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1 The efficiency-frontier approach for health economic evaluation versus cost-effectiveness  
2 thresholds and internal reference pricing: combining the best of both worlds?

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4

5 **ACCEPTED MANUSCRIPT**

6

7 **ABSTRACT**

8 **Introduction:** The efficiency-frontier approach (EFA) to health economic evaluation aims to  
9 benchmark the relative efficiency of new drugs with the incremental cost-effectiveness ratios  
10 (ICERs) of non-dominated comparators. By explicitly considering any differences in health  
11 outcomes and costs, it enhances the internal reference pricing (IRP) policy that was officially  
12 endorsed by Germany as the first country worldwide in 1989. However, the EFA has been  
13 repeatedly criticized since its official endorsement in 2009.

14 **Areas covered:** This perspective aims to stimulate the debate by discussing whether the main  
15 objections to the EFA are technically valid, irrespective of national contextual factors in  
16 Germany with the reservations towards using a cost-per-quality-adjusted life year (QALY)  
17 threshold. Moreover, we comparatively assessed whether the objections are truly unique to  
18 the EFA or apply equally to IRP and cost-effectiveness thresholds.

19 **Expert commentary:** The plethora of objections to the EFA (n=20) has obscured that many  
20 objections are neither technically valid nor unique to the EFA. Compared to cost-effectiveness  
21 thresholds, only two objections apply uniquely to the EFA and concern intended key  
22 properties: (1) no external thresholds are needed; and (2) the EFA is sensitive to price changes  
23 of comparators. Combining these policies and developing them further are under-utilized  
24 research areas.

25 **Keywords:** reference pricing; cost effectiveness; health technology assessment; economic  
26 evaluation; decision making

27

## 28 1. INTRODUCTION

29 Internationally, various pharmaceutical policies aim to balance the access to drugs, ensure  
30 their quality, and control the growth of the drug expenditures [1, 2]. In this Perspective  
31 Article, we focus on pricing policies adopted by policy makers and third-party payers,  
32 particularly the practice of benchmarking drug prices by means of internal (i.e., domestic)  
33 reference pricing, to which the efficiency-frontier approach (EFA) can be seen as an  
34 extension. We believe that the plethora of objections to the EFA has obscured the strengths  
35 and limitations of the approach. This is why the main body of this Perspective Article will aim  
36 to stimulate the debate by scrutinizing the various objections voiced against the EFA on their  
37 merits, irrespective of national contextual factors. However, we acknowledge that some of the  
38 confusion can be attributed to the national setting of Germany, which originally proposed the  
39 EFA and has officially endorsed it as the only country so far, and that is why we will frame  
40 the main body of this Perspective Article within the German context and draw conclusions for  
41 other countries.

42 To begin with, Germany was the first country in the world to introduce internal reference  
43 pricing (IRP) to achieve transparency between similar drugs and to curb their expenditures to  
44 an equivalent level in January 1989 [3, 4]. At first, IRP meant clustering drugs with the same  
45 active ingredient in the domestic market to determine a common price level per cluster, which  
46 was subsequently extended to drugs regarded as therapeutically equivalent in 1991 [4, 5].

47 From 1996 onwards, all newly marketed, patented drugs were excluded from IRP in Germany  
48 to protect the pharmaceutical industry, which led to the launch of many drugs with only minor  
49 modification (so-called “me-too” drugs); consequently, patented drugs without additional  
50 therapeutic benefit were included in IRP again in 2004 [4]. Three years later, in 2007, the  
51 legal framework for pharmacoeconomic evaluations was enacted with the explicit aim of  
52 assessing the prices of new interventions to inform maximum reimbursable price [6, 7], thus  
53 intending a policy applicable to all newly marketed drugs again, including those with  
54 additional therapeutic benefit.

55 When the Institute for Quality and Efficiency in Health Care (IQWiG), Germany’s main  
56 health technology assessment (HTA) agency, was tasked with developing a suitable method to  
57 inform maximum reimbursable prices within the stipulated framework, the quality-adjusted  
58 life year (QALY) was not promoted to the primary endpoint of interest as in other  
59 jurisdictions [8, 9]. The main reasons were ethical, methodological and legal concerns about

60 using QALYs [10], and the absence of a reasonably determined, justified and officially  
61 recognized cost-per-QALY-threshold [11, 12]. Instead, national consultations were held and  
62 the advice of an international expert panel sought [13], which led to adopting the so-called  
63 “efficiency-frontier approach” (EFA) in 2009 [14]. The EFA aims to explicitly consider the  
64 different therapeutic values and costs of comparable interventions in an economic evaluation  
65 to assess interventions’ prices (note: since 2011 the approach could be used in Germany to  
66 inform price negotiations if opted for by either the manufacturer or payer [15, 16]). However,  
67 with the law referring twice to the international standards of health economics, in which the  
68 theorems of resource allocations and health maximization are deeply rooted, the confusion  
69 was made perfect as to whether or not IQWiG’s aim is, or indeed should be, to maximize  
70 health through resource allocation [10]. Moreover, IQWiG does not have the legal remit to  
71 prioritize funds across disease areas [12], nor is such prioritization currently a primary aim or  
72 concern of Germany’s health policy (no fixed ex-ante budget exists for health-care  
73 expenditures of a given year; the Social Health Insurance funds may simply choose to  
74 increase levies the following year to balance their accounts).

75 With the efficiency-frontier approach having been criticized ever since its official  
76 endorsement, we took the opportunity of it now being 10 years since introducing the legal  
77 framework for pharmacoeconomic evaluations in Germany, and about 30 years since  
78 introducing IRP, to place the most common objections to the efficiency-frontier approach into  
79 perspective. To stimulate the debate, we aimed to disentangle the German context from the  
80 efficiency-frontier approach as an analytical tool by reviewing common objections on (1)  
81 whether they are technically valid, irrespective of national contextual factors. Moreover, we  
82 explored whether the objections are truly unique to the efficiency-frontier approach by also  
83 checking whether they applied to (2) the “blunt” alternative of IRP [17], and (3) the often  
84 heard suggestion of using an externally set cost-effectiveness threshold (range).

85 Section 2 will outline a brief theoretical background on each of the three policy alternatives in  
86 their function as potential pricing tools for decision makers like third-party payers. We will  
87 thus not predetermine the objectives of the decision maker, other than comparing the relative  
88 prices (or ratios) of interventions. Section 3 details how we identified objections and against  
89 which criteria we assessed them. Section 4 provides our assessment of the objections based  
90 against the theoretical background outlined in section 2 and the much more detailed  
91 references there within. Section 5 draws four conclusions from having assessed the  
92 objections. Section 6 will provide some commentary on the German context given that the

93 EFA has been officially endorsed only in Germany, while section 7 will identify learning  
94 points and a way forward for international settings alike.

95 **2. (NOT TOO) TECHNICAL BACKGROUND ON REFERENCE PRICING,**  
96 **COST-EFFECTIVENESS THRESHOLDS, AND THE EFFICIENCY**  
97 **FRONTIER APPROACH**

98 Generally, reference pricing is a cost-containment policy that aims to stimulate price  
99 competition between manufacturers of interventions that have been classified as substitutes  
100 based on chemical, pharmacological or therapeutic equivalence [4, 18]. Interventions are  
101 clustered together into one group, for which a maximum reimbursement level is set as the  
102 reference price for all interventions within that group (often based on the price of the cheapest  
103 intervention, or an average or proportion of existing prices [17]). Manufacturers are still free  
104 to set the price of an intervention independently, but the difference of the price and the  
105 maximum reimbursement limit is then to be paid out-of-pocket by the patients [18, 19].  
106 Although prices of interventions are often also compared internationally (known as external  
107 reference pricing, ERP), it is the comparison of interventions available domestically, i.e.  
108 internal reference pricing (IRP) [19], that is in the focus of this paper. For an illustration of  
109 IRP see Figure 1A.

110 Incremental cost-effectiveness thresholds may be seen as representing a pre-defined  
111 willingness-to-pay for a given unit of effect, the implied cut-off when the maximum budget  
112 was to be exhausted, or they may be inferred from previous reimbursement decisions [18, 20,  
113 21]. We will concentrate on the often-cited cost-per-QALY threshold approach as applied in  
114 England [8], which has been implied to be a suitable alternative to the EFA [22-25].  
115 Incremental cost-effectiveness ratios (ICERs) above the upper-bound cost-effectiveness  
116 threshold (of e.g. £20,000–£30,000/QALY in England) suggest that further arguments are  
117 needed to support reimbursing the launch price of an intervention as proposed by a  
118 manufacturer, while ICERs below the lower-bound threshold are generally considered cost-  
119 effective. Moreover, the threshold can be used to benchmark interventions by adjusting the  
120 price of an intervention until the ICER meets the cost-effectiveness threshold [26, 27]; see  
121 Figure 1B.

122 The efficiency-frontier approach can best be illustrated within a cost-effectiveness plane,  
123 which visualizes the costs and health benefits of all relevant interventions on two axes. All  
124 interventions that are not subject to simple or extended dominance are connected in an

125 ascending order of effectiveness. The resulting curve consists solely of efficient interventions;  
126 see Figure 1C. It thereby aids in determining the most appropriate, i.e. non-dominated,  
127 comparator of an intervention in an economic evaluation.

128 [Figure 1 about here]

129 The efficiency-frontier approach extends this concept by differentiating between comparators  
130 and (new) interventions under investigation, and drawing the curve of the efficiency frontier  
131 solely based on the comparators [15]. With the efficiency-frontier approach, a reimbursable  
132 price for the (new) intervention under assessment must then be set in such a way that the  
133 associated costs and effects come to lie on the curve; see Figure 1D. In case the benefit of the  
134 (new) intervention exceeds the highest benefit established with the comparators, the last  
135 segment of the efficiency frontier is linearly extrapolated, hence using the same trade-off rate  
136 for costs and health effects as for the most effective efficient comparator relative to the second  
137 most effective efficient comparator; cf. dashed line in Figure 1D. Consequently, an increase in  
138 effectiveness is valued by using the observed trade-off between costs and effects of the non-  
139 dominated comparators, which has been called a “proportional rule” [28].

140 The efficiency-frontier approach is thus intended to provide guidance to decision makers in  
141 determining by how much the price of an intervention needs to be adjusted for it to become  
142 part of the curve of the non-dominated comparators [13]. Clearly, the same idea is realizable  
143 with an exogenously set incremental cost-effectiveness threshold, as occasionally done in  
144 England [26, 27].

### 145 **3. IDENTIFYING AND ASSESSING OBJECTIONS**

146 We searched for objections to the efficiency-frontier approach by means of a pragmatic  
147 systematic literature review in PubMed and Embase (last search date 03.08.2015). Free text  
148 terms used were (cost benefit\* and iqwig”) as well as (frontier and (efficiency or approach\* or  
149 method\*)). We used further search techniques like the “similar articles” function in PubMed  
150 and forward citation searching in Web of Science and Google Scholar using relevant articles  
151 known beforehand. Inclusion criteria were publications with objections to the efficiency  
152 frontier, written in English or German. In addition, we considered all objections to the  
153 efficiency-frontier approach raised by stakeholders during the formal hearing of IQWiG’s  
154 first-ever health economic evaluation on antidepressants [22, 29].

155 We provide for each objection a short statement summarizing its key concern in quotation  
156 marks, followed by the result of our assessment in three steps: (1) We assessed the technical  
157 validity of each objection with regard to the efficiency-frontier approach. Here, we define  
158 “technically valid” as representing a sound attribute or comment on the efficiency-frontier  
159 approach as a decision tool that applies to the proposed concept within the theoretical  
160 framework outlined above in section 2, independent of any national context. Moreover, we  
161 assessed whether the objection is truly unique to the efficiency-frontier approach by also  
162 considering the “technical validity” of the objection for (2) internal reference pricing (IRP),  
163 which can be seen as the historical context leading to the EFA in Germany, and (3) the cost-  
164 per-QALY threshold, which has been proposed by many stakeholders as an alternative to the  
165 EFA [22-25]. If relevant, we separated considering the cost-effectiveness threshold (CET) as  
166 a hard-decision rule from its use as a benchmark for the (value-based) price level of  
167 interventions with regards to the threshold (i.e., adjusting the price until the ICER meets the  
168 cost-effectiveness threshold) [26, 27].

169 In cases where an objection also applied to the two alternative approaches (i.e., IRP and  
170 CET), we concluded that the objection was not truly unique to the efficiency-frontier  
171 approach. Otherwise, we concluded that it was truly unique to the efficiency-frontier  
172 approach.

173 All three policy options have been assessed from the viewpoint of decision makers like third-  
174 party payers/insurers, as originally intended for the EFA. Hence, we are comparing the three  
175 policy options with regard to their ability of being drug pricing tools, not in terms of resource  
176 allocation tools. Also, we compared each policy as an independent option without  
177 complementing each other, while section 5 discusses potential combinations.

## 178 4. OUR ASSESSMENT OF OBJECTIONS

179 The systematic literature search identified 39 publications that fulfilled the study inclusion  
180 criteria. In addition, we considered the formal comments of 8 stakeholders (i.e., five  
181 pharmaceutical companies, two pharmaceutical industry associations, and one health  
182 economics society) [22]. In total, 20 distinctive objections to the efficiency-frontier approach  
183 were raised, which included topics on allocation (n=4), comparators (n=2), endpoints (n=3),  
184 input parameters (n=4), the practical implementation (n=3), and the epistemological roots  
185 (n=4). For an overview of our assessment of objections see Table 1.

186 [Table 1 about here]

### 187 4.1 Objection 1: “The approach avoids externally set cost-effectiveness thresholds.” 188 [22]

189 EFA: Valid. The efficiency-frontier approach does not require any externally set cost-  
190 effectiveness thresholds as it derives flexible thresholds from the incremental cost-  
191 effectiveness ratios of the non-dominated comparators analyzed (which, in turn, constitute the  
192 segments of the curve of the efficiency frontier) [13, 15].

193 IRP: Valid. Reference pricing schemes do not use or require cost-effectiveness thresholds  
194 given their exclusive focus on prices once interventions have been classified as equivalent  
195 [17, 18].

196 CET: Invalid. By default, cost-effectiveness thresholds require an exogenously set and  
197 explicit incremental cost-effectiveness threshold (range) to allow making any statements  
198 about interventions being cost-effective [30].

### 199 4.2 Objection 2: “The approach does not prioritize funds across disease areas.” [22- 200 25]

201 EFA: Invalid. The efficiency-frontier approach aims to limit the expenditure of (new)  
202 interventions to an amount justified by the available comparators [6, 7], thereby prioritizing  
203 funds implicitly by restricting funding in one area that are freed up for another. By  
204 considering any subtle differences in health outcomes explicitly, however, the efficiency-  
205 frontier approach improves the rather “blunt” IRP schemes [17]. Nonetheless, the focus of the  
206 EFA rests on pharmaceutical pricing within disease areas and not on an intentional, deliberate



207 way of prioritizing resources across disease areas explicitly. When employing the EFA in  
208 isolation, without a subsequent appraisal, the slope of the efficiency frontier in a disease area  
209 may thus be a potentially historical chance result (cf. objection 10 and 11). In our opinion, the  
210 absence of enough comparators to draw a frontier can be regarded as an indicator for the need  
211 of prioritization in its own right; cf. rare diseases. Lastly, the explicit use of the EFA to  
212 prioritize funds across disease areas requires a similar comparison across endpoints, e.g. with  
213 some form of aggregated measure of outcomes (cf. objections 7 and 8).

214 IRP: Invalid. Reference pricing aims to limit the expenditure on interventions in indications  
215 for which comparable alternatives exist; as such, funds are prioritized on disease areas with  
216 fewer alternatives, if at all available [18]. Similar to the EFA, reference pricing can only be  
217 applied with sufficient comparators.

218 CET: Invalid. Cost-effectiveness thresholds aim to maximize health by prioritizing funds to  
219 disease areas where the most QALYs are gained, irrespective of whom [31]. In practice, this  
220 aim may not be achieved, particularly when used only as a funding threshold that ignores the  
221 related issues of affordability and the budget impact [32-34].

#### 222 **4.3 Objection 3: “The approach does not represent societal preferences or the** 223 **maximum willingness-to-pay for new drugs.” [22-25]**

224 EFA: Valid. By default, the efficiency-frontier approach may not reflect the maximum  
225 willingness-to-pay of society, especially in disease areas with only generic competition [13].  
226 When based on the price level of patented comparators, however, the slope of the last segment  
227 of the frontier may at least reveal the current willingness-to-pay of payers [13].

228 IRP: Valid. Reference pricing likewise benchmarks the price of new drugs to existing  
229 comparable alternatives [18]. Nonetheless, the maximum reimbursement limit does not equate  
230 to the maximum willingness-to-pay as demonstrated by patients who are willing to make out-  
231 of-pocket co-payments for the non-reimbursed price difference [4, 18].

232 CET: Valid. Ideally, cost-effectiveness thresholds represent the forgone opportunity costs,  
233 which is why e.g. the threshold proposal of the World Health Organization (WHO) based on a  
234 country’s gross domestic product has been heavily criticized for the missing link to actually  
235 displaced or unfunded services [34]. In practice, however, these thresholds rather often also  
236 reflect the willingness-to-pay of payers (most prominently seen for the threshold proposed for

237 the USA [21]), not necessarily societal preferences or their maximum willingness-to-pay for  
238 new drugs [35-37].

239 **4.4 Objection 4: “The approach avoids explicitly rationing effective drugs on**  
240 **economic grounds.” [38]**

241 EFA: Valid. The efficiency-frontier approach avoids rationing effective drugs on economic  
242 grounds due to its aim of providing guidance on appropriate reimbursable prices in relation to  
243 existing comparators (which can be achieved by reducing the price of interventions whose  
244 effectiveness is lower than that of the comparators) [39]. The EFA has not been intended as a  
245 binary decision rule [13].

246 IRP: Valid. Reference pricing also avoids rationing effective drugs on economic grounds by  
247 offering a lower reimbursed price, with any difference needed to be paid by patients [17, 18].

248 CET: Invalid. Cost-effectiveness thresholds could be used to ration effective but inefficient  
249 drugs on economic grounds [36], while using it to benchmark the price of an intervention for  
250 its ICER to meet the cost-effectiveness threshold may also avoid rationing effective drugs on  
251 economic grounds [26].

252 **4.5 Objection 5: “The approach could be used with an inadequate comparator.” [22]**

253 EFA: Valid. The efficiency-frontier approach could lead to biased results when using an  
254 inadequate comparator [40]. However, as the approach is intended for multiple-technology  
255 assessments that include all relevant alternatives as possible comparators [13, 14], an  
256 intervention should inevitably be compared with the most efficient, non-dominated (and thus  
257 most adequate) comparators.

258 IRP: Invalid. Reference pricing only applies to interventions once they have been classified as  
259 substitutes based on chemical, pharmacological or therapeutic equivalence [4, 18].

260 CET: Valid. Similar to the efficiency-frontier approach, using an inadequate comparator in  
261 the analysis could also lead to biased results with exogenously set cost-effectiveness  
262 thresholds [41]. The risk of choosing an inadequate intervention as comparator might even be  
263 higher when avoiding multiple-technology assessments [40].

264 **4.6 Objection 6: “The approach is open to manipulation by adding a ‘meaningless’**  
265 **alternative to the market.” [22]**

266 EFA: Invalid. Given that the efficiency-frontier approach has been intended to assess the  
267 prices of new interventions, a newly marketed “alternative” was to be assessed itself, meaning  
268 that it should not be considered for the efficiency frontier of non-dominated comparators [13,  
269 14]. A newly added “alternative” could only affect the slope of the curve if it was  
270 misclassified as a comparator [40], and even then only if it became a constituting part of the  
271 frontier (cf. objection 5; for the related concern of strategic pricing of existing alternatives see  
272 objection 12).

273 IRP: Valid. Any newly marketed “alternative” that is considered comparable to existing  
274 interventions was to be clustered with them, or it would enable clustering existing  
275 interventions [17]. As such, its price would potentially alter the reference price of that cluster  
276 [4].

277 CET: Invalid. Similar to the efficiency-frontier approach, a scientifically sound analysis based  
278 on a cost-effectiveness threshold was to use the newly marketed “alternative” as the main  
279 intervention of interest, not as the comparator [41].

280 **4.7 Objection 7: “The approach purposely avoids using the QALY as an endpoint.”**  
281 **[42]**

282 EFA: Invalid. Drawing an efficiency frontier in a cost-effectiveness plane does not forestall  
283 the choice of health effects used [43, 44], and neither does the efficiency-frontier approach  
284 [13, 15]. It largely depends on the national context whether the QALY will be used as an  
285 endpoint, and particularly whether it is promoted to the primary endpoint of interest (cf.  
286 Introduction) [8, 9]. An overview of the strengths and limitations of the QALY is outside the  
287 scope of this Perspective Article and has been given elsewhere [31, 45].

288 IRP: Valid. Reference pricing does not consider QALYs given the focus on prices once  
289 interventions have been classified as equivalent [17, 19].

290 CET: Invalid. Cost-effectiveness thresholds conventionally use an externally set cost-per-  
291 QALY threshold, and thus do not avoid the QALY by default [45].

292 **4.8 Objection 8: “The approach avoids aggregating endpoints.” [22]**

293 EFA: Invalid. The efficiency-frontier approach could be used with aggregated endpoints such  
294 as the QALY [13, 15], or the results for different endpoints could be aggregated by means of  
295 multi-criteria decision analysis (MCDA) techniques [46, 47].

296 IRP: Valid. Reference pricing does not consider aggregated endpoints given the focus on  
297 prices once interventions have been classified as equivalent [17, 19].

298 CET: Invalid. Cost-effectiveness thresholds conventionally use an externally set cost-per-  
299 QALY threshold, and thus intentionally apply an aggregated endpoint by default [45].

#### 300 **4.9 Objection 9: “The approach requires cardinally-scaled endpoints.” [22, 23]**

301 EFA: Valid. The efficiency-frontier approach requires cardinally-scaled endpoints, at least in  
302 the relevant area of analysis [48].

303 IRP: Invalid. Reference pricing does not require cardinally-scaled endpoints given the focus  
304 on prices once interventions have been classified as equivalent [17, 19].

305 CET: Valid. Cost-effectiveness thresholds effectively also require cardinally-scaled  
306 endpoints, at least in the relevant area of analysis [45, 48].

#### 307 **4.10 Objection 10: “The approach does not consider life-cycles of on-patent drugs 308 (from high prices to generic, and thus lower, prices) by comparing them to historic 309 pricing decisions.” [22]**

310 EFA: Valid. The efficiency-frontier approach does not consider the life-cycle of drugs  
311 explicitly as the approach was intended for indication-specific analyses using the current  
312 prices of the existing alternatives [13]. However, it is not inherent to the approach but the  
313 context (and research question) whether the value of the price is chosen to be current, historic,  
314 or varying over time.

315 IRP: Valid. Reference pricing does not consider life-cycles of drugs given the focus on  
316 current prices at the time of establishing, or updating, a cluster of equivalent drugs [17, 19].

317 CET: Valid. Similar to the efficiency-frontier approach, life-cycles of drugs are usually not  
318 considered, with a rare example in Hoyle (2011) [49]. Implicitly, the fixed-threshold approach  
319 may consider historic pricing decisions when the thresholds are based on patented

320 interventions whose costs were previously accepted for reimbursement, but not necessarily  
321 when the threshold is based on e.g. the value of a statistical life [9].

322 **4.11 Objection 11: “The approach does not properly acknowledge the research and**  
323 **development costs of drugs.” [22, 24, 25]**

324 EFA: Valid. The efficiency-frontier approach does not consider the research and development  
325 costs of drugs explicitly. When using it without a separate appraisal that addresses such  
326 additional concerns, disease areas where the prices of the comparators do not (even implicitly)  
327 reflect their research and development costs may be disadvantaged (e.g. indications with only  
328 generic comparators).

329 IRP: Valid. Reference pricing also does not consider the research and development costs of  
330 drugs explicitly, which, however, has not been shown to dis-incentivize pharmaceutical  
331 innovation [18].

332 CET: Valid. Cost-effectiveness thresholds also do not consider the research and development  
333 costs of drugs explicitly [21, 36]. Arguably, research and development costs are implicitly  
334 considered when the threshold is derived from past decisions for patented drugs.

335 **4.12 Objection 12: “The approach could be influenced by altering prices of**  
336 **interventions.” [42]**

337 EFA: Valid. The slope of the efficiency-frontier approach could be influenced by changes in  
338 the price of comparators (which may result in changes of uptake, and lower healthcare  
339 expenditures). However, this presumes for the price-changing company to know beforehand  
340 the price level (and associated costs) at which its intervention becomes part of the frontier  
341 without incurring substantial profit losses. It also needs to become part of that particular  
342 segment of the curve that is used for the assessment (given that the frontier may consist of  
343 more than one segment; cf. Figure 1D). If the comparator is owned by a different  
344 manufacturer it is not apparent why they would lawfully reduce the price (and voluntarily  
345 accept lower profits) to the advantage of a competitor.

346 IRP: Valid. Given that the reference price is set based on the prices of the existing  
347 interventions in a cluster [17, 18], changing the price of existing interventions may impact the  
348 level of the price cap in a cluster. Moreover, there are strong incentives for manufacturers to

349 price their interventions at a higher level than they would have without being subjected to  
350 reference pricing [18].

351 CET: Invalid. Cost-effectiveness thresholds cannot be influenced by altering prices (as it is  
352 explicitly set ex ante), but the ICER can be influenced similarly through strategic price  
353 changes, which may lead to obtaining less QALYs from a fixed budget [26, 37].

354 **4.13 Objection 13: “The approach requires data that may not always be available.”**  
355 **[22]**

356 EFA and CET: Valid. Adequate data are a universal requirement of scientifically sound  
357 analyses [41]. Nonetheless, key data on necessary input parameters may be missing for any  
358 given disease (in case no indirect treatment comparisons are possible), and the chance of data  
359 missing may increase with the number of interventions analyzed.

360 IRP: Valid. Reference pricing can only be performed once sufficient interventions are  
361 available that can be classified as equivalent [18].

362 **4.14 Objection 14: “The approach assumes constant returns to scale and perfect**  
363 **divisibility.” [50]**

364 EFA and CET: Valid. Assuming constant returns to scale (i.e. constant marginal health  
365 benefits of interventions, irrespective of the amount purchased) and perfect divisibility of  
366 interventions is a fundamental limitation of all continuous, linear thresholds [51].

367 IRP: Invalid. Reference pricing does not make these assumptions in the absence of a linear  
368 threshold and the focus on marginal unit prices [18].

369 **4.15 Objection 15: “The approach is very onerous.” [22, 23]**

370 EFA: Invalid. The efficiency-frontier approach is intended to include all relevant  
371 interventions. However, the approach itself does not require unduly greater effort than any  
372 other health economic evaluation performed as a multiple technology assessment (cf.  
373 objection 13). Previous research also explored a “shortcut”-application of the efficiency-  
374 frontier approach to allow for rapid assessments [52, 53].

375 IRP: Invalid. Reference pricing is not very onerous given the exclusive focus on prices once  
376 interventions have been classified as equivalent [17, 18], which may arguably be the most  
377 onerous part.

378 CET: Invalid. Like the efficiency-frontier approach, applying a cost-effectiveness threshold  
379 range is not the most onerous part of an economic evaluation; the complexity rather increases  
380 with the choice of the analysis, i.e. whether it is performed as multiple-technology assessment  
381 or single-technology assessment [17, 33].

382 **4.16 Objection 16: “The approach could lead to negative ex-factory prices if all trade**  
383 **margins are deduced.” [22]**

384 EFA: Valid. If the efficiency-frontier approach let to recommend reducing the price of a drug,  
385 the price could become negative if the distance between the location of the intervention and  
386 the efficiency frontier was very large, indicating an intervention’s inefficiency in relation to  
387 the existing comparators. Any low price level could lead to negative prices if all trade margins  
388 were deduced, and if the results were implemented mindlessly without an appraisal.

389 IRP: Valid. If a reimbursement cap based on reference pricing was to be set at very low  
390 levels, it is conceivable that ex-factory prices could become negative when deducing all trade  
391 margins. However, it has been observed that manufacturers anticipate this when pricing  
392 interventions potentially subjected to IRP [18].

393 CET: Invalid/Valid. Negative ex-factory prices do not occur for cost-effectiveness thresholds  
394 used as hard decision rule given that interventions with very high ICERs would be deemed  
395 cost-ineffective, and access to the market denied [54]. However, it obviously also applies to  
396 cost-effectiveness thresholds used to benchmark prices (when they need to be drastically  
397 reduced).

398 **4.17 Objection 17: “The approach deviates from international health economic**  
399 **standards.” [22-24]**

400 EFA: Invalid. Using an efficiency frontier to inform decision makers has been officially  
401 adopted in two other countries [55, 56], albeit not to benchmark prices as proposed with the  
402 efficiency-frontier approach in Germany [13, 15]. However, the comparison of ICERs from  
403 non-dominated comparators bears close resemblance to the comparison of the ICER for the

404 most expensive intervention funded in the USA [21], and the Programme Budgeting Marginal  
405 Analysis (PBMA) approach in Australia [33].

406 IRP: Invalid. Reference pricing of drugs has been conducted in domestic markets for nearly  
407 30 years [5], with at least 20 European countries using internal reference pricing [18].

408 CET: Invalid. Using cost-effectiveness thresholds to assess interventions' cost-effectiveness  
409 has been applied for decades [23, 57], though it has become the national standard in only a  
410 few countries [9] and some see its importance diminishing [58], partly due to the issues  
411 associated with having one single metric that may not capture all relevant effects [20]. Using  
412 cost-effectiveness thresholds to benchmark prices (and costs) of interventions is seen rather  
413 critically by some [26, 27].

414 **4.18 Objection 18: “The approach lacks theoretical embedding in economic theory.”**  
415 **[22, 50]**

416 EFA and CET: Invalid. The efficiency-frontier approach builds on the well-known concept of  
417 the efficiency frontier in (health) economics and decision sciences [43, 44, 59-64]. It is based  
418 on the same theoretical foundations as the fixed-threshold approach [65, 66].

419 IRP: Invalid. Reference pricing is based on the idea that similar goods with nearly identical  
420 characteristics (i.e. interventions classified as substitutes based on chemical, pharmacological  
421 or therapeutic equivalence [17, 18]) should be selling for the same price.

422 **4.19 Objection 19: “The approach lacks an international debate.” [22]**

423 EFA: Invalid. The efficiency-frontier approach was subjected to an extensive formal hearing  
424 organized by IQWiG in Germany in 2008, and since then the approach has been debated at  
425 national and international conferences and in scientific journals [13, 23-25, 38, 48, 52, 67-74].

426 IRP: Invalid. The Organization for Economic Co-operation and Development (OECD), the  
427 WHO, the European Commission (EC), the Cochrane Collaboration and various academics  
428 have all discussed the advantages and disadvantages of reference pricing [2, 4, 17-19, 75].

429 CET: Invalid. Cost-effectiveness thresholds continue to be extensively debated, which has  
430 been ongoing for a much longer period of time [2, 18, 20, 32, 34, 36, 65].



431 **4.20 Objection 20: “The approach uses an arbitrary method to inform decision**  
432 **makers about uncertainty.” [22]**

433 EFA: Invalid. The efficiency-frontier approach has been suggested to be used in conjunction  
434 with the interquartile range of the recommended reimbursable price as an aid for subsequent  
435 price negotiations [29, 76], which has been misunderstood to be an aid to inform decision  
436 makers about uncertainty. Exploring uncertainty in the EFA is indeed an active research area;  
437 for the impact of uncertainty on the price recommendation see Corro Ramos et al. [77].

438 IRP: Invalid. Reference pricing does not inform decision makers about uncertainty given the  
439 focus on prices once interventions have been classified as equivalent [17, 19].

440 CET: Invalid. For cost-effectiveness thresholds, elaborate uncertainty analyses have been an  
441 important research area to inform decision makers [78, 79].

442 **5. CONCLUSION**

443 Having assessed 20 objections to the efficiency-frontier approach, we found 11 objections  
444 that, in our opinion, could be classified as technically valid.

445 Many of the objections aimed at properties of the efficiency-frontier approach that are  
446 intended to improve the existing reference pricing system in Germany by explicitly  
447 considering health endpoints (cf. objections 7-9). Compared to a cost-effectiveness threshold,  
448 only two objections are truly unique to the efficiency-frontier approach and concern intended  
449 key properties: 1) the efficiency-frontier approach does not require external thresholds due to  
450 being derived from existing comparators, and 2) the efficiency-frontier approach is thus  
451 supposed to be sensitive to price changes of comparators.

452 Based on these findings, we draw the following four conclusions: First, a plethora of  
453 objections to the efficiency-frontier approach has been raised, with many applying equally to  
454 alternative policies and indeed any threshold approach. We appreciate that the relevance of  
455 (some of) the objections listed here may be questioned, which was meant to give a  
456 comprehensive overview of the criticism that the EFA has been attracting. Instead of  
457 speculating about the reasons why this has been happening, we merely opted to assess  
458 whether the objections actually have some technical merit. Knowing that the topic, the EFA  
459 and these “objections” may be considered controversial by some, we have thus opted for a  
460 Perspective Article.

461 Second, there appear to us to be fewer differences between the efficiency-frontier approach  
462 and a cost-effectiveness threshold than may be suggested by the sheer amount of objections.  
463 While we acknowledge that there may be disagreement with our assessment and some, or  
464 indeed all, of the objections may be judged differently by researchers in terms of their  
465 “technical validity”, we have included our judgement as an anchor against which the public is  
466 invited to base his/her own judgement on. Overall, however, the key distinction between the  
467 EFA and CETs is by default their aim and how they reach it, although both approaches may  
468 arguably serve both purposes [28]: The efficiency-frontier approach has been intended for the  
469 assessment of prices by deriving flexible thresholds to benchmark the relative efficiency of  
470 (new) interventions; the fixed-threshold approach has been intended for judging on (new)  
471 interventions’ cost-effectiveness with implications for their reimbursement based on an  
472 external threshold (cf. objection 1 and 12).

473 Third, it seems important to stress that, unlike IRP, neither of the other two approaches bears  
474 the appraisal in itself nor qualifies for an automated reimbursement process (a  
475 misunderstanding shared by WHO's threshold proposal; see Bertram et al. [34]). The primary  
476 aim of these approaches is to provide guidance to decision makers for a subsequent multi-  
477 criteria appraisal, in which various factors in favor for and against reimbursing the launch  
478 price of an intervention are to be considered (including opportunity costs, potential  
479 weaknesses of the approaches for e.g. rare diseases [80, 81], and research and development  
480 costs; cf. objection 11). Any unfavorable assessment with either approach would thus  
481 highlight the need for additional arguments to support an intervention's reimbursement (at a  
482 higher premium).

483 Fourth, there is an under-utilized opportunity for researchers to develop policies further. For  
484 instance, in our view it would be worth exploring using historic market-entry prices within  
485 indications (cf. objection 10) or the on-patent prices across indications. Also, policies could  
486 be used simultaneously to complement each other, where the exogenous threshold may  
487 indicate health opportunity costs while the efficiency frontier approach may then indicate how  
488 the intervention compares to existing alternatives.

## 489 **6. EXPERT COMMENTARY**

490 Without the historical context of healthcare legislation in Germany set out in the introduction  
491 of this paper, it may be difficult to understand the reasons that led to the idea of the  
492 efficiency-frontier approach for reimbursement decision-making. When policy makers  
493 enacted the legal framework for health economic evaluations in Germany in 2007, they  
494 attempted to close a regulatory loophole for patented drugs that had not been covered by  
495 internal reference pricing since 1996 anymore. Moreover, the established reference pricing  
496 system was to be expanded (again) but this time informed by a much more elaborate process  
497 that explicitly considered any subtle differences in benefits and costs between interventions  
498 with additional therapeutic benefit. Accordingly, the approaches and standards valid in other  
499 countries with different legal and cultural contexts were not easily transferrable to the German  
500 setting [12]. Instead, the efficiency-frontier approach appears to have been responding closely  
501 to the ideas of the legal framework by combining the price efficiency of the reference pricing  
502 system (familiar in German reimbursement policy) with the explicit cost-to-benefit  
503 consideration of economic evaluations (unfamiliar in German reimbursement policy); it was  
504 thus striving to combine the best of both worlds.

505 From an international perspective, however, this pricing policy clashed with the alternatively  
506 used cost-effectiveness thresholds and the economic idea of resource allocation, and it led to  
507 the efficiency-frontier approach being widely opposed. This did not go unnoticed by German  
508 policy makers, and by 2011 they have had effectively adopted a reimbursement system based  
509 largely on comparative effectiveness when enacting the ‘Act on the Reform of the Market for  
510 Medicinal Products’ (AMNOG) [16]. Under this system, in brief, if a new drug is able to  
511 demonstrate an additional therapeutic benefit in randomized controlled trials to a (usually  
512 non-placebo) comparator, the manufacturer and the payer enter into price negotiations.  
513 Without such a proven additional therapeutic benefit, pricing of the new drug is capped at the  
514 price of the comparator (cf. IRP) [18]. If the manufacturer disagrees with the price cap, or  
515 negotiations fail, either party could ask for an economic evaluation being conducted to inform  
516 renewed price negotiations [82-84]. So far this has never happened, likely due to the  
517 disincentives for either party; payers benefit from lower prices of the “blunt” IRP system [17],  
518 while manufacturers face the entire financial burden when commissioning an economic  
519 evaluation of uncertain outcome to them and possibly negative impact in case a lower price  
520 was recommended. Thus, unsurprisingly, no economic evaluation has been commissioned  
521 since AMNOG was introduced in 2011 (as of June 2018) [85].

522 With it now being ten years since enacting the legal framework for health economic  
523 evaluations in Germany, the initial attempts to link health economic considerations to the drug  
524 pricing system must be judged as having failed; cost-effectiveness relationships play de-facto  
525 currently no role for drug pricing in Germany. However, evidence-based health technology  
526 assessments in the form of comparative effectiveness research have been successfully  
527 integrated in the reimbursement system since 2011 [82-84], providing a more structured  
528 system to investigate in potentially clustering drugs based on their health impact. From a  
529 societal perspective, it seems obvious to us that it would be desirable to have a similar  
530 rigorous system for the costs of drugs, and the relationship of cost-to-benefits between  
531 different drugs. For the time being, the optimists among us hence hope for health economic  
532 evaluation being only a “sleeping beauty” in Germany [85]. However, for as long as the  
533 financial and political pressure is not strong enough (as in the build up to the 1989 reform),  
534 the current system in Germany is unlikely to change soon. As such, the prices negotiated may  
535 only by chance reach a level considered appropriate [20, 86], which may raise avoidable  
536 opportunity costs.

537 **7. FIVE-YEAR VIEW**

538 In 2019, it will be 30 years since Germany, as the first country, introduced internal reference  
539 pricing [3]. In general, Germany is a prime example for the international struggle of policy  
540 makers trying to find a way that determines appropriate prices for patented drugs while  
541 honoring the commitments of access, quality and price control. At this point, however, it  
542 seems highly desirable to us to include health economic considerations explicitly into the drug  
543 pricing and reimbursement system of any country to avoid ignoring the opportunity costs of  
544 funding decisions, and the relative differences in the achievable health and costs. At least  
545 three issues need to be reconsidered:

546 1. While comparative effectiveness research remains undoubtedly pivotal for analyzing the  
547 therapeutic value of interventions, it should be the first step in a process complemented by  
548 analyzing the opportunity costs associated with the different benefits and expenditures of  
549 alternative therapies, particularly those currently not subjected to reference pricing (i.e.,  
550 interventions with a proven additional therapeutic benefit). The Netherlands are a good  
551 example to show that combining these policies is feasible, as the reimbursement system  
552 established there complements reference pricing with cost-effectiveness analyses [17, 87].

553 2. Moreover, it will need sufficient political will to change the current system in order for  
554 society to benefit from cost-effectiveness considerations as a whole. To achieve this goal, the  
555 procedure for economic evaluations may need to change to raise the appeal and perceived  
556 usefulness for policy makers: The conventional IRP is conducted in Germany on an annual  
557 basis [82-84], while the comparative effectiveness assessment is usually also concluded  
558 within one year [85]. It will thus need a rapid assessment of the health economic aspects to  
559 appeal to decision makers, with a short-cut having been proposed before [52, 53]. Australia's  
560 Programme Budgeting Marginal Analysis (PBMA) approach provides another example for a  
561 rigorous assessment system that suffices with a robust reference/base case, as adding further  
562 complexity to the analysis has seldom changed past funding decisions [33].

563 3. In addition, risk-sharing arrangements need to be explored so as to share the uncertainty  
564 associated with the financial burden of additional research among manufacturers and payers  
565 (as representatives of society) [88]. In Germany, for instance, manufacturers are currently  
566 obliged to pay for the economic evaluation if requested by them. This one-sided financing  
567 arrangement provides disincentives for both payer and manufacturers to commission  
568 economic evaluations, as the gains from the conventional IRP scheme seem to unduly

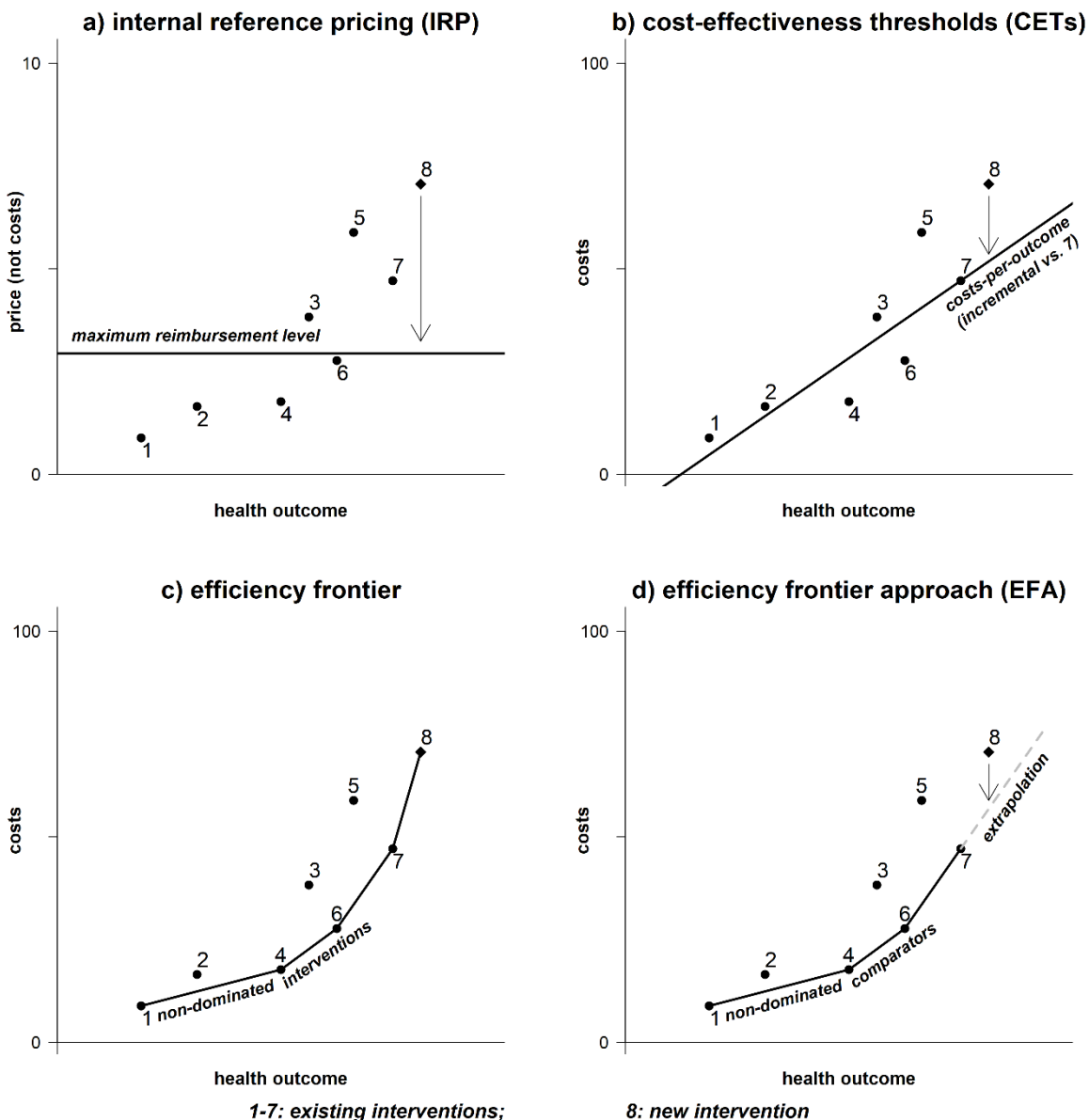
569 advantage the payer and disproportionately burden the manufacturers. One needs to bear in  
570 mind that neither the concentration of market power with the manufacturers in monopolies  
571 nor with the payers in monopsonies will lead to efficient prices [89]. It may thus indeed need  
572 more independent research with the necessary support to investigate in prices in the best  
573 interest of both industry and payers, which is ultimately to benefit society as a whole.

574 **8. KEY ISSUES**

- 575 • The efficiency-frontier approach (EFA) benchmarks intervention's prices based on the  
576 relative efficiency to comparators' incremental cost-effectiveness ratio (ICER).
- 577 • In Germany, the EFA can be regarded as following in the footsteps of internal  
578 reference pricing (IRP), a successful cost-containment strategy celebrating its 30<sup>th</sup>  
579 anniversary in 2019 that was once applicable to all drugs but has been excluding  
580 patented drugs with additional therapeutic benefit for 20 years since 1996.
- 581 • The EFA aims to combine the savings achievable with IRP and the explicit  
582 consideration of cost-effectiveness ratios of economic evaluations, or indeed the best  
583 of both worlds, to inform drug pricing negotiations.
- 584 • The plethora of objections to the EFA, however, has obscured that many objections  
585 are neither technically valid nor unique to the EFA.
- 586 • There is an under-utilized opportunity to research into these policies to further develop  
587 them, e.g. by using them complementary where exogenous cost-effectiveness  
588 thresholds may indicate health opportunity costs while the EFA may indicate how the  
589 intervention compares to existing alternatives.

590

591



593

594 **Figure 1.** Illustration of the different policies and approaches discussed in this Perspective  
 595 Article for 8 interventions in a cost-effectiveness plane. Panel a): Internal reference pricing  
 596 (IPR), with a set maximum price reimbursement level. This level could e.g. be based on an  
 597 average, meaning that the price above the line is not paid for by third-parties; the new  
 598 intervention 8 would either require copayments from patients or needing to reduce its price to  
 599 the maximum reimbursement level. Panel b): Cost-effectiveness threshold (CET) applied  
 600 incrementally to the new intervention 8 versus the most-appropriate comparator intervention  
 601 7. The new intervention 8 is deemed cost-ineffective, and without additional arguments it  
 602 becomes cost-effective only when reducing its price, i.e. shifting intervention 8 downwards  
 603 until it lies on the cost-effectiveness threshold. Panel c): The curve of the efficiency frontier



604 indicates the non-dominated interventions. Panel d): Efficiency-frontier approach (EFA) as  
605 adopted by IQWiG , with inverted axes for the ease of comparison. Interventions 1 to 7 are  
606 used as comparators to assess the new intervention 8. The curve comprises the non-dominated  
607 comparators, with the slope of the last segment being extrapolated forward to account for the  
608 higher benefit achieved with the new intervention 8. In this example, the EFA would lead to  
609 the recommendation of a price reduction, i.e. shifting intervention 8 downwards until it lies on  
610 the efficiency frontier. Also note the potential pricing implications for the dominated  
611 comparators 2, 3 and 5.

612

614 Table 1. Validity and uniqueness of objections to the efficiency-frontier approach

Objection	Step 1: Valid for EFA?	Step 2: Valid for IRP?	Step 3: Valid for CET?
<b>Objections concerning allocation</b>			
1: “does not use explicitly set thresholds”	yes	yes	no
2: “does not prioritize funds across disease areas”	no	no	no
3: “does not represent societal preferences or maximum WTP”	yes	yes	yes
4: “does not ration effective drugs on economic grounds”	yes	yes	no/yes <sup>a</sup>
<b>Objections concerning the comparator</b>			
5: “could be used with an inadequate comparator”	yes	no	yes
6: “is open to manipulation by adding a ‘meaningless’ alternative to the market”	no	yes	no
<b>Objections concerning endpoints</b>			
7: “does not use the QALY as an endpoint”	no	yes	no
8: “does not use aggregating endpoints”	no	yes	no
9: “requires cardinality-scaled endpoints”	yes	no	yes
<b>Objections concerning input parameters (costs, prices, other data)</b>			
10: “does not consider life-cycles of drugs (using historic prices)”	yes/no <sup>b</sup>	yes	no/yes <sup>c</sup>
11: “does not properly acknowledge R&D costs of drugs”	yes	yes	yes
12: “could be influenced by altering prices”	yes	yes	no
13: “requires data that may not always be available”	yes	yes	yes
<b>Objections concerning practical implementation</b>			
14: “assumes constant returns to scale and perfect divisibility”	yes	no	yes
15: “is too onerous”	no	no	no
16: “could lead to negative prices if all trade margins are deduced”	yes	yes	no/yes <sup>a</sup>
<b>Objections concerning the epistemological roots</b>			
17: “deviates from international health economic standards”	no	no	no
18: “lacks theoretical embedding in economic theory”	no	no	no
19: “lacks international debate”	no	no	no
20: “uses an arbitrary method to inform about uncertainty”	no	no	no

CET: cost-effectiveness threshold, EFA: efficiency-frontier approach, IRP: internal reference pricing, N/A: not applicable, QALY: quality-adjusted life year, R&D: research and development, WTP: willingness-to-pay. a: not valid when used as a hard decision rule; valid when used to benchmark (value-based) prices to meet the cost-effectiveness threshold.

b: valid for the initial proposal of using current prices of the comparators; not valid as the initial proposal was context-specific and not inherent to the efficiency-frontier approach.

c: not valid when the value of a threshold implicitly accounts for it (e.g. when based on the costs of patented interventions that were previously accepted for reimbursement); valid when not implicitly account for (e.g. when based on the value of a statistical life).

## 10. REFERENCES

- 617 1. Weisbrod, B.A., *The health care quadrilemma: an essay on technological change,*  
618 *insurance, quality of care, and cost containment.* Journal of economic literature, 1991.  
619 **29**(2): p. 523-552.
- 620 2. Paris, V. and A. Belloni, *Value in pharmaceutical pricing.* OECD Health Working  
621 Papers, No. 63. 2013, Paris: OECD Publishing.
- 622 \* = overview of reimbursement and pricing policies in OECD countries, including reference  
623 pricing, cost-effectiveness analyses, and the efficiency frontier approach  
624
- 625 3. Deutscher Bundestag. *Gesetzentwurf der Bundesregierung: Entwurf eines Gesetzes*  
626 *zur Strukturreform im Gesundheitswesen (Gesundheits-Reformgesetz - GRG);*  
627 *Drucksache 11/2493.* 1988; Available from:  
628 [dipbt.bundestag.de/doc/btd/11/024/1102493.pdf](http://dipbt.bundestag.de/doc/btd/11/024/1102493.pdf).
- 629 4. Busse, R., J. Schreyogg, and K.D. Henke, *Regulation of pharmaceutical markets in*  
630 *Germany: improving efficiency and controlling expenditures?* Int J Health Plann  
631 Manage, 2005. **20**(4): p. 329-49.
- 632 5. vd Schulenburg, J.M., *The German health care system at the crossroads.* Health Econ,  
633 1994. **3**(5): p. 301-3.
- 634 6. Deutscher Bundestag. *Antwort der Bundesregierung auf die Kleine Anfrage der*  
635 *Abgeordneten Birgitt Bender, Elisabeth Scharfenberg, Dr. Harald Terpe, Kerstin*  
636 *Andreae und der Fraktion BÜNDNIS 90/DIE GRÜNEN; Drucksache 16/4927;*  
637 *Ausgestaltung der Kosten-Nutzen-Bewertung von Arzneimitteln; Drucksache 16/5027.*  
638 2007 April 02, 2014]; Available from:  
639 <http://dipbt.bundestag.de/dip21/btd/16/050/1605027.pdf>.
- 640 7. Deutscher Bundestag. *Gesetzentwurf der Fraktionen der CDU/CSU und SPD: Entwurf*  
641 *eines Gesetzes zur Stärkung des Wettbewerbs in der gesetzlichen*  
642 *Krankenversicherung (GKV-Wettbewerbsstärkungsgesetz – GKV-WSG); Drucksache*  
643 *16/3100.* 2006 April 02, 2014]; Available from:  
644 <http://dip21.bundestag.de/dip21/btd/16/031/1603100.pdf>.
- 645 8. National Institute for Health and Care Excellence, *Guide to the methods of technology*  
646 *appraisal 2013.* 2013, London, UK: NICE.
- 647 9. Schwarzer, R., et al., *Systematic overview of cost-effectiveness thresholds in ten*  
648 *countries across four continents.* J Comp Eff Res, 2015. **4**(5): p. 485-504.
- 649 10. Deutscher Ethikrat, *Nutzen und Kosten im Gesundheitswesen: zur normativen*  
650 *Funktion ihrer Bewertung; Stellungnahme.* 2011, Berlin: Deutscher Ethikrat.
- 651 11. Dietz, U., *Kosten-Nutzen-Bewertung: ein Kommentar von Ulrich Dietz, Leiter des*  
652 *Referats Arzneimittelversorgung, Bundesministerium für Gesundheit.*  
653 *Gesundheitswesen,* 2009. **71**(S 01): p. S52-53.
- 654 12. Deter, G., *Die Kosten-Nutzen-Bewertung von Arzneimitteln als Rechtsproblem.*  
655 *Medizinrecht,* 2010. **28**(4): p. 249-255.
- 656 13. Caro, J.J., et al., *The efficiency frontier approach to economic evaluation of health-*  
657 *care interventions.* Health Economics, 2010. **19**(10): p. 1117-1127.
- 658 \* = summary of the expert panel advising the efficiency frontier approach to Germany
- 659
- 660 14. Institute for Quality and Efficiency in Health Care. *General methods for the*  
661 *assessment of the relation of benefits to costs.* 2009 19.11.2009 March 14, 2014];  
662 Available from:

- 663 [https://www.iqwig.de/download/General\\_Methods\\_for\\_the\\_Assessment\\_of\\_the\\_Relation\\_of\\_Benefits\\_to\\_Costs.pdf](https://www.iqwig.de/download/General_Methods_for_the_Assessment_of_the_Relation_of_Benefits_to_Costs.pdf).
- 664
- 665 15. Institute for Quality and Efficiency in Health Care, *General methods: version 4.2*.  
666 2015, Cologne: IQWiG.
- 667 16. Deutscher Bundestag. *Gesetzentwurf der Fraktionen der CDU/CSU und FDP: Entwurf eines Gesetzes zur Neuordnung des Arzneimittelmarktes in der gesetzlichen Krankenversicherung Arzneimittelmarktneuordnungsgesetz – AMNOG*; Drucksache 17/2413. 2010 April 02, 2014]; Available from:  
668 <http://dip21.bundestag.de/dip21/btd/17/024/1702413.pdf>.  
669
- 670
- 671
- 672 17. Drummond, M., et al., *Reimbursement of pharmaceuticals: reference pricing versus health technology assessment*. *Eur J Health Econ*, 2011. **12**(3): p. 263-71.
- 673
- 674 \*\* = multi-country comparison of reference pricing versus cost-effectiveness analyses for drug  
675 reimbursement
- 676
- 677 18. Carone, G., C. Schwierz, and A. Xavier, *Cost-containment policies in public pharmaceutical spending in the EU*. *Economic Papers* 461. 2012, Brussels: European  
678 Union.  
679
- 680 \* = comprehensive overview of drug policies on pricing, reimbursement, market entry and  
681 expenditure control in Europe  
682
- 683 19. Acosta, A., et al., *Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies*. *Cochrane Database Syst Rev*, 2014(10): p. CD005979.  
684
- 685 \* = systematic review of the impact of internal reference pricing policies on changes in expenditures  
686 and prescribing
- 687
- 688 20. Bos, J.M. and M.J. Postma, *Using pharmacoeconomics for policy making: is rational decision making enhanced by applying thresholds for cost-effectiveness?* *Expert Rev Pharmacoecon Outcomes Res*, 2004. **4**(3): p. 247-50.  
689
- 690
- 691 21. Neumann, P.J., J.T. Cohen, and M.C. Weinstein, *Updating cost-effectiveness--the curious resilience of the \$50,000-per-QALY threshold*. *N Engl J Med*, 2014. **371**(9): p. 796-7.  
692
- 693
- 694 22. Institute for Quality and Efficiency in Health Care. *Health economic evaluation of venlafaxine, duloxetine, bupropion, and mirtazapine compared to further prescribable pharmaceutical treatments: Documentation and evaluation of comments on the preliminary report; commission no. G09-01 [German]*. 2013; Available from:  
695 [https://www.iqwig.de/download/G09-01\\_DWAV\\_Kosten-Nutzen-Bewertung-von-Venlafaxin-Duloxetin-Bupropion-u...pdf](https://www.iqwig.de/download/G09-01_DWAV_Kosten-Nutzen-Bewertung-von-Venlafaxin-Duloxetin-Bupropion-u...pdf).  
696
- 697
- 698
- 699
- 700 23. Brouwer, W.B.F. and F.F.H. Rutten, *The efficiency frontier approach to economic evaluation: will it help german policy making?* *Health Economics*, 2010. **19**(10): p. 1128-1131.  
701
- 702
- 703 24. Sculpher, M. and K. Claxton, *Sins of omission and obfuscation: IQWiG's guidelines on economic evaluation methods*. *Health Economics*, 2010. **19**(10): p. 1132-1136.  
704
- 705 25. Wasem, J., *Kosten-Nutzen-Bewertung von Arzneimitteln: Eine unvermeidbare Abwägung*, in *Deutsches Ärzteblatt*.  
706
- 707 26. Webb, D.J. and A. Walker, *Value-based pricing of drugs in the UK*. *Lancet*, 2007. **369**(9571): p. 1415-6.  
708
- 709 27. Claxton, K., et al., *Value based pricing for NHS drugs: an opportunity not to be missed?* *BMJ*, 2008. **336**(7638): p. 251-4.  
710
- 711 28. Gandjour, A., *Presenting Germany's drug pricing rule as a cost-per-QALY rule*. *Health Care Manag Sci*, 2012. **15**(2): p. 103-7.  
712

- 713 29. Institute for Quality and Efficiency in Health Care. *Health economic evaluation of*  
714 *venlafaxine, duloxetine, bupropion, and mirtazapine compared to further prescribable*  
715 *pharmaceutical treatments: final report; commission no. G09-01*. 2013; Available  
716 from: [https://www.iqwig.de/download/G09-01\\_Executive-summary-of-final-](https://www.iqwig.de/download/G09-01_Executive-summary-of-final-report_Health-economic-evaluation-of-venlafaxine-duloxetine-bupropion-mirtazapine.pdf)  
717 [report\\_Health-economic-evaluation-of-venlafaxine-duloxetine-bupropion-](https://www.iqwig.de/download/G09-01_Executive-summary-of-final-report_Health-economic-evaluation-of-venlafaxine-duloxetine-bupropion-mirtazapine.pdf)  
718 [mirtazapine.pdf](https://www.iqwig.de/download/G09-01_Executive-summary-of-final-report_Health-economic-evaluation-of-venlafaxine-duloxetine-bupropion-mirtazapine.pdf).
- 719 30. Weinstein, M. and R. Zeckhauser, *Critical ratios and efficient allocation*. Journal of  
720 Public Economics, 1973. **2**(2): p. 147-157.
- 721 31. Weinstein, M.C., *A QALY is a QALY--or is it?* J Health Econ, 1988. **7**(3): p. 289-90.
- 722 32. Detsky, A.S. and A. Laupacis, *Relevance of cost-effectiveness analysis to clinicians*  
723 *and policy makers*. JAMA, 2007. **298**(2): p. 221-4.
- 724 33. Grocott, R., *Applying Programme Budgeting Marginal Analysis in the health sector:*  
725 *12 years of experience*. Expert Rev Pharmacoecon Outcomes Res, 2009. **9**(2): p. 181-  
726 7.
- 727 34. Bertram, M.Y., et al., *Cost-effectiveness thresholds: pros and cons*. Bull World Health  
728 Organ, 2016. **94**(12): p. 925-930.
- 729 \*\* = critical reflection on cost-effectiveness thresholds commonly used internationally
- 730
- 731 35. Dolan, P., et al., *QALY maximisation and people's preferences: a methodological*  
732 *review of the literature*. Health Econ, 2005. **14**(2): p. 197-208.
- 733 36. Gafni, A. and S. Birch, *Incremental Cost-Effectiveness Ratios (ICERs): the silence of*  
734 *the lambda*. Soc Sci Med, 2006. **62**(9): p. 2091-100.
- 735 37. Claxton, K., et al., *Causes for concern: is NICE failing to uphold its responsibilities to*  
736 *all NHS patients?* Health Econ, 2015. **24**(1): p. 1-7.
- 737 38. Klingler, C., et al., *Regulatory space and the contextual mediation of common*  
738 *functional pressures: analyzing the factors that led to the German Efficiency Frontier*  
739 *approach*. Health Policy, 2013. **109**(3): p. 270-80.
- 740 39. Institute for Quality and Efficiency in Health Care, *General methods: version 5.0*.  
741 2017, Cologne: IQWiG.
- 742 40. Neyt, M. and H. Van Brabant, *The importance of the comparator in economic*  
743 *evaluations working on the efficiency frontier*. Pharmacoeconomics, 2011. **29**(11): p.  
744 913-916.
- 745 41. Drummond, M.F., et al., *Methods for the economic evaluation of health care*  
746 *programme. Third edition*. 2005: Oxford: Oxford University Press.
- 747 42. Rebscher, H., et al., *[Evaluation of cancer therapy from the perspective of a statutory*  
748 *health insurance]*. Urologe A, 2011. **50**(12): p. 1584-90.
- 749 43. Anderson, J.P., et al., *Policy space areas and properties of benefit-cost/utility analysis*.  
750 JAMA, 1986. **255**(6): p. 794-5.
- 751 44. Black, W.C., *The CE plane: a graphic representation of cost-effectiveness*. Med Decis  
752 Making, 1990. **10**(3): p. 212-4.
- 753 45. Weinstein, M.C., G. Torrance, and A. McGuire, *QALYs: the basics*. Value Health,  
754 2009. **12** Suppl 1: p. S5-9.
- 755 46. Danner, M., et al., *Integrating patients' views into health technology assessment:*  
756 *Analytic Hierarchy Process (AHP) as a method to elicit patient preferences*.  
757 International Journal of Technology Assessment in Health Care, 2011. **27**(4): p. 369-  
758 75.
- 759 47. Marsh, K., et al., *Assessing the value of healthcare interventions using multi-criteria*  
760 *decision analysis: a review of the literature*. Pharmacoeconomics, 2014. **32**(4): p. 345-  
761 65.
- 762 48. Caro, J.J., *Methods of economic evaluation for the German statutory healthcare*  
763 *system*. Pharmacoeconomics, 2009. **27**(3): p. 263-4.

- 764 49. Hoyle, M., *Accounting for the drug life cycle and future drug prices in cost-*  
765 *effectiveness analysis*. *Pharmacoeconomics*, 2011. **29**(1): p. 1-15.
- 766 50. Greiner, W., A. Kuhlmann, and C. Schwarzbach, *Ökonomische Beurteilung des*  
767 *Effizienzgrenzenkonzeptes*. *Gesundh ökon Qual manag*, 2010. **15**(05): p. 241-250.
- 768 51. Birch, S. and A. Gafni, *Information Created to Evade Reality (ICER): things we*  
769 *should not look to for answers*. *Pharmacoeconomics*, 2006. **24**(11): p. 1121-31.
- 770 52. Gandjour, A. and A. Gafni, *The German method for setting ceiling prices for drugs: in*  
771 *some cases less data are required*. *Expert Rev Pharmacoecon Outcomes Res*, 2011.  
772 **11**(4): p. 403-9.
- 773 53. Gandjour, A., A. Gafni, and M. Schlander, *Determining the price for pharmaceuticals*  
774 *in Germany: comparing a shortcut for IQWiG's efficiency frontier method with the*  
775 *price set by the manufacturer for ticagrelor*. *Expert Review of Pharmacoeconomics &*  
776 *Outcomes Research*, 2014. **14**(1): p. 123-129.
- 777 54. Davis, S., *Assessing technologies that are not cost-effective at a zero price*. NICE  
778 Decision Support Unit Methods Development. 2014, London: National Institute for  
779 Health and Care Excellence (NICE).
- 780 55. Cleemput, I., et al. *Belgian guidelines for economic evaluations and budget impact*  
781 *analyses: second edition*. KCE Reports 2012 April 02, 2014]; 183C:[Available from:  
782 [http://kce.fgov.be/sites/default/files/page\\_documents/KCE\\_183C\\_economic\\_evaluations](http://kce.fgov.be/sites/default/files/page_documents/KCE_183C_economic_evaluations_second_edition_0.pdf)  
783 [ns\\_second\\_edition\\_0.pdf](http://kce.fgov.be/sites/default/files/page_documents/KCE_183C_economic_evaluations_second_edition_0.pdf).
- 784 56. Haute Autorité de Santé. *A methodological guide: choices in methods for economic*  
785 *evaluation*. 2012 April 02, 2014]; Available from: [http://www.has-](http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-10/choices_in_methods_for_economic_evaluation.pdf)  
786 [sante.fr/portail/upload/docs/application/pdf/2012-](http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-10/choices_in_methods_for_economic_evaluation.pdf)  
787 [10/choices\\_in\\_methods\\_for\\_economic\\_evaluation.pdf](http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-10/choices_in_methods_for_economic_evaluation.pdf).
- 788 57. Drummond, M., *Twenty years of using economic evaluations for drug reimbursement*  
789 *decisions: what has been achieved?* *J Health Polit Policy Law*, 2013. **38**(6): p. 1081-  
790 102.
- 791 58. Carrera, P. and I.J. MJ, *Are current ICER thresholds outdated? Valuing medicines in*  
792 *the era of personalized healthcare*. *Expert Rev Pharmacoecon Outcomes Res*, 2016.  
793 **16**(4): p. 435-7.
- 794 59. Farrell, M.J., *The measurement of productive efficiency*. *J R Stat Soc Ser A Stat Soc*,  
795 1957. **120**: p. 253-290.
- 796 60. Karlsson, G. and M. Johannesson, *The decision rules of cost-effectiveness analysis*.  
797 *Pharmacoeconomics*, 1996. **9**(2): p. 113-20.
- 798 61. Goeree, R., et al., *Cost-effectiveness and cost-utility of long-term management*  
799 *strategies for heartburn*. *Value in Health*, 2002. **5**(4): p. 312-328.
- 800 62. Murray, C.J., et al., *Effectiveness and costs of interventions to lower systolic blood*  
801 *pressure and cholesterol: a global and regional analysis on reduction of*  
802 *cardiovascular-disease risk*. *Lancet*, 2003. **361**(9359): p. 717-25.
- 803 63. Barton, G.R., A.H. Briggs, and E.A.L. Fenwick, *Optimal cost-effectiveness decisions:*  
804 *The role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness*  
805 *acceptability frontier (CEAF), and the expected value of perfection information*  
806 *(EVPI)*. *Value in Health*, 2008. **11**(5): p. 886-897.
- 807 64. Kamae, M.S., et al., *Regression analysis on the variation in efficiency frontiers for*  
808 *prevention stage of HIV/AIDS*. *J Med Econ*, 2011. **14**(2): p. 187-93.
- 809 65. Zeckhauser, R. and D. Shepard, *Where Now for Saving Lives?* *Law and Contemporary*  
810 *Problems*, 1976. **40**(4): p. 5-45.
- 811 66. Weinstein, M.C. and W.B. Stason, *Foundations of cost-effectiveness analysis for*  
812 *health and medical practices*. *N Engl J Med*, 1977. **296**(13): p. 716-21.
- 813 67. Stapf-Finé, H., *Das IQWiG-Institut im Blickpunkt: Umstrittene Kosten-Nutzen-*  
814 *Bewertung von Arzneien*. *Soziale Sicherheit*, 2008. **6-7**: p. 227-232.

- 815 68. Neumann, P.J. and D. Greenberg, *Is the United States ready for QALYs?* Health Aff  
816 (Millwood), 2009. **28**(5): p. 1366-71.
- 817 69. Gerber, A. and C.M. Dintzis, *A distorted picture of IQWiG methodology.* Health Aff  
818 (Millwood), 2010. **29**(1): p. 220-1.
- 819 70. Dintzis, C.M. and A. Gerber, *Some essential clarifications: IQWiG comments on two  
820 critiques of the efficiency frontier approach.* Health Econ, 2010. **19**(10): p. 1139-41.
- 821 71. Sandmann, F., A. Gerber-Grote, and S. Lhachimi, *Factors that led to the  
822 implementation of the efficiency frontier approach in health economic evaluation in  
823 Germany: do not avoid the elephant in the room. Comment on Klingler et al. (Health  
824 Policy 109 (2013) 270-280).* Health Policy, 2013. **112**(3): p. 297-298.
- 825 72. Klingler, C., et al., *Factors that led to the implementation of the efficiency frontier  
826 approach to health economic evaluation in Germany: let's talk more about the  
827 elephant.* Health Policy, 2013. **112**(3): p. 299-300.
- 828 73. Gandjour, A., *Drug pricing and control of health expenditures: a comparison between  
829 a proportional decision rule and a cost-per-QALY rule.* Int J Health Plann Manage,  
830 2015. **30**(4): p. 395-402.
- 831 \*\* = model suggesting that the EFA may lead to a slower growth in healthcare expenditures  
832 than an absolute cost-effectiveness threshold  
833
- 834 74. Muhlbacher, A.C. and A. Sadler, *The Probabilistic Efficiency Frontier: A Framework  
835 for Cost-Effectiveness Analysis in Germany Put into Practice for Hepatitis C  
836 Treatment Options.* Value Health, 2017. **20**(2): p. 266-272.
- 837 75. World Health Organization, *Access to new medicines in Europe: technical review of  
838 policy initiatives and opportunities for collaboration and research.* 2015: WHO  
839 Regional Office for Europe.
- 840 76. Stollenwerk, B., et al., *Communicating the parameter uncertainty in the IQWiG  
841 efficiency frontier to decision-makers.* Health Econ, 2014.
- 842 77. Corro Ramos, I., et al., *Cost Recommendation under Uncertainty in IQWiG's  
843 Efficiency Frontier Framework.* Med Decis Making, 2016.
- 844 78. Briggs, A.H., *Handling uncertainty in cost-effectiveness models.* Pharmacoeconomics,  
845 2000. **17**(5): p. 479-500.
- 846 79. Briggs, A.H., et al., *Model parameter estimation and uncertainty analysis: a report of  
847 the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6.*  
848 Med Decis Making, 2012. **32**(5): p. 722-32.
- 849 80. McCabe, C., K. Claxton, and A. Tsuchiya, *Orphan drugs and the NHS: should we  
850 value rarity?* BMJ, 2005. **331**(7523): p. 1016-9.
- 851 81. Franken, M., M. Koopmanschap, and A. Steenhoek, *Health economic evaluations in  
852 reimbursement decision making in the Netherlands: time to take it seriously?* Z Evid  
853 Fortbild Qual Gesundheitswes, 2014. **108**(7): p. 383-9.
- 854 82. Ognyanova, D., A. Zentner, and R. Busse, *Pharmaceutical reform 2010 in Germany.*  
855 Eurohealth, 2011. **17**(1): p. 11-3.
- 856 83. Gerber, A., S. Stock, and C.M. Dintzis, *Reflections on the changing face of German  
857 pharmaceutical policy: how far is Germany from value-based pricing?*  
858 Pharmacoeconomics, 2011. **29**(7): p. 549-53.
- 859 84. Horn, H., et al., *Early benefit assessment of new drugs in Germany - Results from  
860 2011 to 2012.* Health Policy, 2014. **116**(2-3): p. 147-153.
- 861 85. Gerber-Grote, A., et al., *Decision making in Germany: Is health economic evaluation  
862 as a supporting tool a sleeping beauty?* Zeitschrift für Evidenz, Fortbildung und  
863 Qualität im Gesundheitswesen, 2014(0).
- 864 \*\* = overview of the current drug reimbursement system in Germany (mostly unchanged as of June  
865 2018), with a particular focus on economic evaluations and the efficiency frontier approach

- 866  
867 86. Lauenroth, V.D. and T. Stargardt, *Pharmaceutical Pricing in Germany: How Is Value*  
868 *Determined within the Scope of AMNOG?* Value Health, 2017. **20**(7): p. 927-935.  
869 87. Franken, M., et al., *Unravelling drug reimbursement outcomes: a comparative study*  
870 *of the role of pharmacoeconomic evidence in Dutch and Swedish reimbursement*  
871 *decision making.* Pharmacoeconomics, 2013. **31**(9): p. 781-97.  
872 88. Garrison, L.P., Jr., et al., *Performance-based risk-sharing arrangements-good*  
873 *practices for design, implementation, and evaluation: report of the ISPOR good*  
874 *practices for performance-based risk-sharing arrangements task force.* Value Health,  
875 2013. **16**(5): p. 703-19.  
876 89. Folland, S., A.C. Goodman, and M. Stano, *The economics of health and health care.*  
877 Vol. 6. 2010, New Jersey: Pearson Prentice Hall.

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