Short Communication

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Health technology assessment (HTA) in England, France and Germany: What do matched drug pairs tell us about recommendations by national HTA agencies?

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Aims: To explore health technology assessment (HTA) outcomes of matched drug pairs by national agencies in Germany (Gemeinsamer Bundesausschuss, GBA), France (Haute Autorité de Santé, HAS) and England and Wales (NICE). **Methods:** We considered published GBA decisions, HAS reports and NICE guidance from January 2011 to June 2018. HTAs of matched pairs were compared overall, and for non-cancer and cancer drugs separately. We further analyzed the role of additional attributes related to cancer therapies. **Results:** Matched pairs show higher concordance for GBA/HAS than for GBA/NICE and HAS/NICE. Overall, NICE evaluated technologies more favorably than GBA and HAS. GBA appraisals of cancer drugs, however, tended to be more positive than cancer-related recommendations by NICE and HAS. **Conclusion:** The findings indicate substantial variations in HTAs, although cancer-related outcomes seem to diverge less than non-cancer results.

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Keywords: cancer drug • GBA • HAS • health technology assessment • matched drug pair • NICE

In most European healthcare systems, health technology assessment (HTA) has been implemented as a tool to support decision-making [1]. It is generally presented as a comprehensive and multidisciplinary evaluation process based on both scientific and non-scientific evidence [2]. However, in practice HTA is predominantly used to assess the efficacy, safety and value of medical innovations. Existing variations in recommendations by European HTA agencies can primarily be attributed to differences in their legal and institutional contexts and evaluation criteria, although additional factors may influence reimbursement decisions as well [3].

For our comparative study, we have chosen to focus on the Federal Joint Committee (Gemeinsamer Bundesausschuss, GBA) in Germany, the National Authority for Health (Haute Autorité de Santé, HAS) in France and NICE in England and Wales, each broadly considered as a national HTA agency that follows robust and transparent assessment procedures.

First established as a special health authority within the UK National Health Service in 1999, NICE's status changed later to that of a non-departmental public body. Its recommendations on the use of existing and new health technologies, including rapid reviews for single indications (single technology appraisals, STAs), are legally binding in England and Wales. Consequently, local health resources must be made available to implement guidance issued by NICE [4]. To date, NICE's value assessments have been described as a framework integrating clinical and cost–effectiveness as well as additional factors (such as ethical value judgements) in decision-making [5]. The application of a cost per quality-adjusted life year (QALY) threshold, however, implies that NICE recommendations

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heavily rely on incremental cost–effectiveness ratios (ICERs) as an indicator of value for money [6,7]. Since the higher proportion of negative recommendations for end of life (EoL) treatments (particularly in hematological and oncological drugs) have raised political as well as societal controversy in Britain, specific criteria have been implemented [8]. Later, the Cancer Drugs Fund (CDF) was introduced to improve access to new cancer treatments by providing funding for technologies not (yet) recommended by NICE [9].

Both the French HAS and the German GBA were initially established in 2004, although in entirely different ways. The HAS was implemented as an autonomous public scientific body by the French Ministry of Health to provide authorities with recommendations (or so-called 'opinions') for reimbursing newly marketed medicines. HTA transparency committee opinions (TCOs) are usually based on an assessment of the drug's actual clinical benefit (ACB) and clinical added value (CAV) compared with existing therapies. While the ACB implies a recommendation for inclusion on the reimbursement list in France, the CAV assesses the relative value of a new medicine [10]. An additional assessment of efficiency may be undertaken depending on the technology's innovation level and its likelihood of having significant impact on the expenditures of the health system, albeit a specific ICER threshold is not used [11].

In Germany, early benefit assessments (EBAs) of newly authorized drugs were officially introduced with the enactment of the Pharmaceutical Market Restructuring Act (AMNOG) in 2011. In a two-stage assessment procedure, the independent Institute for Quality and Efficiency in Health Care (IQWiG) – which is usually commissioned by the GBA – assesses the evidence submitted by a manufacturer, and GBA subsequently makes the final decision [12]. With the creation of a special legal framework, the German legislation guarantees drugs with an orphan designation some additional benefit (as long as actual sales do not exceed statutory health insurance expenses of €50 million per year). This again implies that GBA only evaluates the extent of added benefit without commissioning IQWiG [13]. In contrast to NICE in England and HAS in France, both GBA and IQWiG rejected the incremental cost per QALY metric as a measure of value for money. Instead, IQWiG derived the efficiency frontier approach for optional economic evaluation of health interventions, which has not yet been used in the context of EBAs [14].

Against this background, the aim of our study is to compare and explore variations in the HTA outcomes of matched drug pairs by GBA, HAS and NICE, with our primary focus being on cancer-related appraisals. The study is relevant to experts and healthcare decision-makers acting in the heterogeneous environment of HTA, and findings will contribute insight into the ongoing debate on further alignment of national evaluation processes in Europe.

Materials & methods

Data

GBA, HAS and NICE publish reference documents related to assessments and appraisals on their respective websites [15–17]. We identified all GBA EBAs [15], HAS TCOs [16] and NICE STAs [17] completed between 01 January 2011 and 30 June 2018. We then focused on the following data from GBA decisions (in case of missing data from completed IQWiG assessments), HAS reports (considering the full French version) and NICE guidance (in case of missing information from Evidence Review Group reports):

- From GBA EBAs we extracted benefit determination outcomes by assessment category in terms of extent (with additional benefit: major, considerable, minor, non-quantifiable; without additional benefit: no added benefit, lesser benefit), publication date, therapeutic area, clinical evidence (patient-relevant endpoints) and information regarding the orphan drug status.
- From HAS TCOs we extracted evaluation results of the ACB (sufficient or insufficient) and the CAV (with added value: major, substantial, moderate, minor; without added value: no improvement), publication year, therapeutic area and clinical evidence (comparative efficacy).
- From NICE STAs we extracted recommendations (recommended/not recommended), year of publication, type of condition or disease, clinical and cost–effectiveness (ICER per QALY gained), as well as information related to EoL criteria and – after a relaunch in July 2016 – CDF reconsiderations.

Comparative analysis

For the comparative analysis of matched drug pair outcomes by GBA, HAS and NICE we focused on three levels: overall, non-cancer and cancer-related indications. The main indicator for comparison was the proportion of positive HTA outcomes (GBA: with additional benefit; HAS: with added value; NICE: recommended) within each

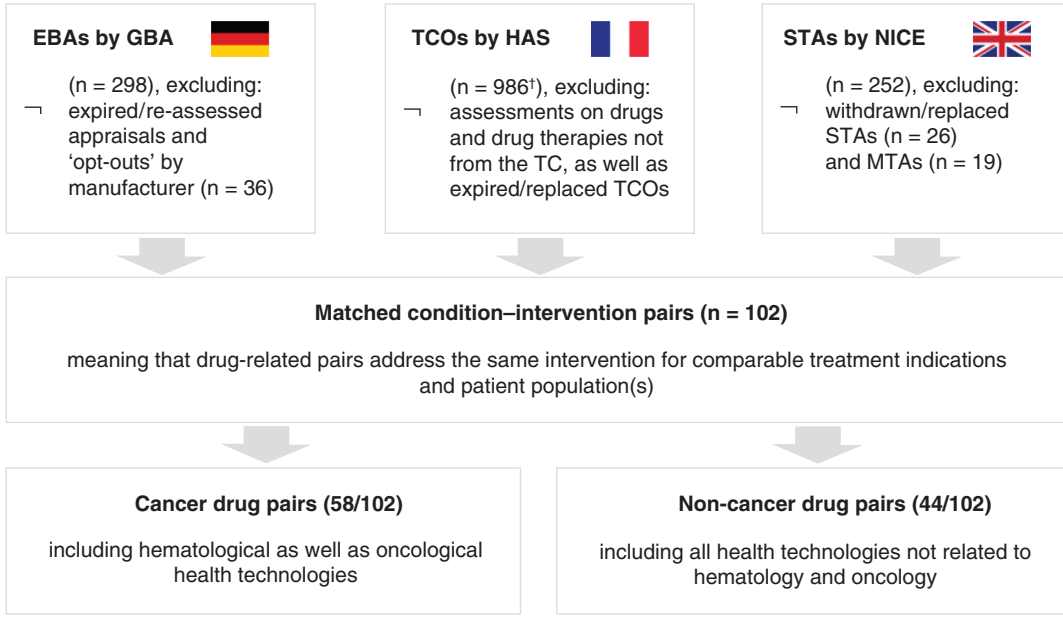

Figure 1. Selection of drug-related matched condition–intervention pairs published between January 2011 and June 2018.
†Data from the French HAS were identified by searching for all published assessments on drugs or drug therapies, and then compared with matched drug pairs from GBA and NICE.
EBA: Early benefit assessment; GBA: Gemeinsamer Bundesausschuss; HAS: Haute Autorité de Santé; HTA: Health technology assessment; MTA: Multiple technology appraisal; STA: Single technology appraisal; TC: Transparency Committee; TCO: Transparency Committee opinion.

treatment indication of interest. To examine the associations between treatment indication (cancer, non-cancer) and positive HTA outcome, we calculated the odds ratio (OR) from 2 × 2 contingency tables. We therefore compared the odds of the occurrence of a positive recommendation by one agency versus the odds of the occurrence of a positive recommendation by another agency. ORs were calculated with 95% CIs by exponentiating their logarithmic limits back to a linear scale. We analyzed the corresponding p-value and defined a threshold of $p < 0.05$ as statistical significance. The concordance (or congruence level) of HTA outcomes was observed to explore variations in different indications among all three agencies to further support the pairwise comparison. By calculating ORs, we compared treatment indication groups (overall, cancer, non-cancer) by outcome for GBA/HAS, GBA/NICE and HAS/NICE.

Comparable to the methodology used by Schaefer and Schlander [18], matching drug pairs had to address the same or at least a comparable treatment indication. This means that HTA outcomes of GBA, HAS and NICE were considered by capturing the technology's main treatment indication, because treatments may differ with regard to the definitions of patient subgroups or selected comparator(s). In the case where there was more than one subgroup for the main treatment indication, we referred to the respective subpopulation with the most favorable HTA outcome.

Furthermore, the potential role of additional attributes related to cancer treatments (including drugs for hematological diseases) was analyzed, such as orphan drug designation in Germany, correlation between ACB reimbursement rates and CAV decisions in France, and consideration of EoL criteria as well as CDF reconsiderations in England. We therefore tested the relationship between attributes and cancer-related HTA outcomes for statistical significance using a chi-square test or Fisher's exact test.

Results

We identified 102 matched drug pairs (cancer-related: 58/102; non-cancer: 44/102) during the study period (Figure 1). By pairwise comparison, HTA outcomes showed higher concordance for GBA/HAS (total: 67%; cancer-related: 72%; non-cancer: 59%) than for GBA/NICE and HAS/NICE (total: 54%; cancer-related: 57%; non-cancer: 50%). Moreover, congruence levels were higher for cancer-related appraisals (57–72%) compared with

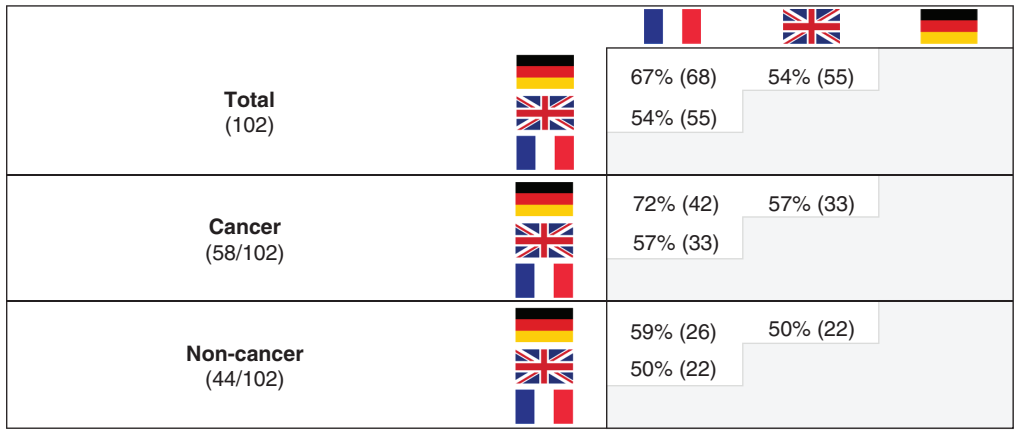

Figure 2. Congruence level of matched health technology assessment outcome pairs from GBA (Germany), HAS (France) and NICE (England).
GBA: Gemeinsamer Bundesausschuss; HAS: Haute Autorité de Santé; HTA: Health technology assessment.

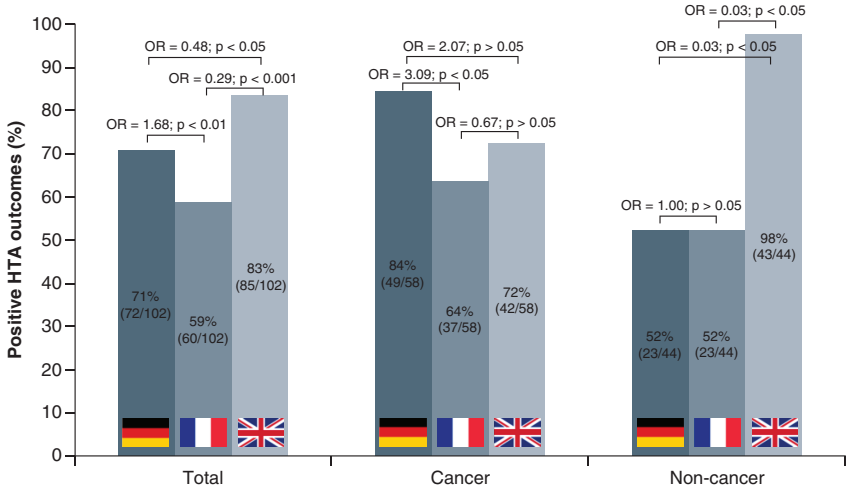

Figure 3. Positive health technology assessment outcomes by treatment indication from GBA (Germany), HAS (France) and NICE (England).
Additional data show calculated odds ratios with the corresponding p-values (with $p < 0.05$ indicating statistical significance).
GBA: Gemeinsamer Bundesausschuss; HAS: Haute Autorité de Santé; HTA: Health technology assessment; OR: Odds ratio.

non-cancer appraisals (50–59%). The percentage distributions shown in Figure 2 are supported by the results when testing pairwise comparison outcomes for significance. On the one hand, ORs were significant when comparing GBA EBAs and HAS TCOs overall (OR: 1.68; 95% CI: 0.94–3.00; $p < 0.01$) and for cancer drugs (OR: 3.09; 95% CI: 1.27–7.52; $p < 0.05$). On the other hand, HAS/NICE and GBA/NICE showed significant lower odds of association for both drugs overall (HAS/NICE, OR: 0.29; 95% CI: 0.15–0.55; $p < 0.001$; GBA/NICE, OR: 0.48; 95% CI: 0.25–0.94; $p < 0.05$) and non-cancer medicines (OR: 0.03; 95% CI: 0.01–0.20; $p < 0.001$).

Overall, 64/102 drugs (63%) differed by appraisal outcome between GBA, HAS and NICE. While NICE recommended 85/102 (83%) technologies, HAS and GBA confirmed positive outcomes for 60/102 (59%) and 72/102 (71%, including 15 orphan drugs) medicines, respectively. However, discrepancies by therapeutic area apparently exist (Figure 3). Both GBA and HAS reported positive outcomes for 23/44 (52%) non-cancer appraisals only, whereas NICE recommended 43/44 (98%) non-cancer technologies (average ICER: £29,001). For example, we identified that five of six medicines used in musculoskeletal disorders were rejected by both GBA and HAS, but were fully recommended by NICE (Table 1). In fact, NICE STAs had significant greater odds of leading to

Table 1. Matched drug pairs by therapeutic area.

Therapeutic area: conditions and diseases	Matched pairs (ODs†)	GBA EBAs: added benefit		HAS TCOs: CAV		NICE STAs: recommendation	
		Yes	No	Yes	No	Yes	No
Cancer	58 (12)	49 (12)	9 (0)	37 (6)	21 (6)	42 (8)	16‡ (4)
Non-cancer	44 (3)	23 (3)	21 (0)	23 (2)	21 (1)	43 (3)	1 (0)
– Cardiovascular	9	7	2	5	4	9	0
– Digestive	2 (1)	1 (1)	1	1	1 (1)	2 (1)	0
– Eye	5	1	4	3	2	5	0
– Infections	6	3	3	6	0	6	0
– Metabolic	5	2	3	1	4	4	1
– Miscellaneous	1	0	1	1	0	1	0
– Musculoskeletal	6	2	4	1	5	6	0
– Neurological	3	1	0	1	0	3	0
– Respiratory	3 (2)	3 (2)	0	3 (2)	0	3 (2)	0
– Skin	3	3	0	1	2	3	0
– Urological	1	0	1	0	1	1	0
Total	102 (15)	72 (15)	30 (0)	60 (8)	42 (7)	85 (11)	17 (4)
Relative share	1.0 (0.15)	0.71 (0.21)	0.29 (0.00)	0.59 (0.13)	0.41 (0.17)	0.83 (0.13)	0.17 (0.24)

†Number of orphan drugs included.
‡In total, 11/16 (69%) cancer drugs (including all orphan drugs) were reimbursed through the CDF.
CAV: Clinical added value; CDF: Cancer Drugs Fund; EBA: Early benefit assessment; GBA: Gemeinsamer Bundesausschuss; HAS: Haute Autorité de Santé; HTA: Health technology assessment; OD: Orphan drug; STA: Single technology appraisal; TCO: Transparency Committee opinion.

a recommendation if non-cancer technologies were compared with cancer-related drugs (OR: 16.38; 95% CI: 2.08–129.11; $p < 0.01$). In contrast, GBA showed a significantly stronger association between cancer treatments and positive EBA outcomes in comparison with non-cancer appraisals (OR: 4.97; 95% CI: 1.97–12.53; $p < 0.001$). HAS TCOs with CAV again did not show any significant effect with either cancer-related (OR: 1.61; $p > 0.05$) or non-cancer medicines (OR: 0.62; $p > 0.05$).

Findings for cancer-related results indeed showed variations in appraisal outcomes (57%), but these were less frequent compared with non-cancer drugs (70%). NICE recommended 42/58 (72%) cancer-related technologies (average ICER: £49,474). EoL criteria were considered for more than 80% (47/58) of the cancer drugs; of the 47 drugs, 37 met EoL criteria (average ICER: £54,454) and 70% (26/37) were recommended by NICE. Accordingly, considerations for EoL treatments seem to have an effect on NICE recommendations, although we found no significant correlation when testing those affected in our sample ($p > 0.05$; Fisher's exact test). Similar results were found for the 11 cancer drugs reimbursed by the CDF (average ICER: £64,248), when assuming these drugs will subsequently be approved and therefore recommended for routine use upon commission ($p > 0.05$, Fisher's exact test).

GBA and HAS assessed 49/58 (84%, including 12 orphan drugs) and 37/58 (64%) cancer-related treatments with added benefit and CAV, respectively. Given that more than 20% (12/58) of the evaluated cancer therapies have been licensed as orphan drugs, an orphan designation seems to be a relevant factor in the higher proportion of positive GBA cancer appraisals ($p < 0.01$; chi-square test). Cancer-related findings from the HAS clearly indicate that the reimbursement rate significantly correlated with the following assessment of CAV ($p < 0.01$; chi-square test).

Discussion

Our findings for matched drug pairs confirm the frequent occurrence of variation in appraisal outcomes found in previous HTA studies [18–20]. While NICE issued more guidance with positive recommendations for new health technologies overall, cancer treatments were relatively more likely to be evaluated positively by GBA. We further observed that HTA results by GBA and HAS indicate higher congruence compared with NICE recommendations, which may be reflected by similarities in the German and French HTA approaches, such as the focus on therapeutic benefit [21].

One of the main differences among the selected countries is the role of HTA agencies with regard to the institutional context and existing reimbursement regulations. While both HAS and NICE publish legally binding

recommendations for reimbursement in France and England, respectively, GBA appraisals inform subsequent pricing negotiations but not reimbursement decisions in Germany [19]. Furthermore, NICE and HAS make recommendations regarding the price or influence the price level (based on the ACB and CAV level) of health technologies, respectively [3]. Finally, unlike the HTA process guidelines of HAS and NICE, the two-stage assessment procedure in Germany does not have a formal appeal process [3,19].

Apart from these (as well as other less important) differences and the gap between the health systems in England, France and Germany ('Beveridge-type' national health system in England vs 'Bismarck-type' social health insurance system in France and Germany), heterogeneity of decision analysis frameworks and evaluation methods seems to be the most relevant factor for variations in HTA outcomes by GBA, HAS and NICE [19,20].

On the one hand, (comparative) clinical effectiveness has been shown to be one of the key criteria in all three HTA settings. Agency-specific guidelines, for example, seem to be relatively similar regarding requirements for clinical evidence submitted by a manufacturer [22]. However, while in both GBA EBAs and HAS TCOs the key element of proof of clinical effectiveness is randomized controlled trials, NICE STAs seem to be more flexible regarding the submission of non-randomized controlled trials or indirect comparison studies [23,24].

On the other hand, cost–effectiveness can be seen as a major component of HTA in England, whereas both GBA in Germany and HAS in France do not explicitly consider costs in technology assessments. HTA outcomes by HAS predominantly rely on comparative efficacy and safety data, as well as pre-existing patient need. Thus health economic assessment is only restricted to medicinal products with high additional value, which may reflect that reimbursement decisions have an impact on effective patient access in France [11,25]. This, again, is significantly different in Germany; while efficacy (with a focus on patient-relevant end points) and robust evidence of benefit have been shown to be relevant factors in IQWiG assessments and GBA appraisals, economic evaluation has not yet played any real role [18].

Cancer drugs pose a special challenge for HTA agencies and, additionally, seem to be of particular interest because evidence indicates that cancer is given priority over other life-threatening conditions [26,27]. The access to reimbursed cancer drugs seems to be less restrictive in France and Germany compared with England [28,29]. This may be reflected by additional attributes, such as orphan drug regulations, but also in how evaluation criteria are prioritized [30]. For instance, GBA cancer appraisals seem to be largely driven by disease morbidity and survival benefit [31]. Although NICE heavily relies on cost per patient by applying a cost per QALY threshold, cancer-related STAs might be relaxed under EoL considerations [32]. As with its introduction, the relaunch of the CDF has been accompanied by criticism regarding its value to patients and society, despite evidence that the overall approval rate of (very expensive) cancer technologies has slightly increased [33–35].

Our results support the generally held perception that existing differences in reimbursement decisions might reflect substantial variations in HTA recommendations, amplified by legal and institutional regulations in the respective HTA setting [18–20,36]. Accordingly, national HTA agencies need evidence-informed deliberative processes to support the legitimacy of their health resource allocation [37,38]. Further improvement in currently used evaluation methods should therefore be required, particularly in regard to better patient access to innovative therapies and greater transparency in the use of scarce healthcare resources. Moreover, long-term collaboration of HTA bodies and other political institutions may underpin a more integrated decision-making process or, in fact, a systematic alignment of the HTA environment in Europe [21,39,40].

Notwithstanding that we extracted data for an extensive period, our results presented here are limited to matched drug pairs only. Consequently, the study sample has not yet been tested for evaluation criteria, which have been shown to be relevant in other country-specific or comparative analyses [6,7,18–20,31,35,36]. We exclusively focused on additional attributes that might be of particular interest with regard to cancer drugs, such as orphan drug status in Germany, reimbursement rates in France and EoL considerations or CDF reconsiderations in England. Due to the subsequent introduction of EBAs in Germany, we only searched for data made publicly available after January 2011. In addition to previous recommendations published by HAS and NICE, we excluded multiple technology appraisals and highly specialized technologies in England. Finally, assumptions were made to compare matched pairs on an equivalent level, because patient subgroup definitions as well as comparator drugs may vary among GBA, HAS and NICE.

This comparative study shows primary key results from ongoing research analyzing evaluation criteria as well as legal and administrative factors that may have an effect on HTA outcomes by these agencies. In addition, cancer drugs will be of special interest to better explain discrepancies among the HTA methods chosen by GBA, HAS and NICE, and to potentially provide more evidence on interventions for rare and ultra-rare disorders.

Conclusion

Our findings confirm variations in appraisal outcomes among national HTA agencies. While NICE evaluated new health technologies more favorably than GBA and HAS, GBA cancer appraisals tended to be more positive than cancer-related recommendations by NICE and HAS.

Interestingly, cancer-related appraisals seem to be less divergent compared with non-cancer results. This is primarily due to differences in institutional context and evaluation criteria, but may also be explained by additional attributes used in the respective HTA context.

Future perspective

This paper suggests the need for further improvement to the currently used methods as HTA agencies need evidence-informed deliberative processes to support the legitimacy of healthcare resource allocation. In future, more integrated decision-making processes and further alignment of the European HTA environment may improve patient access to innovations as well as to effective treatments and, at the same time, increase transparency in the use of scarce health resources. However, while the (potential) implementation of, for example, an EU-wide regulation on HTA is still at a very early stage of development, both experts and regulators will continue to face enormous challenges in supporting evidence-based decision-making in healthcare.

Summary points

- This comparative study used drug-related matched condition–intervention pairs to explore the outcomes of health technology assessments published by the Federal Joint Committee (Gemeinsamer Bundesausschuss, GBA) in Germany, the National Authority for Health (Haute Autorité de Santé, HAS) in France and the NICE in England and Wales.
- During the study period, 102 matched drug pairs (cancer: 57%; non-cancer: 43%) were identified indicating higher concordance for GBA/HAS (67%) than for GBA/NICE (54%) and HAS/NICE (54%), which was further controlled by testing pairwise comparison results for statistical significance.
- Overall, NICE (83%) evaluated health technologies more favorably than GBA (71%) and HAS (59%), even though differences by therapeutic area apparently exist; for example, NICE recommended nearly all of the assessed non-cancer drugs (98%), whereas both GBA and HAS reported positive outcomes for only half of the drugs (52%).
- GBA cancer appraisals (84%) tended to be more positive than cancer-related recommendations by NICE (72%) and HAS (64%), which might be reflected by differences in legal and institutional context, as well as by additional considerations in the assessment of oncological drugs.
- Findings show substantial variations in HTA outcomes from GBA, HAS and NICE, although cancer-related results seem to diverge less compared with non-cancer results.

Author contributions

R Schaefer and M Schlander developed the research design. R Schaefer and L Selberg were responsible for the acquisition of data. R Schaefer and D Hernandez were responsible for data analysis. The initial manuscript was drafted by R Schaefer and revised by D Hernandez and M Schlander. All authors approved the final version to be published.

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