HEALTH **I**NNOVATION NE**X**T GENERATION **P**AYMENT & PR**I**CING MODELS **(HI-PRIX):**

Balancing Sustainability of Innovation with Sustainability of Health Care

M4: Literature review of role of cost-effectiveness and budget impact in pricing and reimbursement decisions and the role of indirect medical costs

WP3: Widening the scope of economic evaluations for pricing and reimbursement decisions: the role of indirect medical costs and environmental impact

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EXECUTIVE SUMMARY

Cost-effectiveness analysis (CEA) is used to assess whether new interventions in healthcare yield sufficient value for money. If interventions prolong life, it is relevant to consider health spending in life years gained not only of the disease(s) at which the intervention was targeted but also other diseases that induce health care use. In the context of CEA, health spending in life years gained on these 'other' diseases is often referred to as future unrelated medical costs or indirect medical costs. In this report we will describe a) theoretical background illustrating the relevance of future unrelated medical costs and its implications for budget impact and pricing of healthcare innovations b) current inclusion of future unrelated medical costs in CEA c) methods to estimate future unrelated medical costs d) discuss areas of research in which these methods could be improved. Our theoretical background makes clear that future unrelated medical costs need to be included in CEA as inclusion leads to different decisions that on balance result in more health. While the budget impact need not be high in many cases, the impact of these indirect medical costs on the ICER can be big if interventions extend life of elderly in poor quality of life. More broad and consistent inclusion of indirect medical cost in CEA could lead to lower drug prices of life extending therapies and the health economics community should lobby to encourage changes in guidelines so that incorporating indirect medical becomes more standard practice. The review of current methods shows that much progress has been made in the field and that most studies take into account that health spending is centered in the last phase of life and allow adjustments to avoid double counting of related medical spending. An area of research that might improve current methods is to take into account uncertainty in the estimates of future unrelated medical. We propose several directions on how these issues can be addressed.

1. Introduction

Unrelated future medical costs (also called indirect medical costs) in cost effectiveness analysis (CEA) are costs for diseases that only arise if an intervention extends life. These costs are termed 'unrelated'/'indirect' as they are caused by other diseases than those at which the intervention is targeted. An example would be costs for treating dementia in life years gained as a result of a successful cancer treatment. In this report we will describe a) theoretical background illustrating the relevance of future unrelated medical costs in CEA and its implications for budget impact and pricing of healthcare innovations b) current inclusion of future unrelated medical costs in CEA c) methods to estimate future unrelated medical costs d) discuss areas of research in these methods could be improved.

2. Theory

2.1 Indirect medical costs, CEA and budget impact

Cost-effectiveness analysis (CEA) is used to assess whether new interventions in healthcare yield sufficient value for money. If interventions prolong life, it is relevant to consider health spending in life years gained not only of the disease(s) at which the intervention was targeted but also other diseases that induce health care use. In the context of CEA, health spending in life years gained on these 'other' diseases is often referred to as future unrelated medical costs or indirect medical costs. There has been quite an extensive discussion in the literature on whether these costs should be included in CEA (seede Vries et al., 2019 for a review). Several mathematical models have been put forward that have illustrated that indirect medical costs need to be included in CEA in order to make decisions that support maximizing health or more broadly welfare (Feenstra et al., 2008; Meltzer, 1997; P. van Baal et al., 2016). Only under strong assumptions (e.g. medical costs do not depend on age, budgets are defined on a per person basis instead of population) one can derive conclusions from such mathematical models that indirect medical costs can be ignored in CEA (Garber & Phelps, 1997; Lee, 2008).

The mechanism why indirect medical costs need to be Included in CEA is that inclusion leads to different decisions that on balance result in more health (de Vries et al., 2019; Meltzer, 1997; P. van Baal et al., 2016). A more intuitive reason to include them is that they also contribute to the health gains that are obtained as for instance the health benefits of treatment of cancer at middle age also depend on the treatment and prevention of cardiovascular disease at later age (Nyman, 2004).

To better understand the impact of unrelated medical costs on the ICER equation (1) breaks down the ICER into different components:

$$ICER = \frac{\Delta\left[L * C\right]}{\Delta(L * Q)} \cong \frac{\Delta L * C + L * \Delta C}{\Delta L * Q + L * \Delta Q} = \frac{\Delta L * C}{\Delta L * Q + L * \Delta Q} + \frac{L * \Delta C}{\Delta L * Q + L * \Delta Q} \qquad \text{(eq. 1)}$$

Where L denotes life years, C medical costs and Q quality of life. Here, $\Delta L * C$ is the term that captures unrelated medical costs while $L * \Delta C$ equals related medical costs. In terms of budget impact, equation (1) makes clear that unrelated medical costs crucially depend on the amount

of life years gained (ΔL). However, for the ICER this is less important as ΔL influences both the numerator and denominator of the ICER. In other words, even if the amount of life years gained is small including future unrelated medical costs can have a big impact on the ICER (de Vries et al., 2021). The impact of future unrelated medical costs is bigger if gains in QALYs are smaller than gains in life years (Meltzer, 1997).

2.2 Equity and pricing implications

Although theory suggests that unrelated costs need to be included in CEA, there have been some worries that including such costs is unethical (Grima et al., 2012; P. van Baal et al., 2017). In general, including indirect medical costs makes life prolonging interventions less cost effective and this is especially the case if interventions extend life of people with low quality of life and who incur high medical spending. Therefore, it is understandable that including future unrelated medical costs may have some uncomfortable implications in the sense that some interventions in certain patient groups become less likely to be adopted. However, rather than having researchers making implicit value judgments by excluding certain costs decision makers are better served by presenting the possible consequences of their decisions. After all, these future unrelated costs will have to be paid for which will reduce the budget left for other healthcare interventions causing health losses in future patients. Ignoring future unrelated medical costs would be equivalent to attaching zero value to health losses in these patients. The relevant policy question is whether we are willing to sacrifice resources to yield health gains in a specific patient group.

In addition to worries about ethical implications, there is also a strategic side to the discussion on the inclusion of future medical costs. Given that the current use of CEA often means that ICERs of new technologies are compared to a fixed threshold this means that inclusion of these costs can have an impact on pricing. Many pharmaceutical products are targeted at extending lives of people in poor health. Therefore, any cost category that results in an ICER may effectively leave less room for profits for the producer. Given the popularity of value based pricing (in which producers price their products up to the threshold) exclusion of indirect medical costs effectively means the value of unidentified health losses in the future is transferred 100% to producers. Here, it needs to be noted that the threshold also needs to take into account of indirect medical costs. However, it is likely that the impact of indirect medical costs on the threshold is not substantial (Perry-Duxbury et al., 2022).

3. Practice

3.1 HTA guidelines

To assess the role of unrelated medical costs in HTA guidelines in Europe we reviewed all HTA guidelines and used the ISPOR 'Pharmacoeconomic Guidelines Around the World' as a starting point for that (https://www.ispor.org/heor-resources/more-heor-resources/pharmacoeconomic-guidelines). Full details of the reviewed HTA guidelines are displayed in Table 1. Here, it is important to note that in the current report the terms 'indirect' and 'unrelated' costs are used interchangeable, as we refer exclusively to medical costs. However, in the broader literature and across different country HTA guidelines the taxonomy of future costs is neither straightforward, nor unambiguous about what types of costs fall under the category 'indirect costs'.

The majority of the HTA guidelines across Europe (21 out of 27 [78%]) only briefly mention indirect costs and when they do, they most often refer to future non-medical consequences such as productivity losses due to illness or additional informal provision. In 74% (20/27) of the reviewed country guidelines there was no recommendation outlined about the inclusion (or exclusion) of future unrelated medical costs, whereas the advice differed for the remaining seven countries. Only six countries make the explicit distinction between direct (related) and indirect (unrelated) medical costs in life years gained – the Netherlands, Hungary, Portugal, Norway, UK, Belgium, and Germany. The latter five explicitly recommend the exclusion of unrelated future medical costs in the base case of the health-economic analysis, but they can be included in a supplementary analysis if deemed necessary (except Norway, where all costs in life years gained must be excluded in all analyses). The Netherlands is the only country whose guidelines explicitly mandate the inclusion of future unrelated medical costs, while Hungary's guidelines do not outline specific recommendations. France does not explicitly define future unrelated medical costs, however, they state that "costs that are considered to be unrelated to the condition or intervention in question are excluded".

Table 1: European countries review of HTA guidelines. UFMC = future unrelated medical costs.

Country	Year	Type	Perspective	"Indirect costs" mentioned?	Contextual definition of indirect costs	Recommendation about UFMC in base analysis	Recommendation about UFMC in additional analysis	Clarification/Comment
Austria	2006	Recommendation	Societal, others also possible	Yes, secondary analysis	Future non-medical costs	None	None	They state that all costs relevant to the perspective should be included, but simultaneously define indirect costs only as productivity losses.
Denmark	1997		Societal	Yes	Future non-medical costs	None	None	
Italy	2020		National Health System, societal also possible	Yes, but only if societal perspective	Future non-medical costs	None	None	
Sweden	2017	HTA guideline	Societal	Yes	Future non-medical costs	None	None	Indirect costs are defined as future non-medical costs, and there is no explicit mention of UFMC
Czech Republic	2017	Submission guideline	National Health System, societal for orphan drugs	Yes, only for orphan drugs	Future non-medical costs	None	None	
Finland	2019		Payer's	Yes	Future non-medical costs	None	None	
Poland	2016		National Health System, societal also possible	Yes, but only if societal perspective	Future non-medical costs	None	None	

Table 1: European countries review of HTA guidelines. UFMC = future unrelated medical costs (continued)

Country	Year	Type	Perspective	"Indirect costs" mentioned?	Contextual definition of indirect costs	Recommendation about UFMC in base analysis	Recommendation about UFMC in additional analysis	Clarification/Comment
Scotland	2022	Submission guideline	National Health System	Yes	non-NHS/social work costs	None	None	Indirect costs are defined as future non-medical costs, and there is no explicit mention of UFMC
Spain - Regions	2014		National Health System, societal also possible	Yes	Future non-medical costs	None	None	
Ukraine	2021		National Health System, societal also possible	Yes, but only if societal perspective	Future non-medical costs	None	None	
Croatia	2011	Recommendation	Public payer's	Yes, at researcher discretion	No further definition	None	None	"Indirect costs" is used as terminology here, which could mean either future medical, non-medical costs, or both, and even so, their inclusion is left open to debate in each case.
Hungary	2021		National Health System, societal also possible	Yes, but only if societal perspective	UFMC mentioned, but no recommendation given	None	None	The guidelines differentiate between future related and unrelated costs in life years gained. However, the document does not give explicit recommendation about UFMC inclusion. Instead, it talks about including indirect costs more generally and only if a societal perspective is adopted, which is not the default.

Table 1: European countries review of HTA guidelines. UFMC = future unrelated medical costs (continued)

Country	Year	Type	Perspective	"Indirect costs" mentioned?	Contextual definition of indirect costs	Recommendation about UFMC in base analysis	Recommendation about UFMC in additional analysis	Clarification/Comment
Russia	2018	Recommendation	Healthcare	Yes, at researcher discretion	No further definition	None	None	Indirect costs are relevant only in a supplementary analysis and only at researcher discretion. No specific definition of indirect costs.
Spain	2010		Societal, National Health System also possible	No	-	None	None	They recommend the societal perspective and list some future unrelated non-medical costs that would normally fall under the societal perspective like productivity costs, however, the document does not explicitly talk about indirect costs.
Baltic states (Latvia, Lithuania, Estonia)	2002	HTA guideline	Healthcare, societal also possible	Yes, but only if societal perspective	Future non-medical costs	None	None	Indirect costs are relevant only if a societal perspective is chosen in a supplementary analysis and only at researcher discretion. When listing out indirect costs they give examples of future non-medical costs.
Ireland	2019		Public payer's	Yes, but only if societal perspective	Future non-medical costs	None	None	Indirect costs are defined as future non-medical costs, and there is no explicit mention of UFMC. However, depending on researcher discretion, one could assume that UMFC are implied because "*current and future costs arising as a consequence of a technology and that occur during the specified time frame of the study should be included in the reference case analysis*."

Table 1: European countries review of HTA guidelines. UFMC = future unrelated medical costs (continued)

Country	Year	Type	Perspective	"Indirect costs" mentioned?	Contextual definition of indirect costs	Recommendation about UFMC in base analysis	Recommendation about UFMC in additional analysis	Clarification/Comment
Slovak Republic	2022	HTA guideline	Healthcare	No	-	None	None	Per ISPOR, the guidelines acknowledge the existence of costs in life-years gained, however only mention the inclusion of future related medical costs.
Slovenia	2013		Health insurance, societal also possible	No	-	None	None	Per ISPOR, the guidelines refer to all future direct/related costs, but do not mention unrelated costs in life years gained.
Switzerland	2022		Healthcare	No	-	None	None	There is no mention of indirect costs
Bulgaria	2015	Regulation from the Ministry of health	Public payer's, societal also possible	Yes, but only if societal perspective	Indirect costs are partly future non-medical costs; Indirect *medical* costs mentioned, but not defined	None	None	There is no explicit mention of UFMC even though the guideline mentions "indirect medical costs", as no further clarification is given.

Table 1: European countries review of HTA guidelines. UFMC = future unrelated medical costs (continued)

Country	Year	Type	Perspective	"Indirect	Contextual	Recomm	Recomme	Clarification/Comment

				costs" mentioned?	definition of indirect costs	endation about UFMC in base analysis	ndation about UFMC in additional analysis	
France	2012	HTA guideline	All health care funders and population whose health is affected	Yes, secondary analysis	Future non-medical costs	Exclude	Exclude	The guidelines refer to indirect costs but only in their future non-medical costs meaning, and even then, the main recommendation is to exclude these costs. Apart from that definition, in their discussion about direct costs they state that "*costs that are considered to be unrelated to the condition or intervention in question are excluded*."
Norway	2012	HTA guideline	Societal	No	-	Exclude	Exclude	Guidelines explicitly state that "costs related to added/extra life years should not be included."
Portugal	1998	HTA guideline	Societal	Yes	Future non-medical costs	Exclude	Exclude	The guidelines acknowledge that there are "*expenses incurred as a result of the fact that patients' life expectancy is increased thanks to the treatment, and they will therefore use more health products in the future*". However, they recommend including only "*the expenses that are a direct result of the treatment in question*."

Table 1: European countries review of HTA guidelines. UFMC = future unrelated medical costs (continued)

Country	Year	Type	Perspective	"Indirect costs"	Contextual definition of	Recommendati	Recommendation	Clarification/Comment

				mentioned ?	indirect costs	on about UFMC in base analysis	about UFMC in additional analysis	
Belgium	2012	HTA guideline	Health care payer (government + patients)	Yes	Indirect costs = UFMC	Exclude	Include at researcher discretion	The guidelines differentiate between future related and unrelated costs in life years gained. UMFC are to be excluded from the base case and may be included in an additional analysis if deemed relevant.
Germany	2022	HTA guideline	Health care sector's	Yes, secondary analysis	Indirect costs = future non-medical costs; UFMC = "non-intervention-associated future costs"	Exclude	Include at researcher discretion	The guidelines define the indirect costs only as future non-medical costs, whereas the future unrelated medical costs are called "non-intervention-associated future costs". UFMC can be included in a separate sensitivity analysis if the extension of life is relevant for the CAE.
England & Wales	2022	Submission guideline	National Health Service	No	-	Exclude	Include at researcher discretion	The guidelines specifically mention that unrelated medical costs need to be excluded. Their inclusion may be justified in very specific cases when the CEA is on diagnostic technologies.
Netherlands	2016	HTA guideline	Societal	Yes	-	Include	Include	UFMC are specifically defined and required.

3.2 Review of methods and tools

As seen in the previous section only a few countries recommend including unrelated medical costs routinely in economic evaluation. Consequently, many economic evaluations of life prolonging interventions do not take into account future unrelated medical costs. At the same time, more methods and tools have been become available that facilitate the inclusion of future unrelated medical costs (Briggs et al., 2018; Jiao & Basu, 2021a; Kellerborg et al., 2020a; Mokri et al., 2023; Perry-Duxbury, Asaria, Lomas, & van Baal, 2020; P. H. M. van Baal et al., 2011). In this section, we will review methods and tools that have been used to estimate future unrelated medical costs. Table 1 summarizes various ways in which future unrelated medical costs have been implemented into health-economic analyses in the years 2010 to 2023.

The starting point for the estimation of future unrelated medical costs in all methods is estimates of per capita health spending by age which comprise spending on all sorts of diseases. These age profiles of medical spending can be linked to survival curves produced by CEA models. This method has been proposed by David Meltzer in his seminal paper on future costs (Meltzer, 1997). The logic behind using such cost profiles is that these cost profiles capture the costs of all (related and unrelated) diseases and using these cost profiles is a much more efficient and reliable way to model costs rather than modeling costs of all diseases separately. Age profiles of health spending per capita profiles vary highly between countries mainly because of differences of what constitutes health spending (Mokri et al., 2023). For instance, in countries where long term care is to a large extent publicly financed such as the Netherlands these cost profiles increase much more strongly with age. Differences in what constitutes health spending translate directly into differences into the impact of indirect medical costs on the ICER. For instance, the impact of future medical costs on the cost effectiveness of life prolonging interventions is much bigger in the Netherlands than in England (Mokri et al., 2023).

Interventions are often targeted at a single disease, and although costs may be high per patient, costs of related disease(s) in itself form only a small portion of per capita spending given the low prevalence of most diseases. However, in order to prevent double counting of the cost of related diseases, the costs of related diseases can be subtracted from total medical spending estimates. Although the impact of such adjustments is often small, some tools have options to do these adjustments directly (Kellerborg et al., 2020a; P. H. M. van Baal et al., 2011). In absence of such direct adjustments a general framework has been developed to do these adjustments using

external data on prevalence of the disease and cost per patient (Perry-Duxbury, Asaria, Lomas, & van Baal, 2020). Using this framework one can also for the fact that in some patient groups costs of unrelated diseases differ from those of the general population (de Vries et al., 2021)

In light of the large volume of empirical studies that showed that health spending increases strongly when death approaches (PAYNE et al., 2007), most tools that produce estimates of future unrelated medical costs take this into account and produce age cost profiles stratified by time to death. Using such estimates stratified by time to death already highlights the observation that much more costs are probably related to any intervention that extends life. After all, originally, unrelated medical costs were defined as costs that conditional on survival are not affected by the intervention (Meltzer, 1997). When modeling costs depending on time to death this assumption is violated. A justification for breaking this assumption is that unobservable characteristics that triggers health losses causes a ripple effect on health care usage in many disease areas. Especially at older age, this seems a reasonable assumption.

Table 2: Summary of studies implementing future unrelated medical costs (UFMC).

Country	Target population	Correction for related costs	Time-to-death correction	Source data	Healthcare providers included in the UFMC estimates	UFMC implementation method	Reference
Germany	All	No	Yes	Krankheitskostenrechnung, Federal Statistical Office Germany	Unspecified	"The lifetime expected costs… are the sum of all discounted healthcare costs that a person is expected to incur during his other remaining years." (no further methods specified). They have a separate estimate for the cost of dying (€15,000), calculated from hospital data.	(Tscheulin & Drevs, 2010)
Netherlands	All	Yes	Yes	2007 COI study	Hospitals, ambulatory care, retail sale and other providers of medical goods, nursing and residential care.	PAID 1.0 is a **tool** to assist researchers to include UFMC into their CEA for the Netherlands in a standardized way.	(P. H. M. Van Baal et al., 2011)
US	45-year-old individuals with Alcohol Use Disorders (AUD)	No	Yes	2003-2012 Medical Expenditure Panel Survey	*Hospital in- and outpatient, pharmacy, office-based physicians, home health institutions*	*Average age-specific annual healthcare expenditures* among the general population, as authors calculated from the MEPS survey. Population estimates were calculated using survey weight adjustment.	(Zarkin et al., 2017)
New Zealand	55−74-year-olds with a smoking history	No	Yes	Individual-level healthcare costs from linked administrative data, 2006-2011	*Hospitalizations and inpatient procedures, including pharmaceuticals; hospital outpatient visits; outpatient drug prescriptions; GP consultations; disability support services;*	*Expected annual healthcare costs* of a New Zealander by age and sex, estimated based on detailed individual-level data.	(Jaine et al., 2018)
US	Total knee replacement patients	No	No	Medicare and Medicaid data.		A simulation model producing the *average annual medical costs unrelated to knee OA*, stratified by age and number of comorbidities.	(Smith et al., 2018)

Australia	Cancer patients	Yes	Yes	New Zealand's individual-level healthcare costs from linked administrative data, 2007/08 to 2009/10 financial years. Events tied to unit costs.	*Hospitalizations and laboratory tests; hospital outpatient procedures and emergency departments; community pharmaceuticals dispensed; GP costs*	Calculated average costs per person-year in each stratum of interest: sex by five-year age group by financial year (2007/08, 2008/09, 2009/10) and by time-to-death. Then, tied those estimates to projected health events per person-year also accounting for population growth.	(Tew et al., 2019)
US	All	Yes	No	Medical Expenditure Panel Survey (2011−2015)	*Hospital in- and outpatient, pharmacy, office-based physicians, home health institutions*	Used a two-part model to produce age-specific per capita estimates of healthcare costs owing to competing diseases (all diseases except breast/colorectal/cervical cancer).	(Ratushnyak et al., 2019)
Philippines	All	No	No	2012 National Health Accounts	All forms of public and private health spending (private, public, and general hospitals (in- and outpatient care); ambulatory health care; pharmaceuticals and medical goods)	Average per-capita country healthcare expenditure by age and sex directly used as in the survey.	(Avanceña et al., 2019)
US	Patients with Chloridoids difficile infection	No	No	Real-world claims data from the PharMetrics Plus database (IQVIA; Durham, NC), containing >140 million individuals with commercial insurance coverage throughout the US, 2010-2017	All adjudicated medical and prescription drug claims; inpatient and outpatient claims and procedures; retail and mail-order pharmacy claims;	Calculated all-cause medical costs from the claims data (unspecified method). Did not correct for related costs due to the structure of the source data.	(Feuerstadt et al., 2020)

Country	Target population	Correction for related costs	Time-to-death correction	Source data	Healthcare providers included in the UFMC estimates	UFMC implementation method	Reference
Netherlands	All	Yes	Yes	2007 COI study	Hospitals, ambulatory care, retail sale and other providers of medical goods, nursing and residential care.	PAID 3.0 (**Tool**)	(Kellerborg et al., 2020b)
England & Whales	All	Yes	Yes	(Asaria, 2017)	Hospital Episode Statistics data from 2011 along with aggregate data on the number of general practitioner (GP) visits in a year.	PAIDUK (**Tool**)	(Perry-Duxbury, Asaria, Lomas, & Van Baal, 2020)
Australia	All	No	No	Disease Costs and Impact Study (DCIS) 2001 of the Australian Institute of Health and Welfare	Hospital costs (in- and outpatient), allied professionals, medical services; nursing homes; dental services; pharmaceuticals, and nursing homes.	Average HCE by disease and age - "Healthcare costs for diseases and injuries unrelated to IHD due to additional years of life gained were also taken from the Disease Costs and Impact Study (DCIS) 2001." (unspecified method)	(Marklund et al., 2020)
US	All	Yes	Yes	Medical Expenditure Panel Survey (2007−2015)	*Hospital in- and outpatient, pharmacy, office-based physicians, home health institutions*	Breakdown of total healthcare expenditure - similar to PAID	(Jiao & Basu, 2021b)
Germany	All	No	No	Statistics Germany	Statistics Germany's estimates by disease	Average healthcare expenditure by age and other covariates -estimated via by aggregating expected healthcare costs at age j, conditional on having survived up to age j. Survival obtained from a life table.	(Gandjour, 2021)
US	HIV positive	Yes	No	Various *(systematic review)*	Various *(systematic review)*	*This is a systematic review of studies that estimate the lifetime cost of managing HIV.* The studies mostly focus on FMC that are not direct but are also not completely independent of the disease in question (HIV patients have an increased	(Tran et al., 2021)

						chance of heart and chronic diseases). Technically, these costs should not be classified as UFMC, but rather should be included as related diseases in the FMC. However, they are being discussed in the context of unrelated diseases.	
US	Cirrhosis patients	No	No	U.S. Bureau of Labor Statistics 2018 Expenditure Survey	Unspecified	The source data comes from an all-cause expenditure survey, which also includes healthcare expenditure. As such, the authors used these same estimates to model both future medical and non-medical costs. "Future related medical costs were assumed to be included in treatment/medical costs which vary depending on the health state a patient is in. We assumed that all future unrelated medical costs were additive and are included in future consumption costs (Table A4)."	(Avanceña et al., 2021)
UK	Early breast cancer	Yes	Yes	As PAIDUK	As PAIDUK	Used the PAIDUK tool to account for UFMC	(Glynn et al., 2023)
Kenya	All	Yes	No	2020 WHO Global Health expenditure Database & 2013 Kenya House-hold Health Expenditure and Utilization Survey	Aggregate data on primary healthcare, immunization, disease-specific costs; Capital formation in the health system	Total HCE by age and sex from which the costs of the related disease were subtracted.	(Marklund et al., 2023)

Areas of research that might improve current estimates of future unrelated medical costs are a) to take into account uncertainty- in the estimates of future unrelated medical costs and b) to better take into account characteristics of the target group at which interventions are targeted. We argue that the second issue is difficult to address in a standardized manner and should be left to researcher discretion. Current methods all take as a starting point medical spending patterns by age which can be adjusted to tailor the specific healthcare use patterns of a particular patient group. However, if there is evidence that healthcare use in a specific patient group differs drastically from the average population (conditional on age, gender and time to death) it might be preferable to derive estimates from alternative sources. An example of this would be the economic evaluation of statin treatment in people on kidney dialysis. Here, the costs of dialysis treatment are unrelated to statin treatment but the costs thereof are substantial and preferably directly estimated from alternative data sources in that patient group rather than indirectly from spending patterns derived from the general population. In many trials total (and not just of the disease of interested) health care use is monitored which can be extrapolated using standard methods to model the impact of indirect medical costs. Let's take another example where the intervention is smoking cessation targeted at people with COPD. In this case, eliminating the smoking can of course have positive health effects, however, the target population will likely still differ from the general population in terms of lifetime healthcare usage due to their underlying propensity for unmodelled comorbidities due to their COPD (Martinez et al., 2014). Hence, the target population is also an important factor in determining the unrelated medical costs and their impact on the ICER. The lack of patient group-specific average lifetime costs, in fact, seems to be one of the reasons why (Epstein et al., 2023) chose not to make use of the PAID tools as is, and instead develop their own methodology to investigate the importance of unrelated medical costs in CEA.

4. Uncertainty

An issue that has received little attention so far in when estimating indirect medical costs is the role of uncertainty. Given the fact that probabilistic sensitivity analysis has become standard practice in CEA (Caro et al., 2012), the availability of uncertainty estimates for future medical costs is relevant for the widespread inclusion of such costs in economic evaluations. Uncertainty surrounding these costs may be caused the amount of life years gained (ΔL) and uncertainty regarding the costs in life years gained (C). Uncertainty in ΔL is usually depends on the exact intervention and this uncertainty usually is accounted for in CEA. However, it needs to be noted that uncertainty regarding ΔL is a more relevant budget impact than for the ICER as ΔL influences both the numerator and denominator of the ICER. Uncertainty regarding C depends on various factors, of which we will address several.

Given that usually age specific per capita spending is used as a starting point for most tools, quantifying uncertainty in these patterns would also be the best place to start when thinking about incorporating uncertainty in tools. How to do that depends of course on the available data. If age specific spending patterns are derived from individual level data, quantifying uncertainty is straightforward. However, if aggregate level data is used things become less obvious whether probability distributions can be assigned to costs, and how much these distributions vary between healthcare sectors and different health systems. Also, the effect of time to death on spending patterns is uncertain and most studies on time to death are already a bit old. To illustrate the relevance of uncertainty, Figure 1 displays uncertainty regarding the ratios used to decompose average costs in PAID (Wong et al., 2011). Figure 1 shows that hospital expenditures for colorectal cancer in the last year of life (conditional on age) are much higher in the last year of life for men compared to expenditures for colorectal cancer for men who survive for at least another five years. However, the uncertainty surrounding the strength of the time to death (TTD) effect (as measured by the cost ratio) is quite large. For instance, the costs ratio at age 60 is on average 50 but 95% prediction intervals are 40 to 60.

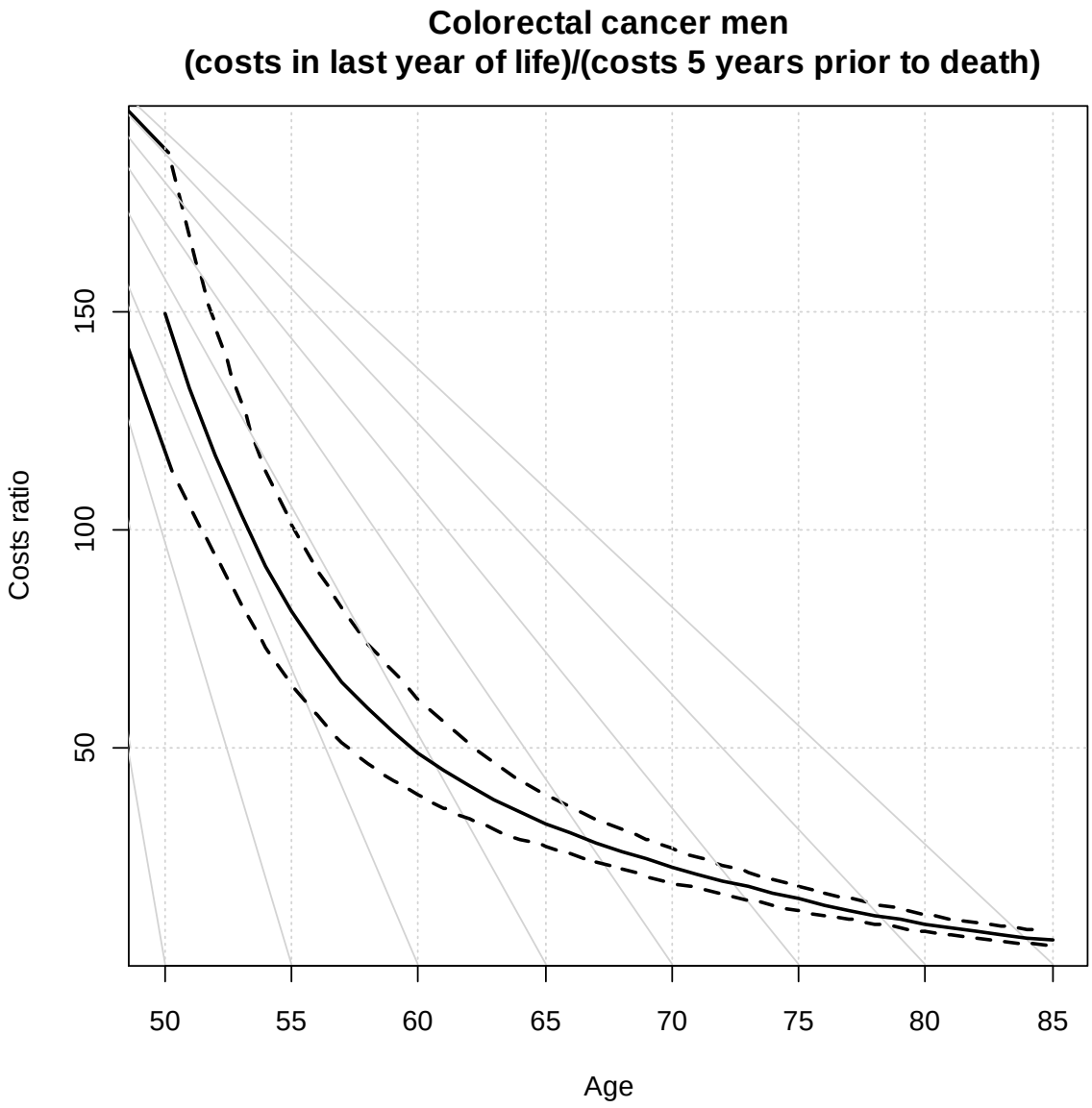

Figure 1: *Predicted ratio of hospital expenditures for colorectal cancer in the last year of life divided by hospital expenditures for men who do not die within 5 year (source: .*(Wong et al., 2011)).

Furthermore, empirical studies have shown that the influence of proximity to death is not restricted to the last year of life. A study using data from England showed that time to death influences HCE up to fifteen years prior to death and the influence in the last 5 years of life are substantial (Seshamani & Gray, 2004). To illustrate how the effect of TTD gets stronger the lower TTD is, Figure 2 displays similar cost ratios as displayed in Figure 1 but stratified by different periods of TTD.

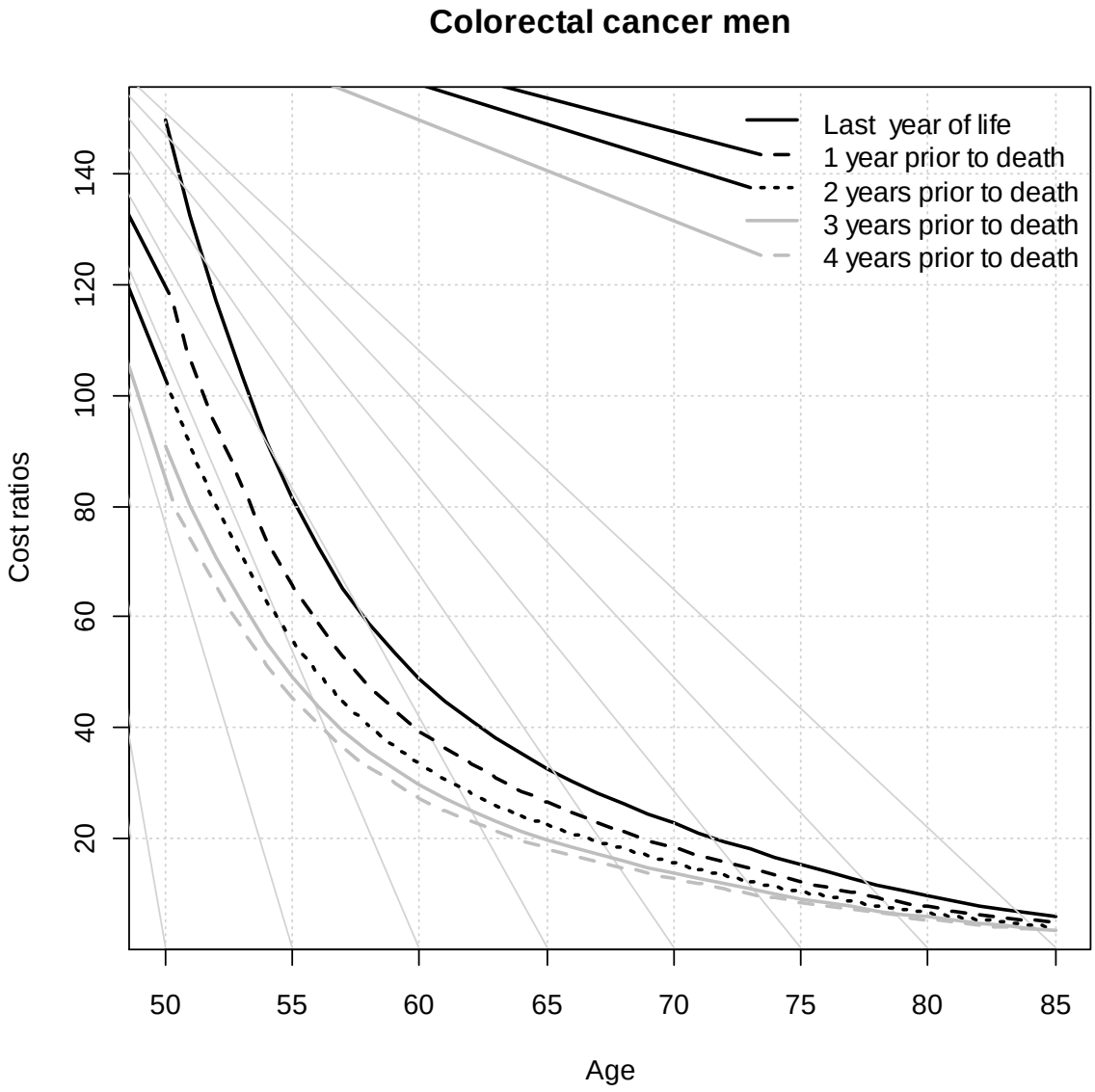

Figure 2: *The effect of time to death on yearly hospital costs for colorectal cancer. In the denominator for all costs rates are average hospital expenditures for colorectal cancer of men who do not die within 5 years (source:*Wong et al., 2011).

A more fundamental source of uncertainty lies in the fact that in all tools cross sectional data are interpreted from a longitudinal perspective. This carries the implicit assumption that health care consumption will not change in the future. However, in the past, there has been an upward trend in total health care expenditure in most western countries including the Netherlands. If we interpret a current cross section age pattern of health care expenditures in a longitudinal way, we implicitly assume that health care expenditures remain constant from now on. Similar, as is

done with life expectancy, we can make a distinction between *period* and *cohort* lifetime health care costs (Guillot, 2011). Period lifetime health care expenditures equal the average health care expenditures given someone's length of life if he or she experienced the particular area's age-specific health care expenditures for that time period throughout his or her life. It makes no allowance for any later actual or projected changes in health care expenditures. Cohort lifetime healthcare expenditures can be calculated using known or projected changes in health care expenditure patterns in later years. However, all methods use to estimate future medical costs in economic evaluations use current or past health care consumption patterns to estimate future consumption patterns. The question then becomes whether current health care consumption is a good predictor for future health care consumption? In other words: Is the health care consumption of an 80-year-old person today representative of the health care consumption of a current 70-year-old in 10 years? To answer this question, Table 3 displays estimates of hospital expenditures by age for the Netherlands for men in the period 1998 to 2008. From this table we can see that we would have underestimated the hospital expenditures of an 80-year-old man in 2008 based on the health expenditures of an 80-year-old man in 1998 by about 35%. This illustrates that the assumption that health care consumption patterns remain constant is not a strong assumption, and that we should try to forecast how health care expenditures change in the future. Here, it should be noted that the use of cohort and period perspectives is often mixed in CEA practice. For instance, in CEA of new oncology drugs often survival is extrapolated from the trial which implies a cohort perspective. However, in many CEA models background mortality is derived from standard period life tables. The period perspective is consistent with a ceteris paribus approach in which the only thing that might trigger changes is health and healthcare use. Such an approach is in line with the theoretical foundations of CEA. However, one might question the relevance of this approach when evaluating interventions that have effects far into the future. An easy example of such an intervention might be smoking cessation of which both the potential health benefits and well as future healthcare use depend crucially on innovations in health care.

Table 3: *male hospital expenditures by age for different years (source* (P. H. van Baal & Wong, 2012)*). Period (column) and cohort(diagonal) perspective.*

Year/ Age	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
70	5616										
71	5888	6041									
72	6165		6495								
73	6446			6979							
74	6729				7496						
75	7015					8047					
76	7302						8635				
77	7590							9264			
78	7878								9937		
79	8164									10658	
80	8448										11434

5. Conclusions

Cost-effectiveness analysis (CEA) is used to assess whether new interventions in healthcare yield sufficient value for money. If interventions prolong life it is relevant to consider health spending in life years gained not only of the disease(s) at which the intervention was targeted but also other diseases that induce health care use. In the context of CEA, health spending in life years gained on these 'other' diseases is often referred to as future unrelated medical costs or indirect medical costs. In this report we will describe a) theoretical background illustrating the relevance of future unrelated medical costs and its implications for budget impact and pricing of healthcare innovations b) current inclusion of future unrelated medical costs in CEA c) tools to estimate future unrelated medical costs d) discuss areas of research in which such tools could be improved.

Our theoretical background makes clear that future unrelated medical costs need to be included in CEA as inclusion leads to different decisions that on balance result in more health. While the budget impact need not be high in many cases, the impact of these indirect medical costs on the ICER can be big if interventions extend life of elderly in poor quality of life. More broad and consistent inclusion of indirect medical cost in CEA could lead to lower drug prices of life extending therapies and the health economics community should lobby to encourage changes in guidelines so that incorporating indirect medical becomes more standard practice. The review of current tools shows that much progress has been made in the field and that most tools take into account that health spending is centered in the last phase of life and allow adjustments to avoid double counting of related medical spending. Future research should focus on how current methods can facilitate better quantification of uncertainty in the estimates of indirect medical costs.

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