

Gandjour, Afschin

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Comment on: “10 Years of AMNOG: What is the Willingness-to-Pay for Pharmaceuticals in Germany?”

Afschin Gandjour¹

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A recent study published in *Applied Health Economics and Health Policy* [1] leverages results from previous decisions under the Arzneimittelmarkt-Neuordnungsgesetz (AMNOG, translated as the Pharmaceuticals Market Reorganisation Act) to ascertain the implicit willingness to pay (WTP) for pharmaceuticals from the standpoint of the German health care payer/decision maker. The study assessed WTP for drugs treating three distinct diseases in Germany after the 2011 initiation of the AMNOG process, namely, diabetes, cardiovascular disease, and psoriasis. The authors contend that their findings, coupled with those from Lauenroth et al. [2], offer a foundational understanding of implicit WTP in AMNOG negotiations. This understanding could potentially facilitate “the way to establishing a more explicit (i.e., transparent) threshold as happened previously in England and Wales with NICE [National Institute for Health and Care Excellence].”

Furthermore, the study scrutinizes outcomes at both baseline and follow-up for every new medication and its comparator: hemoglobin A1c (HbA1c) for diabetes drugs, life-years gained for cardiovascular drugs, and the Psoriasis Area and Severity Index (PASI) score for psoriasis drugs. “All three outcomes are commonly used as primary endpoints.”

However, it is noteworthy that although the authors view these primary endpoints as relevant from the perspective of the German health care payer/decision maker, the German decision makers prioritize patient-relevant outcomes over primary endpoints [3]. For example, HbA1c is not considered a patient-relevant outcome for treatment of type 2 diabetes [4]. Considering that the majority of diabetes drugs examined in the study were intended for the treatment of

type 2 diabetes, the calculated WTP for HbA1c changes in type 2 diabetes patients holds little relevance to the German health care decision makers. Consequently, the WTP pertaining to shifts in HbA1c levels for patients diagnosed with type 2 diabetes amounts to zero from this particular perspective. Similarly, since edoxaban, a cardiovascular drug, does not significantly impact overall survival (OS) [5], the calculated WTP for OS changes is zero from the German “health care decision-maker/payer” perspective.

Moreover, the study does not differentiate WTP calculations based on whether or not the level of added benefit was deemed proven by the Federal Joint Committee. For instance, the study incorporates tildrakizumab and dimethyl fumarate as treatments for psoriasis, yet these drugs did not exhibit an overall added benefit.

However, as stipulated by the German Social Code Book V (§ 130b), in cases where a drug lacks an added benefit, the WTP should not surpass that of the least expensive comparator. This implies that if an added benefit is not confirmed, the WTP ought to be either zero or negative. Given this, the inclusion of drugs without demonstrated added benefits may decrease the incremental cost-effectiveness ratio (ICER), potentially leading to an underestimation of the WTP for enhancements in clinical outcomes.

Furthermore, the proportion of drugs without proven added benefits factored into the ICER calculation across the three therapeutic domains can wield an impact on the discrepancies observed in ICERs in these areas. A more appropriate approach would involve conducting the comparison exclusively for drugs with proven added benefits.

Lauenroth et al. [2], who calculate the ICER of cancer drugs, distinguish between levels of added benefit. Nonetheless, Lauenroth et al. [2] also encounter the challenge of considering an endpoint, progression-free survival (PFS), that lacks patient relevance. Furthermore, the reported ICER calculation for cancer drugs with an added benefit, amounting to “US\$24,219 per additional life-year gained,” appears questionable. In Exhibit 1 of the study, the “incremental

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✉ Afschin Gandjour
a.gandjour@fs.de

¹ Frankfurt School of Finance and Management, Adickesallee 32-34, 60322 Frankfurt am Main, Germany

treatment costs after price negotiation” are listed as \$43,953. Dividing this value by the “life-months gained in pivotal trial” from the same exhibit (6.4 months) results in a notably higher ICER of \$82,412. This latter estimate is more aligned with an ICER reported for cancer drugs with an added benefit based on OS (but not PFS) as an endpoint (€101,493 per life year gained = €39,751/0.39 life years) [6].

In relation to cardiovascular drugs, the study “converted mortality reduction into life-years gained by multiplying the mortality reduction by the difference between life expectancy and the average age of the study population.” Evidently, the life-expectancy parameter employed in the study pertained to life expectancy at birth in the general population. However, the difference between life expectancy and the average age of the study population does not equate to the remaining life expectancy. Notwithstanding, utilizing the remaining life expectancy of the general population is questionable due to the likelihood of trial participants facing higher mortality beyond the trial due to underlying risk factors. Additionally, the study does not clarify why it extrapolated trial-based outcomes for cardiovascular drugs but not for drugs in the other two indications.

Concerning psoriasis drugs, ambiguity pervades multiple aspects. First, there is a lack of clarity regarding which PASI score (100, 90, 75, or 50) was used and whether it was used consistently. The authors computed €663.46 for a 1 % decrease in PASI score for psoriasis. As per Figure 1 of their article, this calculation is based on PASI 75. However, the Discussion section, which defines PASI 50 as clinically important, applies the WTP derived from PASI 75 to calculate a WTP based on PASI 50. Such a calculation is inappropriate as converting from PASI 75 to PASI 50 is not feasible since PASI 50 scores should be derived from the underlying clinical trials. Furthermore, the denominator in the ICER calculation (“€663.46 for a 1 % PASI decrease”) appears to represent a 1 % increase in responders rather than a 1 % PASI decrease, given that PASI 75 results are typically reported in terms of the percentage of responders. If so, the calculation of the WTP “for a clinically important change” remains inaccurate. Consequently, the study’s conclusions necessitate re-assessment.

Last, the authors compute ICERs as reflections of the WTP but neglect to expound upon the applicability or utility of this information. Notably, the elephant in the room is the efficiency-frontier (EF) method, developed by the Institute for Quality and Efficiency in Health Care (IQWiG) as the official approach for cost-effectiveness analysis in Germany until 2022 [7]. The EF method employs the ICERs of existing drugs as a reference benchmark for the WTP in subsequent assessments within the same therapeutic area, aligning with the study’s approach, albeit not explicitly stated. While the EF method has been both theoretically and empirically validated [8, 9], the IQWiG replaced it in December 2022 with an ICER calculation devoid of a WTP threshold.

Declarations

Availability of data All data are contained within the manuscript.

Authors' contributions AG is the sole author responsible for conception, drafting, and approving the submitted version.

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Conflict of interest The author declares no competing interests.

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