

# Valuing new medicines in the early 21:st century

KATARINA STEEN CARLSSON<sup>1, 2, \*</sup>  
BENG T JÖNSSON<sup>3</sup>

<sup>1</sup> Department of Clinical Sciences, Malmö, Lund University, Sweden

<sup>2</sup> The Swedish Institute for Health Economics, IHE, Lund, Sweden

<sup>3</sup> Stockholm School of Economics, Stockholm, Sweden

**Abstract:** What is the actual value of new medicines? The answer to this question is the key to rational use of new technologies in health care and for design of appropriate incentives for innovation. In this paper we present methods, data and study results for valuing new medical technologies in a life cycle perspective, relevant for development of a new approach to contract and payment for innovation that can replace present systems for pricing and reimbursement. Focus is on value in clinical practice, and on the data needs and methods needed for the development of outcome-based payment systems that balances risks and rewards for innovation in health care. We provide an overview of studies from the Swedish context on the value of new medicines introduced in the treatment of diabetes, cancer, cardiovascular disease and rheumatoid arthritis. These studies using national health data and quality registers emphasise the importance of continuing efforts to collect relevant data for assessment of value after a medicine reaches the market and starts to be used in clinical practice. It is only when medicines are used in clinical practice that the benefits for real-world patient populations can be identified, measured and valued. Analyses of real-world data will also assist further development and tailoring of treatment strategies to optimize the value of the new technology. While an effective patent system rewards innovation for a limited period of time, many innovations may continue to provide value to society long after patent protection, and these values must be included in the assessment of value of innovation.

**JEL classification:** I11, O32, O33

**Key words:** valuing medicines, ex post valuation, register based analyses, regional variation in utilization

## 1 Introduction

Traditionally economic issues related to innovation have been analysed from the perspective of a private market with patent protection for innovators. The patent institution creates a trade-off between static and dynamic efficiency, and most studies relate to the consequences of the incentives for pricing and use. A study by Lou and Commanor in the US showed that launch prices for new drugs were related to therapeutic value (Lu and Comanor, 1998). Also in the Swedish markets with price control on pharmaceutical, initial pricing is related to value (Ekelund and Persson, 2003). However, recently there has been further studies on pricing for new cancer drugs mainly paid by private and public insurers, (Berndt et al.,

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\* **Correspondence to:** Katarina Steen Carlsson, The Swedish Institute for Health Economics; PO Box 2127; SE-220 02 Lund; Sweden. E-mail: katarina.steen\_carlsson@ihe.se

2015). While the paper shows a positive correlation between price and value (increased survival benefit), it also shows an increased price per unit of benefit over time. This has created a renewed interest in the life cycle costs and benefits of innovations in health care in general, and pharmaceuticals in particular (Howard et al., 2015). In this paper, we review some examples for Swedish studies, focusing on methodology and data requirements for studies. We also discuss the results in relation to the findings in similar international studies.

New health technologies such as new medicines are the result of investment in research and development that generate new knowledge on diseases and their treatments. Once developed and tested, the cost of using a new technology may be fairly easy to determine, even if there may be uncertainties about optimal dosages, length of treatment, potential side effects etc. But what is the actual value of new health technologies? Knowing the answer to this question is the key to the rational use of new technologies in health care. For one, what is the value of the new technology compared to existing treatment options? What is known about when and how the technology should be implemented? Is it worth its price for the payer?

The answers to these questions can only be given with a high degree of uncertainty before the technology is used in clinical practice. When payment is linked to input rather than output, the risk is mainly carried by payer and the health care system. The trend towards outcome and value based models for health care provision is an approach to change the distribution of risk and rewards, with the aim of improving outcome and cost-effectiveness. This trend has mainly been seen for health care services, but increasingly different types of market access agreements, including contracts where payment is related to outcome, have been introduced for medicines and devices as well. Those payment models, complementing and partly replacing traditional pricing and reimbursement decisions, requires collection of data for the audit of contracts and for payment purposes. The definition, measurement and valuation of outcomes for appropriate incentives and reward for innovation is a complex issue. Contract theory provides some general rules for design of optimal contracts under different market conditions.

There are also a number of methodological and practical issues involved in defining, measuring, and valuing the outcomes of new technologies for health. In this paper, we summarize examples from the Centre for Business and Policy Studies research programme on The Value of New Medicines to illustrate strategies and designs for measuring value of health technologies using data from clinical practice.

The paper is organized as follows. Section 2 summarizes the methods applied for estimating the value of new medical technologies including key data and their potential sources. Section 3 presents five empirical examples of measurement of value of new medical technologies based on Swedish real-world data and discuss the strategies applied by researchers in each of these examples. Section 4 concludes the paper and outline a future research agenda.

## **2 Valuing new medical technologies: methodological strategies**

The choice of method for valuing new medicines will depend on the perspective of the analysis, the data available to describe key parameters and the specific aim of the analysis. A first issue regards when the analysis is done: ex-ante and ex-post. A study applying an ex-ante perspective typically has the aim to explore the value of a new technology under alternative scenarios. Studies supporting reimbursement decisions at early stages of the introduction of new medical technologies use the ex-ante perspective by necessity. No long-term evidence exists at this stage but simulation models and careful use of available observational data and clinically relevant assumptions provide valuable decision support.

At later stages of the life-cycle of a new medical technology, analyses using an ex-post perspective add new information on the effectiveness in clinical practice using real-world data. Ex-post studies following large observational cohorts over time can obtain high external validity. At the same time, an analysis of the comparative effectiveness of the new treatment technology will be vulnerable to selection issues and treatment assignment is not random (Ramsberg and Neovius, 2016). Recent years have seen an increasing research and health policy interest for generating new knowledge on treatment outcomes for real-world data (Luce et al., 2012).

Another key issue is the choice of strategy for measurement of the value of new medical technologies. The analysis may start from detailed measurement of change in output (health/well-being/welfare) in the population from epidemiological data. The challenge of such a top-down strategy is to identify the fraction of the outcome improvement attributable to the increased use of the new technology recognizing that other factors may also contribute to health improvements. The top down strategy is suitable when the research question entails broader definitions of technology change (see e.g. Cutler et al., (2006)).

The top-down strategy with a focus on measuring health by readily available outcome measures, e.g. overall reduced mortality, need elaborated strategies to establish causality between the use new technology and the improved length of life (see e.g. Lichtenberg, (2016b), Lichtenberg, (2016a)).

Empirical analyses may instead use detailed measurement of the change in inputs (new vs standard treatments) at the micro-level and assess change in benefits to patients. Such a bottom-up strategy will entail challenges such as adequately long time series on outcome of treatment; high costs of detailed monitoring in sufficiently large samples to rule out other causal factors; disentangling effects of specific technologies in patient groups with multifactorial treatment; and feasible for analysis of specific technologies but an inherent risk of overestimation of aggregated benefits. The bottom-up strategy has been used for the evaluation of specific interventions (e.g. Johnston et al., (2006), Roback et al., (2009)) or overall technological improvements in selected patient groups (e.g. Health Economics Research Group et al., (2008), Luce et al., (2006), Philipson and Jena, (2005)).

New health technologies may generate direct patient values in terms of increased health and wellbeing often measured in quality adjusted life years, QALYs in practice. Improved health may also generate indirect values in that health is instrumental in many parts of life including productivity in market and non-market activities. Empirical studies have typically focused on the direct patient values and the associated impact on health sector resource use. Occasionally studies have also incorporated consequences for productivity. While economists' may agree that the value of a new technology in theory should also include its impact on resource use outside the health sector such as formal and informal care, these values are rarely included in empirical studies due to lack of data.

As an example, Table 1 presents an operationalization of the steps for a bottom-up evaluation of the monetary value of health gains from interventions to treat or prevent cardiovascular disease, CVD, over the period 1985–2005 in the UK (Health Economics Research Group et al., 2008).

**Table 1: Steps for estimating the value of health gains from specific interventions to treat or prevent cardiovascular disease, CVD, as applied in Health Economics Research Group et al., (2008).**

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1	Identify specific interventions for patients with CVD
2	Estimate the QALYs gained for each intervention in each patient group
3	Estimate the numbers of patients in each patient group
4	Adjust for overlapping patient groups
5	Estimate the uptake of each intervention by each patient group in each year
6	Compute the numbers of users of each intervention in each patient group
7	Compute the numbers of new users each year
8	Adjust for compliance with treatment
9	Adjust for polytreatment
10	Compute the total QALYs gained from each intervention
11	Monetise the total QALYs gained
12	Undertake a sensitivity analysis.

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CVD – cardiovascular disease, QALY – quality adjusted life years.

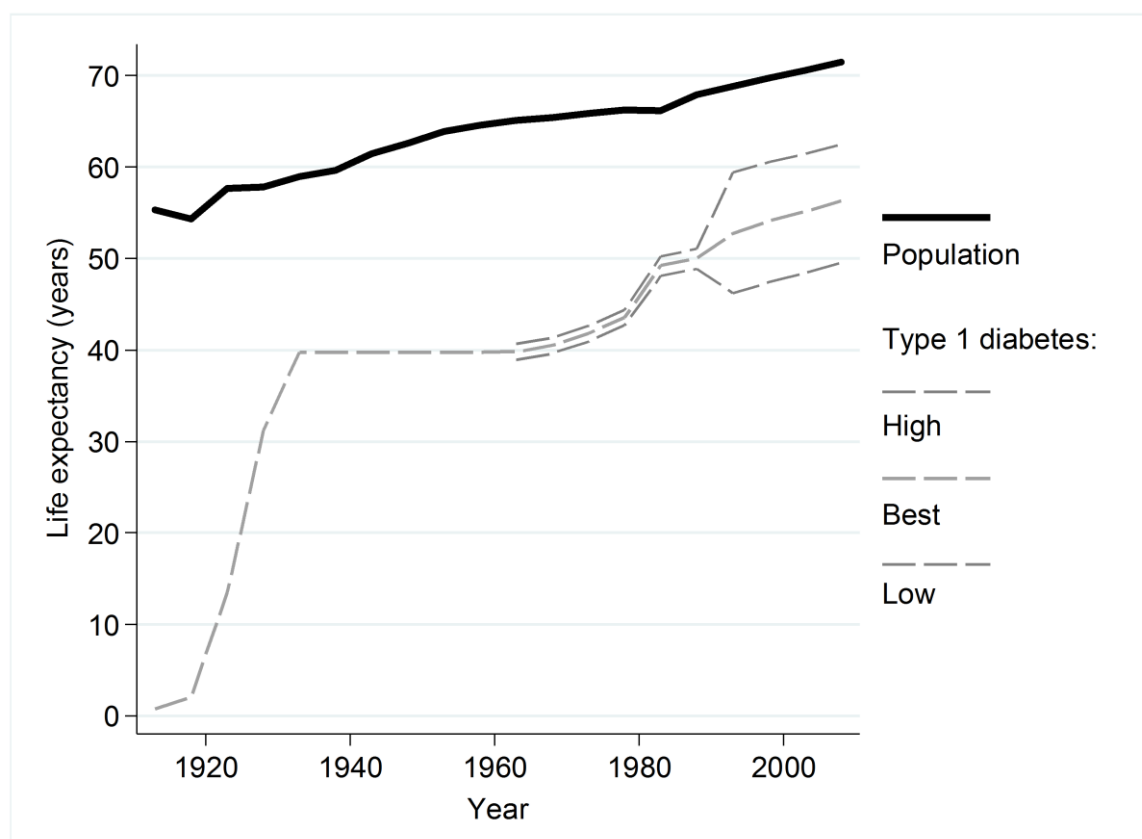
### **3 Empirical results and contributions from economic analyses from the Value of New Medicines research programme**

Below we use results from the research programme on The Value of New Medicines conducted by the Centre for Business and Policy Studies 2011-2013 as illustrations of empirical valuations of new medicines (Jönsson and Steen Carlsson, 2013, Jönsson and Steen Carlsson, 2014).

#### **3.1 Long time perspectives to measure gain in life years: valuing medicines in the treatment of diabetes and chronic myeloid leukaemia**

The survival prospects for people with diabetes has seen dramatic improvement during the 20th century. Figure 1 illustrates the gap in life expectancy for a newly diagnosed child with type 1 diabetes and a child of the same age in the population over 100 years. In the early 1900s, there was no effective method of managing the absence of endogenous insulin production characterising type 1 diabetes. Anyone stricken by diabetes prior to 1920 could hope to survive for possibly another two years. In January 1922, a first patient was treated and he survived seven years. Around the time of the Second World War, the gap in remaining life expectancy between a person developing type 1 diabetes at the age of 10 and an average of the remaining life expectancy of other children of the same age had narrowed from 52 to 17 years. Following this initial dramatic increase, life expectancy for people with type 1 diabetes changed little until the late 1970s (Steen Carlsson et al., 2013, Weiderpass et al., 2001). This also meant that the gap vis-a-vis the general population increased during this period. In the last 30 years, the gap in life expectancy compared to the general population has again narrowed.

**Figure 1: Life expectancy for a patient who developed type 1 diabetes at the age of 10 years during 1910-2010. Source Steen Carlsson et al., (2013).**



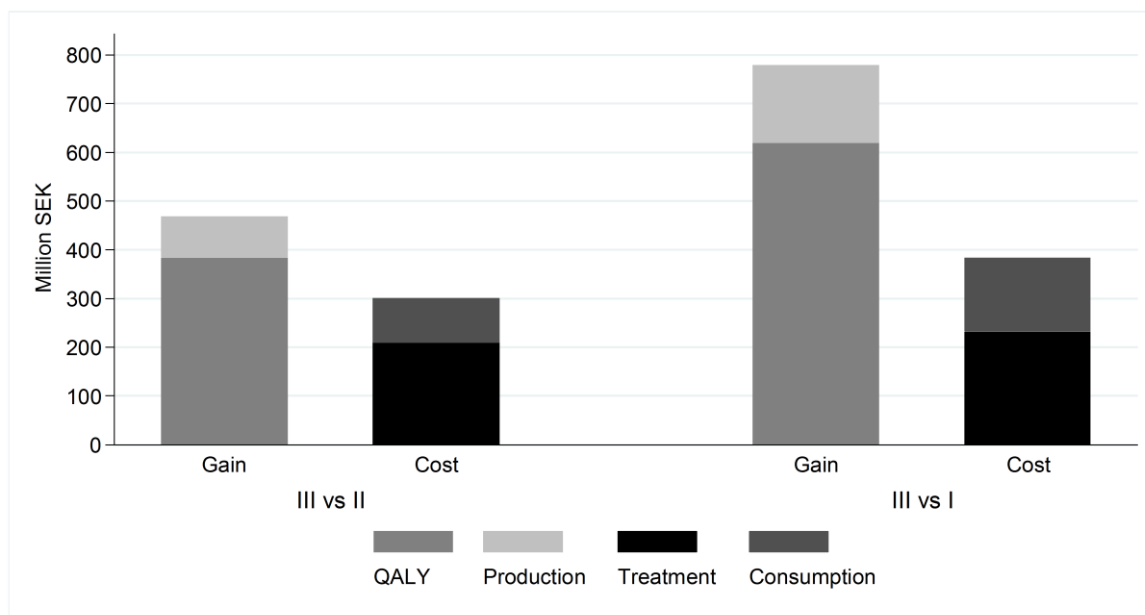
In addition to continuously improving insulin treatment by, for example, developing new types of insulin with different characteristics (such as short-acting and long-acting insulin analogues) that improved the insulin molecule, technological developments also have resulted in improved, and even disruptive (Bower and Christensen, 1995), methods of administration and self-management tools for people with diabetes. In addition, developments in preventive treatment of cardiovascular disease have been crucially important for prolonging the survival of people with diabetes. However, estimates of life-years gained with preventive treatment in diabetes are marred by uncertainty and are likely to be conservative. Cohorts that are now aged 50–60 years and developed type 1 diabetes as children or adolescents have not always had access to modern diabetes treatments. This means that studies published to date have not yet been able to monitor modern diabetes treatments for sufficiently long periods of time to be able to conclusively determine the full value of improvements in insulin treatment and other developments of diabetes treatment during the 20th century.

Another disease, which more recently has been subject to the introduction of a disruptive technology leading to significant improvement in survival, is chronic myeloid leukaemia (CML). The introduction of imatinib, the first tyrosine kinase inhibitor (TKI), around the turn of the century changed CML from a fatal disease to a chronic disease manageable with long-term treatment. Earlier treatment options had included stem cell transplantation available for a subset of young patients or combination treatment with combination of interferon-alpha and hydroxyurea for those who could tolerate these medicines often associated with severe side-effects.

The added social value of the TKI imatinib during the initial implementation period, 2002–2008, when an estimated 75% of CML patients under the age of 70 received imatinib

and nearly half of patients above the age of 70 years has been estimated in two Swedish studies using real world data (Lundqvist et al., 2013a, Ohm et al., 2015). The analysis estimated the potential health benefits, productivity gains, treatment costs and costs of consumption associated with life-years gained in a Swedish setting for a cohort of newly diagnosed CML patients who would receive imatinib at the same rate as those in 2002–2008. CML has an incidence of about 1 per 100,000 inhabitants in Sweden, which corresponds to about 90 people per year. Findings were compared with two earlier treatment ‘eras’. Era I, the 1970s, offered only symptomatic treatment and Era II, the 1990s, offered stem cell transplants for younger patients, interferon alpha therapy, and symptomatic treatment. Era III is the period during which imatinib has been first-line treatment for CML.

**Figure 2: Increased gain and cost of the treatment of chronic myeloid leukaemia (CML). Era III, during which imatinib has been first-line treatment compared with previous technologies during Era II and Era I. Million SEK. Source Lundqvist et al., (2013a).**



The authors found that each new treatment technology introduced for CML increased life-years, but also produced higher health care and consumption costs. The benefits in terms of health and productivity gains, however, outweighed the increased costs. Figure 2 shows the difference between costs and benefits over time. Era III generated additional value equivalent to 168 million SEK over Era II for an annual cohort of 90 patients with new-onset CML. Compared to Era I, during which only symptomatic treatment was available, the additional value was 396 million SEK. Stated differently, if substantial expenditure in research and development had not occurred, treatment for CML patients would not have progressed beyond what was available in the 1970s. This ex-post analysis then shows that significant value would then have been lost to society, even for this relatively small patient population.

Research and development for CML has not been restricted to the development of new medicines. As early as in the 1990s, stem cell transplantation was available, mostly to patients under the age of 50 for whom a suitable donor was available. This intervention has the potential to eliminate the cause of CML and, if successful, is associated with significant survival gains. Risks are serious, however, with reported transplant-related mortality rates at 7% to 14% during the first three years following treatment (Oyekunle et al., 2011)). The

development of different strategies, medicines and stem cell treatment, has benefitted people with CML today by offering a broader set of alternatives. Nonetheless, decisions could have been different and without incentives for innovation, the development of new medicines might have stalled given the significant progress in survival from stem cell treatment among young people during the 1990s. As shown in Figure 2, the incremental value from adopting Era III treatment imatinib as first-line therapy was lower compared to the Era II technology than compared to the Era I technology. Over the remaining lifetime of an annual cohort of 90 incident patients, however, the discounted economic gain was estimated at 168 million SEK, or around 1.9 million SEK per patient.

### **3.2 Step wise introduction as new results are published and uncertainty is reduced: The example of medicines in prevention of cardiovascular disease and in breast cancer treatment**

Life-years gained is also the key outcome measure in studies that have estimated the value of tamoxifen and trastuzumab for the treatment of breast cancer, and lipid-lowering and antihypertensive treatments administered as primary and secondary prevention in cardiovascular disease (Lindgren and Jönsson, 2012, Lundqvist et al., 2013a, Lundqvist et al., 2013b). These studies have included estimates of quality-adjusted life expectancy in the ex-post valuation of new medicines primarily introduced to increase survival. There are two different reasons why capturing quality of life is important for determining the value of new medicines. Firstly, there are a number of treatments that can improve health status and well-being for the patient, but have no effect on survival as such. Focussing on life-years gained alone will mean that the analysis will not capture benefits that are important to patients and thus create value. Secondly, estimations that only show life years gained without taking into account the patient's actual state of health may actually overestimate the treatment benefit, since all survival gain does not have the same quality of life. It is thus important that the analysis should be capable of ranking health benefits, so that a life year gained without any pain or restrictions of function is rated higher than a life year with pain, anxiety or impaired function.

Lundqvist et al. (2013b) analysed targeted therapies for the treatment of breast cancer, tamoxifen and trastuzumab. When tamoxifen was introduced in breast cancer care in the late 1970s, it was originally prescribed for metastatic breast cancer. Tamoxifen is used in the treatment of women with breast cancer tumours that respond to hormonal treatment (ER-positive), which accounted for approximately 80% of cases in 2010 according to the Regional Cancer Centre Stockholm-Gotland (Regionalt Cancercentrum Stockholm-Gotland, 2011). It was obvious at an early stage that tamoxifen is also effective as an adjuvant to surgery, chemotherapy and radiation. Over time and as new scientific data have become available, the treatment duration for adjuvant tamoxifen was extended from one to two years, and later to five years. A recently published study supports continued treatment for up to ten years in women with ER-positive breast cancer (Davies et al., 2013). The study by Lundqvist et al., (2013b) used data for the first 25 years of actual use of tamoxifen in Sweden, 1979-2004, and before more recently introduced medicines made registry data more difficult to analyse and interpret. Table 2 summarises the study's estimates of the number of patients treated, the health benefit, measured as QALYs, and a monetary expression of value. The study determined that over 75 000 women had been treated with tamoxifen in total. Together they were estimated to have received nearly 46 000 QALYs at a monetary value of just below 39 billion SEK.

**Table 2: Number of patients treated, aggregate health gains measured as QALYs, and monetary value of health gains (million SEK) from tamoxifen in Sweden during 1979-2004. Source Lundqvist et al (2013b).**

	Patients treated Number (%)	Aggregated health gains QALY (%)	Monetary value Million SEK (%)
Disseminated disease	19 500 (26)	8 100 (18)	6 800 (18)
Adjuvant therapy	55 700 (74)	37 500 (82)	31 700 (82)
Of which			
1 year	4 900	2 000	1 700
2 years	16 400	8 800	7 500
5 years	34 300	26 700	22 600
Total	75 100	45 600	38 500

QALY – Quality Adjusted Life–Year. Rounded figures.

The number of women who received tamoxifen for disseminated metastatic disease during the 25-year period was stable at around 750 women per year. About 18% of the total value derived from 25 years of use of tamoxifen in breast cancer care in Sweden was attributed to this group in more advanced stages of the disease. As is seen from the distribution of health benefits and value in Table 2, patients receiving tamoxifen as adjuvant therapy accounted for a majority of the total value, 82%. One explanation for this is that nearly three times as many women received tamoxifen as adjuvant therapy (n=55 700) than received it for the metastasized disease (n=19 500). In addition, the health benefit per woman treated was greater when the drug was used in adjuvant therapy than after the cancer metastasized.

Tamoxifen is an example of how the use in clinical practice produces a gradual increase in knowledge that allows more patients to be treated and more potential value of the technology to be realized. In the early phase, around 500 women received adjuvant tamoxifen annually until the mid-1980s. As new scientific results were published and awareness of the value of tamoxifen grew, the number of women with breast cancer who were treated with tamoxifen in Sweden rose to around 2 000 annually by the second half of the 1980s. During the 1990s the number of treated women rose further and was equivalent to around 4 000 women annually by the early 2000s. This increase was mainly a result of extending the recommended time period for adjuvant treatment from one to two years and subsequently to five years. The analysis showed that more than 70% of the total health benefit of adjuvant tamoxifen therapy occurred during the last ten years of the twenty-five-year treatment periods. The increased health benefit in terms of life-years gained was due more to a greater number of women treated than to increased treatment duration. The marginal utility of prolonged treatment was lower, but nevertheless cost-effective thanks to the reduction in price over time.

The second targeted treatment for breast cancer, trastuzumab, was introduced more recently and is used for the treatment of HER2-positive breast cancer (Lundqvist et al., 2013b). Trastuzumab was approved in Sweden for the treatment of metastatic breast cancer in 2001; adjuvant use began in 2005. According to Wilking et al. (2010) approximately 14% of women with early breast cancer and 25% of women with metastatic breast cancer are HER2-positive. The Lundqvist et al study determined the value of introducing trastuzumab based on available data from a period of eleven years from 2001 to 2011. In total, the study determined that around 6 500 women had been treated with trastuzumab and achieved a total of 6 800 QALYs at a monetary value of 5.8 billion SEK (Table 3). Data on the use of trastuzumab was available for a shorter time period, 11 years, compared with 25 years for



tamoxifen. Hence the proportion of the overall treatment period during which the drug was used for a smaller indication and in more severely ill patients is greater for trastuzumab than for tamoxifen. It is clear that this shorter period of observation – particularly the shorter time period during which the authors monitored use as an adjuvant to chemotherapy and radiation – meant that only some of the value of this new medicine was captured in the study. Time will show how much more value may be realised. The results in Table 3 show that, until 2011, the health benefit and associated value were almost equally divided between use of trastuzumab for metastasized disease and its use as an adjuvant. Our interpretation of the results is that, in the future, benefits for trastuzumab will follow a value trajectory similar to that for the older medicine, tamoxifen. In the final year of the study, around 1 000 women received trastuzumab, 600 as adjuvant therapy. Trastuzumab was patent protected during the entire 2001–2011 study period.

**Table 3: Number of patients treated, aggregate health gains measured as QALYs, and monetary value of health gains (million SEK) from trastuzumab in Sweden years 2001–2011. Source Lundqvist et al (2013b).**

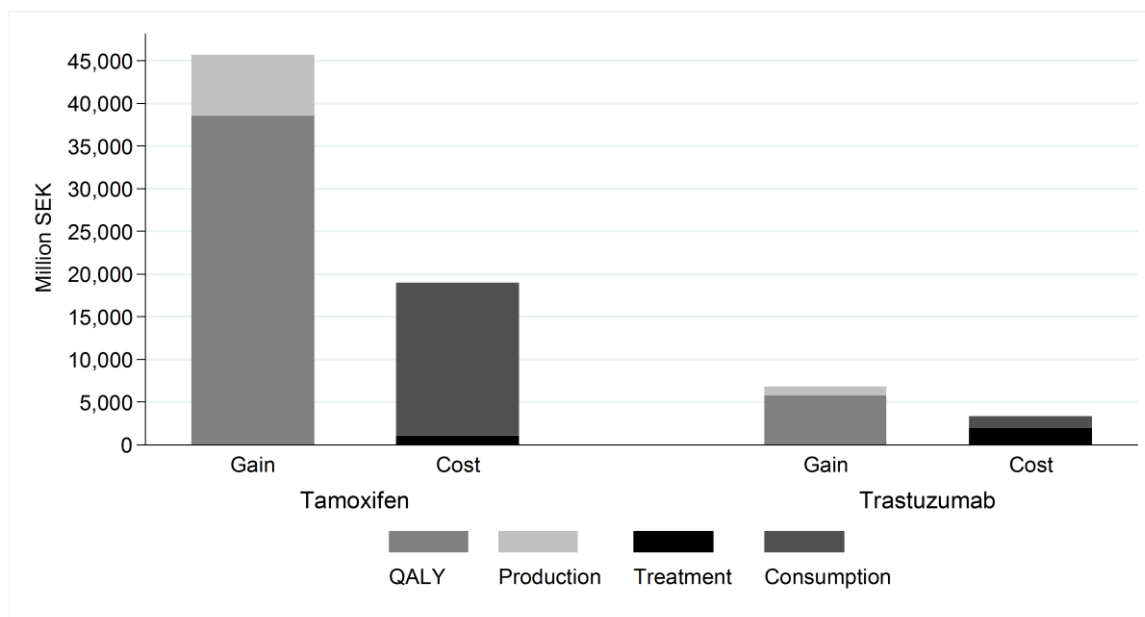
	Patients treated	Aggregated health gains	Monetary value
	Number (%)	QALY (%)	Million SEK (%)
Disseminated disease	3 300 (51)	3 300 (48)	2 800 (48)
Adjuvant therapy	3 200 (49)	3 500 (52)	3 000 (52)
Total	6 500	6 800	5 800

QALY – Quality Adjusted Life–Year. Rounded figures.

Future use of trastuzumab will depend, amongst other things, on the number of women with HER2-positive breast cancer, the proportion of this population receiving treatment, and the duration of treatment for each patient. However, estimating benefits of trastuzumab per se is increasingly challenging as new medicines are introduced and used either concomitantly or sequentially with other treatments such as tamoxifen.

The study compared the value of the realised economic gain from the use of tamoxifen during 1979–2004 (patented and off-patent) and trastuzumab during 2000–2011 (patented only). Figure 3 illustrates economic gain of each medicine over available treatment options.

**Figure 3: Increased gain and cost of hormone-responsive and HER-2 positive breast cancer following the introduction of tamoxifen and trastuzumab. Million SEK. Source Lundqvist et al., (2013a).**



One observation is that the longer time perspective used in the analysis of tamoxifen highlights that economic value is accumulated throughout a medicines life cycle. The cost-benefit analysis in Figure 3 shows that treatment costs have been low (1 billion SEK) compared to the total gain (45 billion SEK). From a societal point of view, consumption costs are the greatest component of costs – 17.9 billion SEK out of a total cost of 18.9 billion SEK (96%). Consumption costs are based on age-related average private and public consumption. A somewhat different picture emerges from the analysis of the more recent drug trastuzumab. Estimates are based on the early implementation phase while the drug was still on patent. The far right bars in Figure 3 show gains and costs for trastuzumab.

1. Productivity gains accounted for a smaller share of overall gains compared with tamoxifen. This can be explained largely by the fact that for nearly half of the observation period, trastuzumab was only used for patients whose disease had metastasized. Treatment during this advanced stage is less likely to have an impact on productivity than is adjuvant treatment for patients in earlier stages of the disease.
2. Consumption costs accounted for 42% of total costs. There are two explanations for this. Firstly, during the early implementation phase trastuzumab was still patent-protected and the manufacturer was able to recover more of the costs of research and development. Secondly, during this early period, patients whose illness was more severe accounted for a relatively large proportion of the total number of patients treated. This group will gain comparatively few life years and thus increase consumption costs less.

These findings from the analysis of breast cancer treatment are examples of the importance of showing the societal gain and costs from a long-term perspective, and also take into account price changes after patent expiration. The analyses clearly demonstrate that the value of new technologies increasingly accrues to patients/consumers over time. In

the shorter term, treatment costs account for a greater share of the total costs. Because the treatment is more likely to still be patent protected, this is also the time when the costs of research and development costs may be recouped.

### **3.3 Price – quantity interplay and patent protection period: The example of lipid-lowering treatment**

Another example of the importance of considering the longer-term and the full life-cycle perspective when estimating the value of new health technologies relates to lipid-lowering treatment with the aim of reducing risks of cardiovascular disease. Lindgren and Jönsson, (2012) estimated the value of lipid-lowering therapy using simvastatin from its launch in Sweden in 1987 until 2008, based on registry data, and forecasted its continued use to 2028. This study showed a steep increase in the number of individuals commencing treatment with simvastatin when the price was reduced as a consequence of patent expiration(- 90%).

The consumer surplus for simvastatin for the entire study period was estimated at 1,083 EUR per person per year of treatment. It is of interest to note that according to the authors' estimates, 95% of this value occurred after the patent of the branded product had expired. There were two main factors behind these results. Firstly, the number of statin prescriptions filled during the first ten years after approval was modest compared with current levels. As is often the case, medicines are often prescribed cautiously during the early introductory phase. This can be explained partly by uncertainty about the real-life clinical effectiveness of the medicine; many clinicians may prefer to prescribe trusted established therapies, especially if the price of the new alternative is significantly higher. Secondly, patent protection is effective only during a limited period of the total life cycle of a medicine. The estimations by Lindgren and Jönsson were based on the assumption that statins will continue to be used until 2028, which means 16 years with patent protection and 26 years with generic competition. Simvastatins may conceivably be replaced by other medicines by then, but it is also possible that they may continue to create value.

In the analysis of simvastatin, savings from reduced health care costs and diminished loss of productivity were estimated at 59 EUR per capita. The producer surplus – the profit – was estimated at a total of 52 EUR per capita, corresponding to 5% of the total economic surplus, that is, consumer and producer surpluses together. Similar results on the distribution of surplus of statins were found in a recent publication on data from England and Wales covering 1990-2012 (Refoios Camejo et al., 2014).

### **3.4 New medicines and the estimation of impact on productivity loss: The example of TNF inhibitors in the treatment of rheumatoid arthritis**

Several studies have demonstrated quality of life gains for rheumatoid arthritis patients treated with tumor necrosis factor (TNF) inhibitors (Gulfe et al., 2010, Karlsson et al., 2011, Lindgren et al., 2009) while survival seem unaffected by TNF inhibitors. Here, we highlight methods for estimating the value of reductions in productivity losses and freeing up resources within the health care system. Kalkan et al., (2014) reported on trends for 1990–2010 in the cost of sickness absenteeism and disability pensions where rheumatoid arthritis was reported as the primary cause. The authors noted a reduction in productivity losses at an aggregate national level. The greatest difference was found in disability pensions. In the early 1990s, rheumatoid arthritis was given as the primary cause in 3% of all disability pensions, compared to 1.5% in 2010. A similar reduction was seen in the number of newly granted disability pensions, from 2% to 1%.

The above study analysed parallel trends in aggregate data; however, data were insufficient for drawing conclusions about a causal relationship. Individual-level register

data and/or registry enriched randomized controlled trials are needed to monitor actual effectiveness of new health technologies. Neovius, (2013) used TNF-inhibitor treatment of rheumatoid arthritis to estimate change in workdays lost after diagnosis and the impact of biological treatment, respectively.

Findings included significant loss of productivity amongst people with established rheumatoid arthritis. Working-age rheumatoid arthritis patients lost twice as many work days annually as matched population-based controls. The total loss of productivity due to rheumatoid arthritis was estimated at 2.3 billion SEK in 2008. Consistent with previous research, Neovius also detected a pattern of rapidly increasing loss of productivity prior to rheumatoid arthritis diagnosis and a reduction following the start of disease-modifying antirheumatic therapy. One year after the diagnosis, rheumatoid arthritis patients lost on average six additional work days each month compared to individuals of the same age, sex, and level of education (11 versus 5 work days lost per month).

However, the rheumatoid arthritis patient group was not homogenous; a small group of patients accounted for a large proportion of the overall loss of productivity. The statistical analysis showed that four years after diagnosis, on the one side of the distribution 19% of patients were on full-time sick leave or disability pension and, on the other side, 46% had not registered any sick days with the Swedish Social Security Agency [Försäkringskassan] at any point. A small proportion, 8%, had lost 1–49 work days whereas a slightly larger proportion, 21%, had been away from work for 50–199 days; 7% of patients had been away from work for 200–364 days. It is clear that society incurs significant costs due to rheumatoid arthritis as a consequence of reduced work capacity, and new and more effective treatments may reduce it.

Biological treatments have been hailed as a treatment revolution in rheumatology. Sales statistics indicate a tenfold increase in total sales during 2000–2009. In 2012, TNF inhibitors accounted for more than 7% of the total cost of medicines. In Sweden, three of the top five selling medicines that year were biologics. At the same time, the statistics in Neovius, (2013) indicate a trend similar to that seen with the introduction of the breast cancer medicines tamoxifen and trastuzumab. The first patients to be offered a new medicine will be those whose illness is the most severe. Patients who started biological treatment in 2005 experienced a gradual increase in the number of annual sick days, up to an average of nearly 200 days in the year that treatment was started. These patients were diagnosed more than six years earlier (median duration). Once biological treatment began, sickness absenteeism stabilised in this group in comparison to a continuing upward trend amongst matched population-based controls. A study of patients with new-onset rheumatoid arthritis during 2006–2008 showed that more than 90% were treated with conventional disease-modifying drugs or cortisone alone (Neovius, 2013; p 24, Figure 11). Biological treatments were prescribed mainly for younger patients (30% of patients aged 18–29 years and 4% of patients aged 70–79 years). A further study analysed treatment effectiveness in terms of disease activity in patients with new-onset rheumatoid arthritis during 2002–2006. Patients who did not achieve satisfactory health improvements on methotrexate alone were randomised to receive either a biological or a non-biological disease-modifying drug as an adjuvant to methotrexate. Even in this group of relatively new-onset rheumatoid arthritis patients, a sharp rise was seen in the number of days of sick leave before adjuvant treatment began. In both the biological and non-biological adjuvant therapy group, patients experienced a reduction in days of sick leave, from approximately 17 days per month at the time of randomisation to approximately 13 days per month after one year (Neovius, 2013). The difference in clinical outcomes based on disease activity was statistically significant, but no statistically significant difference was observable in the number of days on sick leave after one year in this study of 258 patients.

Overall, the results indicated small differences in outcomes in the selected patient population, whilst the difference in treatment costs was large. Rheumatoid arthritis clearly imposes a significant cost burden on society as a consequence of reduced capacity to work. Just over 20 years ago, a label extension for methotrexate provided clinicians with an additional tool in the fight against health and productivity loss due to rheumatoid arthritis. Around ten years later, TNF inhibitors brought about a therapeutic revolution, initially in rheumatology and subsequently in a wider range of indications. Good scientific evidence supports the positive effect of these new rheumatoid arthritis treatments on productivity losses. At the same time, the studies by Neovius and Kalkan et al cited above highlight the challenges associated with investigating causal relationships for specific outcomes such as reducing of sickness absenteeism due to rheumatoid arthritis.

The cost effectiveness of these new medicines remains unclear which is an unacceptable situation given the vast amounts spent on these products. For example, more than 12 billion SEK in total was spent by the Swedish health care system on TNF inhibitors on treatment of rheumatoid arthritis and other patient groups with this treatment indication during 2005–2012 according to the Swedish National Board of Health and Welfare's annual compilation of statistics on the use of medicines (Socialstyrelsen, 2013).

#### **4 Conclusions and a health-economic research agenda**

An important conclusion from the research programme on The Value of New Medicines at the Centre for Business and Policy Studies was the need for an increased use of ex-post calculations of the value of new medicines when used in routine health care and daily praxis. These ex-post calculations assist decision makers in health care including payers by reducing uncertainties that are present when new medicines are first introduced and estimates on efficacy and (cost-)effectiveness are prognoses based on protocol based trials conducted for regulatory assessment. There is an urgent need to further expand efficient knowledge generation from real-world data where ex-post assessment of the value of the new technologies is evaluated in broader patient populations and compared with treatment alternatives relevant to the present jurisdiction and patient group.

The findings and conclusions from the Swedish studies cited in this paper are also in line with international results. For instance, Philipson and Jena, (2005) applied a product life cycle perspective when they assessed the value of antiretroviral drugs used in the treatment of HIV/AIDS in the US. They estimated based on retrospective data and prognosis for future need of drug treatment of HIV/AIDS that 95% of the total surplus over the long-term would accrue to patients while 5% would be recouped by manufacturers. Other examples include (Refoios Camejo et al., 2014) study on the use of statins in the UK, and (Lakdawalla et al., 2010) evaluation of the war on cancer.

We note the successes presented her, besides providing consumer surplus, also provide capital for the research on future compounds where the outcome and value is still uncertain and not all will turn out to meet efficacy and safety goals. The choice of methodology for estimating the value of new medicines, or any other technology, is determined by two principal factors: the research question and access to data. The research question determines which patient population, the medicine, and other treatment components to be considered. Access to data and the quality of the data collected are crucially important for making accurate estimations.

Nevertheless, although the debate continues about the pros and cons of various methods, this is not an argument against estimations per se. Our conclusion is that there is a large unmet need for increased insights and knowledge generation regarding the value of new medicines, both in terms of actual use and outcomes. From a societal point of view,

there is an urgent need for more knowledge regarding the relative effectiveness of new drugs when used in clinical practice, and compared to current or otherwise relevant treatment options.

Perhaps the most important challenge is how to make data sets available for analysis. Many medicines that are now regarded as standard treatment were initially met with guarded enthusiasm or even scepticism. At the early stages of introduction, particularly during the time when patents allowed higher prices to be charged, the use of lipid-lowering statins and the breast cancer drug tamoxifen were limited by relatively high prices and lack of evidence to support more widespread use. Two important lessons from the examples presented in this paper are (1) It may take time to realise a new medicine's full potential for generating value; and (2) The allocation of value to society and the developer will shift over a medicine's lifecycle.

The first lesson emphasises the importance of continuing efforts to generate knowledge after a medicine reaches the market and starts to be used in clinical practice. An example of how continued knowledge generation after launch supports decision makers is the results on adjuvant tamoxifen therapy for ten years (Davies et al., 2013). The second lesson is a reminder of the importance of having an effective patent system that rewards innovation with a monopoly on sales for a limited period of time. The costs of research and development for new drug are most likely to be recouped while it is still under patent protection.

Finally, the examples of gains achieved in the treatment of diabetes, cancer, cardiovascular disease and rheumatoid arthritis may not represent the maximum total benefit of any of the medicines. The analyses used best available historic data on actual use and forecasts for future use. As such, they did not account for what a sooner introduction and more efficient implementation with more rapid evaluation of relative effectiveness of the new treatments would give but rather what was the observed developments. Health economists have an important role to play in formulating research questions, conducting analyses and assisting decision makers with analyses based on context relevant data and simulations.

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