better health outcomes would have been for the high-cost hospitals to substitute these highly cost-effective interventions for some of the "flat-of-the-curve" (less cost-effective) interventions they were apparently providing more of to their post-MI patients than were their lower-cost counterparts. In other words, the pathway toward better outcomes and lower costs could have been illuminated by cost-effectiveness analysis!

REASON #2. IF WE STOP OVERPAYING DOCTORS AND DRUG COMPANIES, THERE WILL BE ENOUGH MONEY TO PAY FOR ALL USEFUL HEALTH CARE.

The U.S. pays more for drugs and physician services than most other countries (including Sweden). But the consequences of price regulation, and the relaxation of patent protection, on innovation are unknown. The effect of payment levels on the supply of physicians in the U.S. is also undeniable, as

evidenced by the decline in the supply of generalists and the relative attractiveness of specialty care for medical school graduates. Price reductions in either of these areas have unknown implications for overall health care cost and quality, but the general consensus is that the U.S. needs more, not fewer, generalists to serve as the "medical homes" for patients.

REASON #3. IF WE DO MORE PREVENTION, THERE WILL BE ENOUGH MONEY TO PAY FOR ALL USEFUL HEALTH CARE.

This widely-held belief is a myth. Evidence from systematic reviews of economic evaluations of clinical preventive services reveals that preventive services usually cost more than they save. Many preventive services are relatively cost-effective in terms of cost per QALY gained, but many are not, and only a few are cost-saving. In fact, in the most widely cited systematic review, preventive services as a class were no more cost-effective than treatments or diagnostics (Cohen et al., 2008).

REASON #4. IF WE DO MORE COMPARATIVE EFFECTIVENESS RESEARCH, WE CAN IDENTIFY USELESS HEALTH CARE, SO THERE WILL BE ENOUGH MONEY TO PAY FOR ALL USEFUL HEALTH CARE.

It is very difficult to prove a negative in comparative effectiveness studies. A comparative study may show no significant difference between the outcomes from competing clinical strategies, but failure of a statistical significance test does not prove that there is no incremental benefit. Comparative effectiveness studies may bound the difference, but it is necessary to use cost-effectiveness analysis to determine whether the possibility of a small incremental benefit is worth the cost.

REASON #5. QALYS DISCRIMINATE AGAINST THE DISABLED, THE ELDERLY, AND CHILDREN.

While it is true that quality-of-life weighting in cost-effectiveness analysis diminishes the value of survival gains for persons with impaired health status, analyses are seldom applied to disabled subpopulations. The charge of discrimination against the elderly is based largely on the fact that preventing the death of a 90-year-old results in fewer years of life expectancy gained than for younger persons, and the charge of discrimination against children is that discounting diminishes the value of the long stream of potential future QALYs gained. Ironically, these two claims could equally be applied in reverse, to argue for discrimination in favor of young people and in favor of the elderly, respectively.

REASON #6. THE MARKET WILL DETERMINE THE RIGHT LEVEL OF SPENDING ON HEALTH CARE, AND THE RIGHT ALLOCATION OF RESOURCES.

Health economists worldwide recognize that markets for health care and health insurance exhibit many of the textbook criteria for market failure, including information asymmetry, barriers to entry, and moral hazard. Markets do have advantages in promoting efficiency in some aspects of health care delivery, but that does not mean that the overall result will be an efficient outcome in terms of health production. The negative correlation between health spending and health observed across geographic areas in the U.S. testifies to market failure and the need for intervention to ensure that health care resources are allocated efficiently. Cost-effectiveness analysis is needed to guide the policy interventions to improve the efficiency of health care.

REASON #7. QALYS DON'T REFLECT EVERYTHING THAT PEOPLE CARE ABOUT IN HEALTH CARE (PSYCHOLOGICAL VALUE OF KNOWING, CARING, ACCESS, EQUITY)

Of course this is true, but this doesn't imply that information on cost per QALY is not important for decision making in health care. The U.S. Panel on Health and Medicine was very clear in saying:

> "CEA is an **aid to decision making**, not a complete procedure for making resource allocation decisions in health and medicine, because it cannot incorporate all the values relevant to such decisions." Source: *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press, 1997.
>
> The fact that cost-effectiveness analysis should not be used exclusively to make resource allocation decisions does not imply that it should not be used at all.

In many European countries, including Sweden, formal methods of economic evaluation, mostly cost-effectiveness analysis, are mandated for health technology assessments. Guidelines for the practice of CEA are followed rigidly by some health authorities, even though the guidelines in different countries are often at odds with each other. For example, Sweden is one of the few countries that include economic productivity losses, including early retirement, among the costs in its mandated analyses. Perhaps this reflects a less clear demarcation between the roles of government in health care and in other sectors of the Swedish economy. As another example, most national guidelines agree with the U.S. reference case recommendation for equal discounting of costs and health consequences, but a few countries, such as the Netherlands, use different discount rates for costs and health effects. And unlike the U.S. reference case, which requires uncertainty analysis but does not require formal probabilistic

sensitivity analysis (PSA) in all cases, NICE virtually requires PSA. The strict adherence to these country-specific guidelines would seem to be at odds with the more flexible stance taken by the U.S. Panel, which recognizes that the quantifiable sources of uncertainty and values may be less important to decision making than the limitations of the underlying mathematical models and the limited degree to which the gain in quality-adjusted life years fully reflects the value of a health technology to patients.

The appropriate level of reliance on formal economic evaluation is intermediate between these two extremes. Control of health care costs in the U.S., as in Sweden, the Netherlands, and Britain, cannot be achieved humanely without confronting the tradeoff between expenditures and health outcomes. Sweden and other European countries rightly recognize economic evaluation as an essential tool in evaluating the evidence on comparative effectiveness of health services. However, because cost per QALY is not a complete measure of what people value from health services, excessive standardization of its measurement and reporting of the uncertainty of its estimation are unnecessary and possibly counterproductive.

Whether decisions are made by public agencies or left to market forces, transparent, understandable representations of benefits, harms and costs are essential to inform decision makers at all levels, including the general public. While a reference case is important to enable comparability of incremental cost-effectiveness ratios, the main value of CEA lies not in the number it produces but in the process of being open and transparent about the necessary tradeoffs between health care expenditures and health outcomes.

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HEALTH ECONOMICS INTO THE JUNGLE OF CANCER-"OMICS".

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INTRODUCTION

I first met Bengt Jönsson in the late 1990s while working on the development of new anti-cancer drugs, and from 2004 onwards I had the privilege of working closely with him on a number of projects, principally in the field of cancer. To honour his important contribution to the field of cancer economics, I will attempt to summarize 10 years of collaborative work. During this period, several reports investigated how cancer care is provided in different parts of the world.

THE "KAROLINSKA REPORTS"

The first two reports, for Europe, were published by the Karolinska Institutet in 2005 and 2007 (www.comparatorreports.se). The first focused on access to cancer drugs with a special emphasis on new cancer drugs, for which Bengt developed a novel methodology. The second linked access to treatment with overall outcome (survival).

The new drugs, such as rituximab, trastuzumab and imatinib, included some of the major breakthroughs in cancer drug development during 1990s. These three drugs were already established in 2005 as true contributions to the treatment of different cancers, like lymphoma (rituximab), HER2+ breast cancer (trastuzumab) and chronic myeloid leukemia (CML) (imatinib). This being said, there was still a lot of controversy around the drugs, mainly related to the cost of

treatment. Some of the key findings in the first “Karolinska Report” are still valid. Firstly, there were major gaps in estimating the burden of cancer and its treatment across Europe. This is partly linked to the lack of proper cancer registration in many European countries, but also to a lack of information on treatments used in the established cancer registries, including the Nordic registries with the longest history dating back to the 1950ies. Secondly, access to treatment, especially to the newer and more costly treatments, varies greatly across Europe. Differences are both between countries, linked to the economic situation in different parts of Europe (Western versus Central/Eastern Europe), and within countries in, for example, the UK and Sweden.

The findings of the reports were widely discussed. The debate was especially heated in the UK where access to many of the new cancer drugs seemed both slower and lower than in other European countries like France and Germany and appeared to be linked to a relatively poor outcome (Coleman 2007). However, some of the reactions were more focused on “killing the messengers” than on the underlying cause.

While there were admittedly a number of shortcomings in the reports, in particular relative to the linkage between access and outcome, they were largely due to a lack relevant data. We did not have good data allowing proper analysis of the impact of new technologies on outcome for many forms of cancer. Nevertheless, during the following 4-5 years several follow-up reports showed a clear link between access to cancer treatment and improved survival. The most striking example is the impact of imatinib on the outcome of CML in Sweden and in the US (Björkholm et al 2011; Höglund et al 2013; Pulte et al 2011) Other examples are the outcome in advanced lung cancer (von Plessen et al 2008) and the marked improvement in the outcome of breast cancer based on an increasing use of adjuvant medical treatment (Kalager et al 2009). On the other hand, the effect on outcome of some other new cancer drugs, e.g. in colorectal and renal cancers, has been much more limited. (Ocana et al 2011; Shah et al 2013) Yet these drugs have come at a substantial cost to the health care system thereby limiting investment in other areas of cancer care.

THE IMPACT OF THE REPORTS

Looking back, the first reports appear to have had some impact, particularly in the UK. The data on the situation in the UK prompted several specific reports compiled in the UK that confirmed the large differences in access even within the country. The discussion on access had also highlighted the work of NICE and issues linked to their process. Still, as pointed out by Bengt (Jönsson 2009), “Being NICE is not the only problem”. An example of this is that NICE had given positive opinions on trastuzumab both in 2001 and 2006 but access to the drug

still showed large geographical variation in the UK. A similar debate was prompted by the Karolinska reports in Norway, where large regional differences in access to trastuzumab had been shown but resulted in a much more equal use of the drug within a year. On the other hand, the reports showed major regional differences in the spending on cancer drugs also in Sweden where the impact is still limited.

Another positive and very important development triggered by these discussions is the very efficient set-up of a new cancer registry in the UK, the National Cancer Intelligence Network (NCIN 2013). The NCIN is a UK-wide initiative, working to drive improvements in standards of cancer care and clinical outcomes by improving and using the information collected about cancer patients for analysis, publication and research. NCIN is co-located with the National Cancer Research Institute (NCRI) and works closely with cancer services in England, Scotland, Wales and Northern Ireland. The aims and objectives of NCIN cover five important areas to improve the quality and availability of cancer data from its collection to use. These areas include:

- Promoting efficient and effective data collection throughout the cancer journey
- Providing a common national repository for cancer datasets
- Producing expert analyses, to monitor patterns of cancer care
- Exploiting information to drive improvements in cancer care and clinical outcomes
- Enabling use of cancer information to support audit and research programmes

This UK initiative serves as a good example of what is needed in the future in order to be able to evaluate the impact of new technology in the cancer area on a population level.

FUTURE RESEARCH

I believe that the Karolinska reports, although criticised by many, started a discussion and opened up a new area in the field of outcomes research and the economics of cancer. The methods may have been simple, measuring access by macro models and linking access to epidemiological data. Still, based on the feedback we have received the methods have constantly developed further. The main reports focus on Europe, special reports focused on North and Latin America, Middle East, Australia, New Zeeland, Japan, China as well as South Africa (www.comparatorreports.se). And while the main work focused on cancer in general, special reports exist for breast cancer, lung cancer, haematological diseases as well as rare cancers (www.comparatorreports.se). Interestingly we

are currently witnessing an emerging debate and focus on the costs of cancer care in the US. This opens the field for further research, but most importantly, the need for better data to assess the outcome and cost of cancer treatments has become even more evident.

CLINICAL TRIALS

Too much emphasis on a new technology is based on data generated in the pivotal trials (clinical efficacy). This first part of the clinical development process will merely show that the treatment may work. In advanced stages of cancer the measure of progression free survival (PFS) is a commonly accepted surrogate end-point, although it is not transferable to prolonged overall survival (OS) in many cases (Booth and Eisenhauer 2012). There may be initial interesting data on a treatment with effect on PFS, later showing a limited effect on OS. Among others, there may be biological factors as well. There is need for further research to establish relevant links between surrogate endpoints used in trials, and patient relevant outcomes and focusing on overall survival and quality of life (QoL) improvements. Another well-known limitation with controlled clinical trials is that patients do not mirror patients treated in clinical practice; patients in clinical trials are usually younger and have fewer co-morbidities and/or the comparator arm may not reflect standard of care.

REAL LIFE DATA

We need therefore to add information to the results from clinical trials by collecting “real life data”. This area, clinical effectiveness, is underdeveloped in general and in cancer in particular, as clinical strategies differ in many ways from clinical trials. There is hence a need to develop knowledge of outcome in clinical practice. Outcomes research and clinical effectiveness should be steered toward critical discussions related to health care costs, cost-effectiveness, and the comparative value of the available options for appropriate care of patients with cancer (Lyman 2013).

Economics has rapidly become important for decision makers in health care. When there are several treatment options or strategies available, the choice is (at least partly) based on outcome as well as resource use for the different options, i.e. the principle of cost-effectiveness. As pointed out regularly by Bengt, cost-effectiveness has to have *linked* data on resource use and outcome. It is therefore necessary to collect both types of data simultaneously for individual patients to be able to establish causality. Cost-effectiveness depends on the use of a given treatment in a defined patient in relation to a defined alternative. With the move towards personalised medicine, particularly in cancer, there is an increased need for studies in clinical practice, as the target patient

groups are becoming smaller and the cost per QALY may be high (Weinstein and Skinner 2010).

The assessments of resource use and outcome for health economic studies need careful consideration, and it is necessary for oncologists and health economists to work closely together to define required data on patients and treatments necessary for the assessment of outcome. We need to “economise” to make sure that data are collected once only and with good quality.

If European countries would, as Bengt has argued, set up joint clinical effectiveness studies, good data on clinical effectiveness generated in a controlled format would be available faster. At minimum, we need data on biology, relevant co-morbidities, follow-up date for diagnostics and treatments given and outcome in terms of survival and quality of life. Investment and organisation of data collection must be given highest priority. Patient records should be organised and transfer data automatically, making extraction of data easy. Progress is being made even though the process may seem slow in relation to the need for much better data.

CONCLUSIONS

The projects described here are just a few examples of the important contribution Bengt Jönsson has made and is making to the field of cancer. Bengt´s work and experienced input is not just important from a health economic point of view, but it forms the final important part of the translational process in modern cancer research.

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THE NET-BENEFIT APPROACH FOR STATISTICAL ANALYSIS IN COST-EFFECTIVENESS ANALYSIS

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INTRODUCTION

During the 1990s it became common to base health economic evaluations on clinical trials with individual cost and health effects data, which opened up the possibility of using statistical methods to analyse uncertainty arising from sampling variability. Following this development an increasing number of health economic studies focused on appropriate methods for the estimation of confidence intervals for the incremental cost-effectiveness ratio (ICER). The first studies published in 1994 by O'Brien et al. and Van Hout et al., where followed by an intensive methodological discussion on the appropriate methods for the estimation of confidence intervals for the ratio. Although simulation studies usually showed that the Fieller's and non-parametric bootstrap methods were the most accurate ones based on statistical criteria (Polsky et al. 1997, Tambour & Zethraeus 1998), there was an on-going discussion of the problems associated with the construction and interpretation of confidence intervals for the ICER and the most appropriate way of representing uncertainty in cost-effectiveness analysis (Briggs & Fenn 1998).

In the late 1990's a new approach for analysing uncertainty in cost-effectiveness analysis – *the Net Benefit Approach* - was presented. The net benefit approach was primarily developed as a response to the need to estimate confidence intervals for the ICER and was simultaneously presented by the research group at the Centre for Health Economics at the Stockholm School of Economics (Tambour, Zethraeus & Johannesson 1997 & 1998) and by Stinnett & Mullahy (1998). The net benefit approach is based on a simple reformulation of the decision rule of cost-effectiveness analysis in terms of a net benefit measure that can be expressed either in units of money (Tambour, Zethraeus & Johannesson 1998) or health (Stinnett & Mullahy 1998). A monetary net benefit is obtained by rearranging the cost-effectiveness decision rule $\frac{\mu_{\Delta C}}{\mu_{\Delta E}} < p$ (the additional costs of producing one more unit of health effects for a new therapy compared with a control should not exceed the maximum price p society is willing to pay for one more unit of health effects), into a net benefit decision rule, $p\mu_{\Delta E} - \mu_{\Delta C} > 0$ (the monetary value of the health improvement should exceed the additional costs), where $(p\mu_{\Delta E} - \mu_{\Delta C})$ is the net benefit in monetary terms, and where $\mu_{\Delta E}$, and $\mu_{\Delta C}$ are the mean difference in effects and costs between two treatment alternatives.

The net benefit approach has contributed substantially to simplifying the statistical analysis of uncertainty in cost-effectiveness analysis. It has not only facilitated confidence interval estimation, but also hypothesis testing, sample size calculations, Bayesian analysis and the issue of whether to collect more information for a decision. It also provides a formal relation between cost-effectiveness acceptability curves and statistical inference (Löthgren & Zethraeus 2000). Further, the net benefit approach also gives the Fieller's limits of the confidence interval for the incremental cost-effectiveness ratio (Heitjan 2000, Zethraeus & Löthgren 2000). The advantages of using the net benefit approach for analysing uncertainty in cost-effectiveness analysis are summarised in a comprehensive review (Zethraeus, Johannesson & Jönsson et al. 2003). Here we again show that the net benefit approach gives the Fieller's limits of the confidence interval for the ICER[26].

TWO EQUIVALENT DECISION RULES OF COST-EFFECTIVENESS ANALYSIS

Assume, in the case of two treatment alternatives, that two samples of bivariate cost (C) and effect (E) data of a control and a new treatment are available from

[26] The close relation between the Fieller's method and the (monetary) net benefit approach has previously been shown in Zethraeus & Löthgren (2000) on which this paper is heavily based. Heitjan (2000) showed that the set of values of *p* at which the confidence interval for the health net benefit just covers 0 is equal to the Fieller's method confidence interval for the ICER.

some general bivariate distribution (the data are not assumed to be bivariate normally distributed) as

$$\binom{C_{ji}}{E_{ji}} \sim \left(\binom{\mu_{C_j}}{\mu_{E_j}}, \begin{pmatrix} \sigma_{C_j}^2 & \sigma_{C_j E_j} \\ \sigma_{E_j C_j} & \sigma_{E_j}^2 \end{pmatrix} \right), i = 1, \dots, n_j \qquad (1)$$

where $j = 0{,}1$ index the control and new treatment, respectively. μ_{C_j} and μ_{E_j} denote the expected (mean) values, $\sigma_{C_j}^2$ and $\sigma_{E_j}^2$ denote the variances and $\sigma_{C_j E_j}$ denotes the covariance between the costs and effects for treatment j. Denote the mean cost difference between the new and control treatment by $\mu_{\Delta C} = \mu_{C_1} - \mu_{C_0}$ and the mean effect difference by $\mu_{\Delta E} = \mu_{E_1} - \mu_{E_0}$. The incremental cost-effectiveness ratio R is defined as $R = \frac{\mu_{\Delta C}}{\mu_{\Delta E}}$, (assuming $\mu_{\Delta E} \neq 0$) and represents the incremental mean cost of producing one more unit of health effects achieved by the new treatment (given that $\mu_{\Delta E} > 0$ and $\mu_{\Delta C} \geq 0$). The new treatment is cost-effective according to the following decision rule

A new treatment is cost-effective if: $\begin{cases} R < p, given\ that\ \mu_{\Delta E} > 0, \\ R > p, given\ that\ \mu_{\Delta E} < 0. \end{cases}$ (2)

The cost-effectiveness decision rule in (2) can be expressed equivalently in terms of a net benefit decision rule showing that the new treatment is cost-effective if $(p\mu_{\Delta E} - \mu_{\Delta C}) > 0$, where the monetary net benefit measure is defined as $NB(p) = p\mu_{\Delta E} - \mu_{\Delta C}$. The estimators commonly used to estimate R and $NB(p)$ are based on the sample mean of the observed costs and effects in the two treatment samples. The ICER and net benefit estimators are given by $\hat{R} = \frac{\hat{\mu}_{\Delta C}}{\hat{\mu}_{\Delta E}}$ and $\widehat{NB}(p) = p\hat{\mu}_{\Delta E} - \hat{\mu}_{\Delta C}$, respectively, where the mean effect and cost difference estimators are given by the sample mean differences of effects and costs, respectively as $\hat{\mu}_{\Delta E} = \bar{E}_1 - \bar{E}_0$ and $\hat{\mu}_{\Delta C} = \bar{C}_1 - \bar{C}_0$, where $\bar{E}_1, \bar{E}_0, \bar{C}_1$, and $\bar{C}_0$ are the sample mean effects and costs of the new and control treatments, respectively. Note that $\widehat{NB}(p)$, $\hat{R}$, $\hat{\mu}_{\Delta E}$, $\hat{\mu}_{\Delta C}$ denote estimators which are separated from the estimates $\widehat{nb}(p), \hat{r}, \hat{\mu}_{dE}, \hat{\mu}_{dC}$ obtained in a specific trial.

A RELATION BETWEEN THE NET BENEFIT AND THE FIELLER'S METHOD

Following the results of the central limit theorem, for sufficiently large samples sizes, the net benefit estimator will be normally distributed as

$$\widehat{NB}(p) \sim N\left(NB(p), \sigma^2_{\widehat{NB}(p)}\right), \qquad (3)$$

where the net benefit estimator variance $\sigma^2_{\widehat{NB}(p)}$ can be expressed as

$$\sigma^2_{\widehat{NB}(p)} = p^2 Var(\hat{\mu}_{\Delta E}) + Var(\hat{\mu}_{\Delta C}) - 2pCov(\hat{\mu}_{\Delta E}, \hat{\mu}_{\Delta C}), \qquad (4)$$

with estimate $\hat{\sigma}^2_{\widehat{NB}(p)}$ obtained by substituting the variance and covariance expressions in (4) by the corresponding sample estimates. Note that the normal distribution results are valid whether or not the individual cost and effect distributions are normal or not. The more skewed and non-normal the individual distributions are the larger sample sizes are needed for the normal distribution approximation to be valid. A standard (1- α) level two-sided confidence interval for the net benefit is given by $\widehat{nb}(p) \pm z_{\alpha/2}\hat{\sigma}_{\widehat{NB}(p)}$, where $z_{\alpha/2}$ is the $\alpha/2$ percentile of the standard normal cumulative distribution function (CDF). Given α we can solve for the prices p at which the bounds of the two-sided confidence interval just covers zero. By rearranging the confidence interval expression $\widehat{nb}(p) \pm z_{\alpha/2}\hat{\sigma}_{\widehat{NB}(p)} = 0$, inserting the definition of the net benefit estimate and its standard deviation and quadrating we obtain the following second order equation in p:

$$\frac{\hat{\mu}^2_{dC} + p^2\hat{\mu}^2_{dE} - 2p\hat{\mu}_{dE}\hat{\mu}_{dC}}{p^2\widehat{Var}(\hat{\mu}_{\Delta E}) + \widehat{Var}(\hat{\mu}_{\Delta C}) - 2p\widehat{Cov}(\hat{\mu}_{\Delta E}, \hat{\mu}_{\Delta C})} = z^2_{\alpha/2} \qquad (5)$$

This expression is analogous to the Fieller's expression for the confidence interval limits for a ratio described by Fieller (1954). The Fieller's method is based on that $\hat{\mu}_{\Delta C} - R\hat{\mu}_{\Delta E}$ is joint normally distributed, which implies that $\frac{\hat{\mu}_{\Delta C} - R\hat{\mu}_{\Delta E}}{\sqrt{R^2 Var(\hat{\mu}_{\Delta E}) + Var(\hat{\mu}_{\Delta C}) - 2RCov(\hat{\mu}_{\Delta E}, \hat{\mu}_{\Delta C})}} \sim N(0,1)$. The Fieller's confidence limits for *R* is obtained by solving the following second order equation (see e.g. Briggs & Fenn 1998):

$$\frac{\hat{\mu}^2_{dC} + R^2\hat{\mu}^2_{dE} - 2R\hat{\mu}_{dE}\hat{\mu}_{dC}}{R^2\widehat{Var}(\hat{\mu}_{\Delta E}) + \widehat{Var}(\hat{\mu}_{\Delta C}) - 2R\widehat{Cov}(\hat{\mu}_{\Delta E}, \hat{\mu}_{\Delta C})} = z^2_{\alpha/2}, \qquad (6)$$

which is obtained by substituting *R* for *p* in (5) above. Thus solving for *p* in (5) gives exactly the same roots as solving for R in (6) and we have that $p_1 = R_1$ and that $p_2 = R_2$. This implies that the prices at which the net benefit confidence limits are equal to zero are identical to the slope of the rays for the Fieller's confidence limits for the incremental cost-effectiveness ratio. The close relation between the Fieller's and net benefit method can be explained by the fact that both methods are based on a normality assumption.

AN ILLUSTRATION

To show the relation between the Fieller's and net benefit approach graphically we use data from Obenchain et al. (1997), which is a retrospective analysis of antidepressant therapy in 1 242 US patients. They investigated whether it was cost-effective to treat depression with Fluoxetine instead of tricycle antidepressants. Effectiveness was defined as the proportion of patients being on their initial treatment after 6 months. The ICER estimate ($\hat{r}$) was US$-16, implying (see *Figure 1*) that Fluoxetine dominated tricycle antidepressants. *Figure 1* shows 1000 bootstrap replicates of the ICER and the parametrically calculated Fieller's limits of a 95% confidence interval for the ICER. The upper and lower limits of the confidence interval are given by the slope of the two rays from the origin ($R_1 = 173 \; and \; R_2 = -206$).

FIGURE 1. ICER BOOTSTRAP REPLICATES AND 95% FIELLER CONFIDENCE LIMITS FOR THE ICER

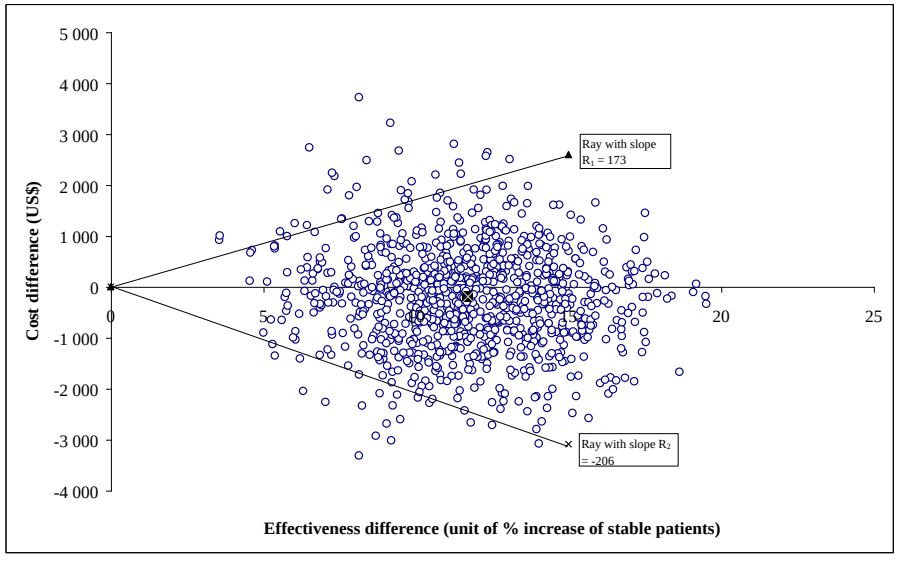
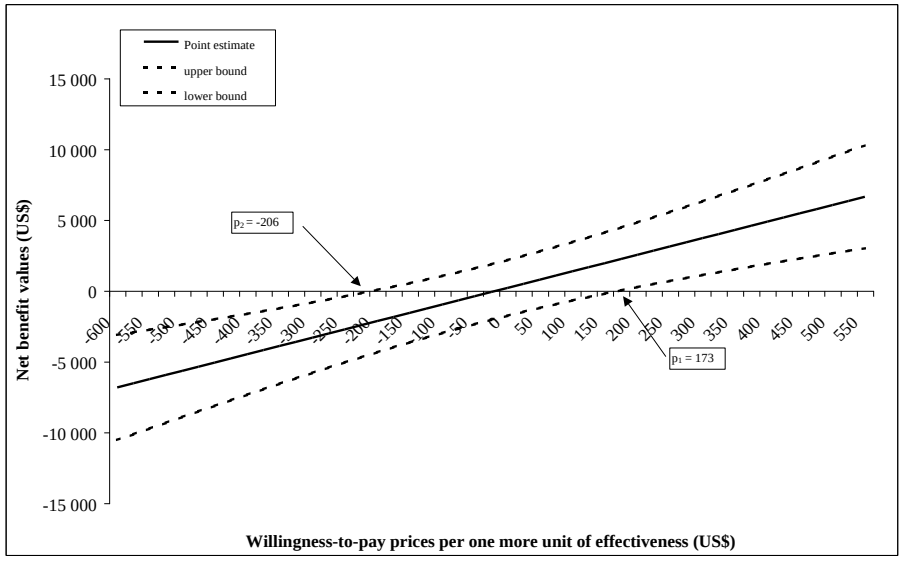


Figure 2 shows the net benefit estimate $\widehat{nb}(p)$, given by the bold line, and the 95% confidence intervals for different willingness to pay prices (p). p_1 corresponds to the price for which the lower bound of the confidence interval just

covers zero while p_2 corresponds to the price where the upper bound of the confidence interval just covers zero. It is clear that $p_1 = R_1$ and $p_2 = R_2$ and that the net benefit approach will also produce the Fieller's limits for the confidence interval for the ICER.

FIGURE 2. CONFIDENCE INTERVALS FOR THE NET BENEFIT FOR DIFFERENT WILLINGNESS TO PAY PRICES ***(p)****.*



CONCLUDING REMARKS

The net benefit approach to cost-effectiveness analysis was first developed as a response to the need to estimate confidence intervals for the incremental cost-effectiveness ratio. It turned out that the net benefit approach offered several advantages for analysing uncertainty in cost-effectiveness analysis and that e.g. hypothesis testing, sample size calculations, Bayesian analysis and analysis of questions about the value of further medical research were facilitated. A formal relation between cost-effectiveness acceptability curves and statistical inference was provided and in addition, as shown above, the net-benefit approach also produces the Fieller's limits of the confidence interval for the incremental cost-effectiveness ratio. Finally the use of the net benefit approach explicitly recognizes that the price per effectiveness unit has to be known to provide cost-effectiveness analysis with a useful decision rule. Thus, there are many strong reasons to continue to use the net benefit approach to analyse uncertainty in cost-effectiveness analysis based on individual cost and health effect data.

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PREFERENCE MEASUREMENT:

RELIEVING HEALTH ECONOMICS OF ITS ACHILLES HEEL

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INTRODUCTION AND MOTIVATION

Cost-effectiveness analysis (CEA) is generally applied by health economists for assessing healthcare interventions. Bengt Jönsson has contributed greatly to this field; in 2005 alone, he boasts co-authorship of nine international publications (Jönsson et al. 2005; Kanis et al. 2005; Lindgren et al. 2005a, 2005b; Lundkvist et al. 2005a, 2005b; Ringborg et al. 2005a, 2005b; Zethraeus et al. 2005). However, the weakness of CEA is that it cannot answer the question, "Is the intervention worth the resources that could be used outside the healthcare sector?". To answer this question, one needs cost-benefit analysis (CBA), which pits benefits measured in money against cost, again measured in money. Apart from reservations about "monetising health", the problem with CBA has been the measurement of benefits because this calls for willingness-to-pay (WTP) values, which in turn are an expression of (subjective!) preferences.

Preferences are the weak spot of economic theory quite generally because with a change in preferences, literally anything can be explained. For instance, an increase in the demand for watches could always be the result of a shift in consumers' preferences in favour of watches. However, such shifts are difficult to observe and even more difficult to predict.

In health economics, preferences are a true Achilles heel. Everyone knows the saying, often levelled at patients by health professionals, "Don't give a damn as long as you're healthy, but willing to give away everything as soon as you're sick". This can be interpreted to mean that preferences are unstable and even inconsistent (the famous crossing of indifference curves that must be excluded

for transitivity to hold). However, inconsistent preferences can be used to argue against consumer sovereignty in health care. One is tempted to conclude that in view of instability and inconsistency, measuring preferences with regard to health and health care is a futile endeavour.

Against this backdrop, this contribution tries to do three things. First, it seeks to refute the notion that observed instability in the value of health relative to other objectives (called 'consumption services' in the Stigler/Becker (1977) sense for simplicity) is necessarily caused by an instability of preferences. Second, it illustrates how preferences for health can be measured experimentally, resulting in willingness-to-pay (WTP) estimates. And third, it presents evidence suggesting that measured preferences "behave" as expected and help to predict actual choices with regard to health.

ON THE STABILITY OF PREFERENCES WITH REGARD TO HEALTH

Posit the following simple model

$$EU = \pi \cdot u_s[C_s] + (1-\pi)u_h[C_h],$$

with

$$u_h[C] > u_s[C].$$

Thus, the individual's expected utility is given by his or her utility u_s in the sick state which simply depends on the level of consumption C_s and utility u_h in the healthy state determined by consumption services C_h. The probability weights are π and $(1-\pi)$, respectively, with π denoting the probability of being sick in the future. Also, a given level of consumption services C generates more utility in the healthy than in the sick state.

The slope of an indifference curve in $(C,1-\pi)$-space can be derived by setting $dEU = 0$ for holding expected utility constant and solving,

$$\frac{dC}{d(1-\pi)} = -\frac{u_h[C_h]-u_s[C_s]}{\pi u'_s[C_s]+(1-\pi)u'_h[C_h]}.$$

Here, u'_s and u'_h symbolise the marginal utility of consumption in the two states. Note that the slope of the indifference curve can be made to depend on the state of health. Simply assume $u'_h > u'_s$ and consider two cases. When the individual is healthy, then $\pi = 0$, causing the denominator to be large. His or her indifference curve is flat, indicating the health is not too important relative to consumption services. Conversely, let the individual be sick, hence $\pi = 1$. This time, the

indifference curve is steep, indicating great importance of health relative to consumption services. Therefore, microeconomics is perfectly able to represent the adage cited above (Zweifel and Telser 2009).

However, the first objective of this contribution is to show the converse, i.e. that with perfectly stable indifference curves, it is still possible that health is valued more highly in the sick than in the healthy state. To this end, consider now the individual as a producer both of consumption services C and chances of being healthy in the near future, $(1-\pi)$. In the short run, the transformation curve is in $(C,1-\pi)$-space, as above. In the longer run, it is in (C, ET_h) space because a lower probability of being sick implies a higher expected duration ET_h of the healthy state before falling sick according to the mean waiting-time formula $ET_h = 1/\pi$ to allow for the change from one state to another to be completed. This transformation curve has a positive slope around the origin (see Figure 1). The reason is that more healthy time allows the individual both to generate more labour income and/or to have more time for producing consumption services, very much in the spirit of Grossman (1972).

Two things should be noted about Figure 1. First, the feasible set is smaller when the individual currently is in bad health (transformation curve labelled *s*) than when he or she is in good health (transformation curve labelled *h*). Second, this reduction is assumed to be more marked with regard to the individual's ability to produce health than to produce consumption services. This assumption is crucial because it causes the transformation curve *s* to run (almost everywhere) steeper than its counterpart *h*.

Now introduce truly stable (homothetic) preferences, with the marginal rate of substitution invariant to consumption (the indifference curves have the same slope along a ray out of the origin). Let the optimum in the healthy state be $Q*$, as always at the tangency point. However, $Q**$, the optimum in the sick state, cannot possibly lie on the same ray as $Q*$ because the transformation curve is too steep there. Tangency can be achieved only by moving towards the northwest, where its slope is reduced. Now if consumption services and chances of being healthy were tradable commodities, one would observe relative market prices, given by the slopes of the two straight lines through $Q*$ and $Q**$, respectively (see Figure 2). The steeper slope of the line through $Q**$ indicates that the relative price of chances for health in the sick state would be higher than through $Q*$, the healthy state. Of course, such market prices do not exist; however, individuals are likely to behave as though 'health' was relatively more important than other objectives when ill than when in good health. The crucial point is that the seeming instability in preferences can be traced to the state

dependence of individuals' production possibilities. Therefore, the argument that individual preferences cannot provide guidance for valuation because of their instability between the ‚healthy' and ‚sick' states need not be accepted. Attempts to measure preferences for health are not futile.

FIGURE 1: STATE DEPENDENCE IN THE PRODUCTION OF HEALTHY TIME

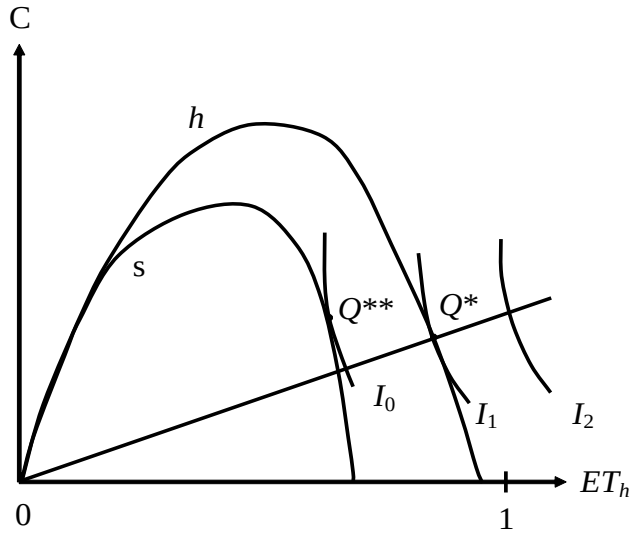
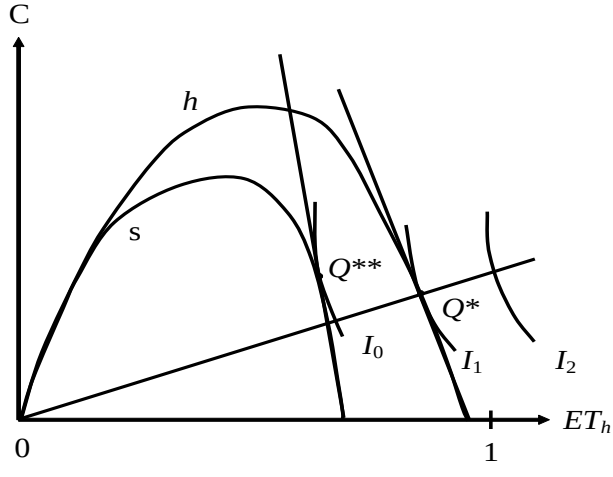


FIGURE 2: STATE DEPENDENCE OF THE RELATIVE VALUE OF HEALTH GIVEN STABLE PREFERENCES



Inferring valuations from the condition

Marginal willingness to pay > Market price (= Marginal cost)

is, however, not possible in the case of health care, for at least two reasons. First, WTP on the demand side is inflated by health insurance. To see this, assume that a patient's maximum out-of-pocket WTP for a drug is $100. However, with a coinsurance rate of 25 percent in health insurance, the drug may cost as much as $400 at the pharmacy, and the patient will still buy it because $100 = 0.25 \cdot 400$. The second reason is that on the supply side, prices are most often negotiated or even administered, thus failing to reflect marginal cost. Thus, market observations are not informative, making experimental evidence a valuable if imperfect substitute.

SOME EXPERIMENTAL EVIDENCE REGARDING THE STABILITY OF HEALTH-RELATED PREFERENCES

Some evidence comes from a Discrete Choice Experiment (DCE) performed in 2007, involving about 1,100 members of German social health insurance. DCEs are preferable to the conventional Contingent Valuation (CV) approach on at least two accounts. First, in a DCE all attributes of a product are varied simultaneously, whereas in a CV, only its price is allowed to vary. Anyone who has ever shopped around for a particular item knows that when going from one store to the next, a lot of its attributes change, from packaging to friendliness of sales staff. Therefore, the DCE approach is more realistic than the CV alternative. Second, simultaneous variation of attributes makes strategic choice behaviour on the part of respondents more difficult.

The product in question is a new insulin preparation (Sennhauser and Zweifel 2014). The DCE is designed to measure WTP for three attributes: The reduction in the risk of hypoglycaemia (the one attribute fully acknowledged by the medical profession), the weight gain during treatment, slightly more flexibility in the timing of the injection, and no need to swing the preparation before injection. IQWiG (Institut für Qualitätssicherung und Wirtschaftlichkeit im Gesundheitswesen), the German counterpart of NICE in the UK, had already decided that the last two "innovations" are to be considered irrelevant. To IQWIG's surprise, as also to that of the authors, the "irrelevant outcomes" were associated with substantial WTP values. In hindsight, this becomes understandable. Not having to inject right at the dinner table and being sure that the substance has the right dilution to be effective can be quite a relief.

However, the real novelty of the study is its use of two price attributes and two populations. On the one hand, one may think of an out-of-pocket payment that

would mainly fall on current diabetics. On the other hand, if the preparation were to be included in the benefit list of German social health insurance, contributions paid also by non-diabetics would have to (slightly) increase. Therefore, there are two sets of WTP measures, one given that payment would be out-of-pocket, the other, given that it would be through increased contributions.

Table 1: Relative value of attributes according to health status, in Euro

Marginal out-of-pocket WTP, in €/year for reduction of	**No Diabetes**	**Diabetes Type 2**	**Ratios**
Hypoglycemia	1.28 (10.8)	0.98 (4.0)	1.25
Weight gain	28.72 (11.2)	28.61 (5.4)	1.00
Ratios	22.4	35.8	

Note: z-values in parentheses

The focus of Table 2 is on the stability of valuations, as claimed in Section 2. There, a reduction of 1 percentage point in the risk of hypoglycaemia is compared to a reduction by 1 kg of weight gain if the preparation would have to be paid our-of-pocket. Reading the table horizontally first, one notices that non-diabetics (who however were asked to imagine that they would one day become diabetic with a particular probability) exhibit a (probability-weighted) WTP of 1.28 Euro per percentage point, even 25 percent more than type 2 diabetics. When it comes to avoiding weight gain, the two groups have exactly the same WTP. This suggests preferences to be rather stable – at least as soon as healthy individuals consider a possible future 'sick' state, as in their decision to purchase health insurance or to undertake preventive effort. Reading Table 2 vertically tends to confirm this finding. Admittedly, compared to non-diabetics, diabetics value the avoidance of weight gain somewhat higher than a reduction in the risk of hypoglycemia. However, their WTP ratio of 35.8:1 can be said to be still in the same ballpark as 22.4:1. In sum, this particular DCE may be seen as supporting the claim that revealed valuations may reflect state dependence of individuals' production possibilities rather than of their underlying preferences.

HEALTH A MERIT GOOD?

In the example presented, health care was defined as a purely private good. This neglects the possibility of psychological externalities; in particular, citizens may see health and health insurance as a merit good that needs to be made available to poor fellow citizens through subsidisation. Taxpayers may be willing

to finance new diabetes medication to those who can ill afford to pay the out-of-pocket price or may accept an increase in contributions to social health insurance in the aim of having new medications covered. If so, this would imply that e.g. compensations required for accepting MC-type restrictions listed in Table 1 are overstated. If respondents had been made aware that accepting these restrictions might lower contributions paid by the poor, they might have opted for the MC alternative more easily in the DCE [although this argument is not strong in the case of Switzerland since poor individuals receive a means-tested premium subsidy (see Kreier and Zweifel, 2010 for more detail)].

Another DCE allows a preliminary test of this prediction. Conducted in 2008, it was designed to measure Swiss citizens' preferences for income redistribution (Zweifel and Neustadt 2013). Its attributes include not only the amount of income distribution but also nationality of recipients (Swiss citizens, immigrants from western European countries, immigrants from the rest of the world) and its structure (in favour of the aged, the working poor, the unemployed, families with children, and persons in ill health). If health and health insurance indeed constitute merit goods, then positive WTP for redistribution should be observed (although the overall marginal WTP turns out to be negative).

In fact, however, extra income redistribution favouring persons in ill health is rejected more strongly than redistribution in favour of other beneficiaries. The amount of compensation required for a one percentage point increase (from currently 25 to 26 per cent of GDP) is an estimated CHF 18/month, compared to 12 CHF/month across all uses (1 CHF = 1.05 US$ at current exchange rates). The reason may be that respondents are aware of the substantial amount of income redistribution already inherent in the means-tested subsidization of insurance premiums (see the experimental evidence above). Therefore, defining health care and health insurance as a private good in preference measurement is unlikely to neglect important merit good characteristics that would impart bias to estimated WTP values (at least in Switzerland).

CONCLUSIONS

The point of departure of this contribution is the observation that unstable (and possibly inconsistent) preferences constitute the Achilles heel of microeconomics, but even more so of health economics, where the medical profession habitually argues against consumer sovereignty. Therefore, experimental preference measurement holds the promise of relieving health economics of its Achilles heel. However, there are several counter-arguments. The first, advanced by the medical profession, holds that preferences change between the states 'healthy' and 'ill'. It is often accepted even by health economists [see e.g. Bryan and Dolan (2004)]. Here, it is shown that a higher

relative value of (chances of good) health can be related to a state dependence of individuals' production possibilities rather than to a state dependence of their preferences. Moreover, a Discrete Choice Experiment (DCE) suggests that willingness-to-pay (WTP) values for a new insulin preparation are quite similar among (healthy) non-diabetics and (ill) type 2 diabetics. A second criticism states that WTP values derived from experiments are not predictive of actual decisions (Johanesson and O'Conor 1997). However, this applies much more to conventional Contingent Valuation rather than DCEs, as evidenced e.g. by Bryan et al. (2000) as well as in the DCE revolving around hip protectors cited above suggesting DCEs do have predictive power.

A third counter-argument considers experimental WTP values to be problematic because they disregard distributional issues (Bryan and Dolan 2004). Note that this criticism applies to any benefit-cost analysis and indeed cost-effectiveness analysis as well. However, nothing prevents researchers from stratifying estimated WTP values by income and giving extra weight to values pertaining to low-income individuals in the aggregation to total WTP. However, there is some evidence suggesting that income redistribution for health uses may trigger lower (even negative) WTP values than for other uses (at least in Switzerland, with its subsidisation of health insurance premiums).

In sum, experimental evidence (especially of the DCE type) can be used to inform health policy. This said, there is a great need for cross-checking of results because many things can go wrong in experimental economic research!

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