Economics of gastroenteropancreatic neuroendocrine tumors: a systematic review

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Abstract

Background: Despite current interest, enthusiasm and progress in the development of therapies for gastroenteropancreatic (GEP) neuroendocrine tumors (NETs), there are substantial gaps in the published literature regarding cost-of-illness analyses, economic evaluation and budget impact analyses. Compounding the issue is that data on resource utilization and cost-effectiveness of different diagnostic and therapeutic modalities for GEP-NETs are scarce.

Methods: A systematic review on the economic impact of GEP-NETs was carried out using four databases: *EMBASE, PubMed*, the *National Health Service Economic Evaluation Database* and *Cochrane review*. Fully published articles from January 2000 to May 2017, in English and Spanish, were included. All articles that satisfied the inclusion criteria were included in the systematic review; summary descriptive statistics were used to describe the methodological characteristics.

Results: The 14 studies selected included cost-of-illness analyses ($n = 4$), economic evaluations ($n = 7$) and budget impact analyses ($n = 3$). Almost all studies were performed in the United States. Healthcare costs for patients with NETs included medication, outpatient visits, hospitalizations, and check-ups/tests. Reducing adverse events is an area where cost savings could be achieved; however, there was not enough evidence on the cost impact of adverse events.

Conclusion: There is a lack of data related to resource utilization in the field of GEP-NETs. Therefore, cost-effectiveness and budget impact studies of existing and emerging treatments are urgently needed to help the decision-making process for patients with NETs.

Keywords: budget impact, cost-of-illness, costs, economic burden, economic evaluation, gastroenteropancreatic neuroendocrine tumors, resource utilization, systematic review

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Introduction

Neuroendocrine tumors (NETs) are neoplasms arising from neuroendocrine cells which are distributed widely throughout the body.[1] These tumors can cause clinical conditions, including Zollinger–Ellison syndrome, hypoglycemia and watery diarrhea hypokalemia-achlorhydria (WDHA) syndrome, bronchospasms, flushing and other symptoms due to the release of specific hormones and neuroamines into the bloodstream. NETs localized to the gastrointestinal tract (GI-NETs) or pancreas (P-NETs) are collectively referred to as gastroenteropancreatic (GEP)-NETs.

The incidence of GI-NETs has consistently and significantly increased over the past three decades.[2,3] During this time, estimates in the United States (US) have shown a 6.4-fold increase in incidence from 1973 to 2012 across all sites, stage

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and grades.[4] In some European countries, the annual GEP-NET incidence has reached 5.83 per 100,000 people.[5] This may reflect a true increase in the number of new cancers, or the impact of new or improved diagnostic tests and technologies. This increase in prevalence has resulted in a higher financial burden of this disease in European countries. According to the surveillance, epidemiology and end results (SEER) program registry data, prevalence of GEP-NETs is among the highest incidence rate, with 3.56 per 100,000 people in GEP sites and 0.84 per 100,000 people in NETs.[4]

GEP-NETs are diagnosed at all stages; approximately 45.1% of diagnoses occur at the localized stage, 23.1% of diagnoses occur when the patient has metastases, while 16.5% occur when the patient has regional lymph node involvement.[4] In patients with P-NETs, advanced disease is particularly common at diagnosis; approximately 60% of patients are diagnosed at a metastatic stage.[6] Clinical management of GEP-NETs is also challenging due to the heterogeneous nature, anatomical location, and clinical course of these tumors. Clinical interest in GEP-NETs has substantially increased in recent decades, possibly due to the development of novel diagnostic and therapeutic modalities, including targeted agents. Despite the current interest and enthusiasm for classical and newly developed therapies for GEP-NETs, data on economics, including cost-of-illness, budget impact and economic evaluations of different diagnostic and therapeutic modalities are scarce.

In an era of healthcare budget restrictions, this information is crucial for decision-making of patient management and resource allocation. In an increasing number of countries, new healthcare interventions must show clinical efficacy and cost-effectiveness before reimbursement or addition to formularies. This increased emphasis on demonstrating value for money using economic evaluation has arisen because of the increased pressures on healthcare expenditure in health services, driven largely by demographic changes, increased patient expectations and the rapid development of technology. Economic evaluation to assess the cost-effectiveness of medicines has been widely labeled as the 'fourth hurdle' to market, in addition to the traditional three hurdles of safety, efficacy and quality, required for the licensing of a new medicine. While pharmacoeconomics is undoubtedly useful for purchasers, it does not address the issue of affordability, which is an increasing concern.[7] Healthcare purchasers are not only concerned with maximizing efficiency but also with remaining within their annual budgets. These two objectives are not always consistent. Therefore, there is a role for both economic evaluation and budget impact analyses to independently inform healthcare decision-making. The complementary role of these approaches has already been recognized by some decision-making bodies.[8,9]

The aim of this paper was to review the recent literature on the pharmacoeconomics of GEP-NET diagnostics and management strategies, as such, the cost-of-illness, economics and budget impact evaluations and to identify gaps in knowledge to guide decision-making in the management of these tumors.

Methods

The systematic literature review used four databases: *EMBASE, PubMed*, the *National Health Service (NHS) Economic Evaluation Database* and *Cochrane reviews*. The articles were searched in these databases by title and abstract using two different groups of keywords. In order to select the search terms, we considered the Health Information Research Unit at McMaster University (Hamilton, ON, Canada), which specified the search filters for *MEDLINE* (in Ovid syntax) and the *PubMed* translation, and the NHS Centre for Reviews and Dissemination, which also specified the recommended search terms in a systematic search. Therefore, the following search terms were used: [(neuroendocrine AND tumor) OR (neuroendocrine AND tumo*) OR (neuroendocrine AND neoplas*) OR (carcinoid AND tumo*) OR (carcinoid AND syndrom*)) AND ((cost AND benefit*) OR (cost AND effect*) OR (cost AND utilit*) OR (cost AND minim*) OR cost* OR (economic AND evaluation*) OR economic* OR (budget AND impact) OR (economic AND impact) OR (resource AND util*)]. Grey literature was included from a search in Google Scholar; in addition, other papers were included using citation tracking from the retrieved and selected papers.

The systematic review followed recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

on reporting systematic reviews.[10] Papers published from January 2000 to May 2017, in English and Spanish, were included. Exclusion criteria comprised studies that were: neither cost-of-illness analyses, nor economic evaluations, nor budget impact analyses; economic evaluations that were not completed (and therefore did not include the incremental cost-effectiveness ratio); reviews; not focused on the disease of interest; and only published as an abstract. A data extraction form included questions on the studies' context (e.g. geographical study location), sampling and sample characteristics (e.g. disease), methods and results (e.g. type of costs, measure of outcome, perspective) and conclusions (e.g. results summary, study funding). The first screening was conducted by two researchers. Subsequently, each abstract and paper selected was reviewed by two investigators and data extraction was performed independently. The decision for inclusion of an article in the review was made by agreement among other experienced investigators. Whenever there was a disagreement, the papers were reviewed by another investigator. Microsoft Excel was used to summarize the results from the systematic literature review.

After all articles that satisfied the inclusion criteria were collected, summary descriptive statistics were used to describe the methodological characteristics. Costs were converted to 2017 Euros (€) using country-specific or country-group-specific inflation on average consumer prices.[11] The annual costs and mean unit values were adjusted by the interannual inflation rate from the price year to 2017. If required, the unit and annual costs from 2015 were multiplied by the European Central Bank's 2017 exchange rates. For papers not reporting the year in which the costs were calculated, the publication year was used.

Results

The search identified a total of 288 studies. Of those, 30 studies were duplicates and were excluded. Of the remaining studies (n = 258), 222 were excluded because they were congress abstracts, or not associated with NETs. A total of 36 articles that met the initial inclusion criteria were included in the full-text review. Finally, eight studies were selected, which consisted of cost-of-illness analyses (n = 4); economic evaluations (n = 3) and budget impact analyses (n = 1), shown in Figure 1.

The number of publications about the economics of GEP-NET diagnostics and therapies trended upwards from 2012, with five out of eight included studies published since 2015. Details of the cost-of-illness, economic evaluations and budget impact analyses are summarized in Tables 1, 2, and 3, respectively. Almost all studies (seven out of eight) were conducted in the US, except one economic evaluation which was conducted in Mexico. The average age, weighted by sample size, of populations included was 53 years, although only two out of eight studies reported age. All studies specified the diagnosed disease of patients included, which were: carcinoid syndrome (CS; n = 3), NETs in general (n = 2), P-NETs (n = 2), GI-NETs (n = 2), lung NETs (n = 2), and pancreatic islet cell tumors (n = 1). Half the studies indicated the degree of severity of diagnosed diseases. None of the economic evaluations and cost-of-illness studies specified whether or not patients included in the study had received previous treatments. Overall, two of three economic evaluations and three of four cost-of-illness analyses were based on clinical trials.

Cost-of-illness analysis

In terms of economic burden or cost-of-illness analysis, four studies were found.[12–15] Overall, two articles investigated the resource utilization or economic burden generated in patients treated for NETs;[12,13] two articles examined the economic impact of reduction of adverse events, such as diarrhea, in patients with CS (Table 1).[14,15]

Both studies that analyzed treatments for NETs also evaluated pharmacological and chemotherapy treatments; the economic burden was not calculated using a decision analysis because the time horizons for the analyses were 1 and 3.5 years. Therefore, there was no need to do complex long-term cost estimations. Strosberg and colleagues[12] reported primary data and carried out a deterministic and probabilistic sensitivity analysis, but did not report the perspective of analysis, whereas Chuang and colleagues[13] reported secondary data, used the National Health System and patient perspectives, but did not report the perspective of the analysis. In both studies, the costs included were medication, outpatient visits, hospitalizations, and diagnostic tests. Stroberg and colleagues[12] concluded that advanced NET progression had an impact on resource utilization regardless of tumor site, particularly with respect

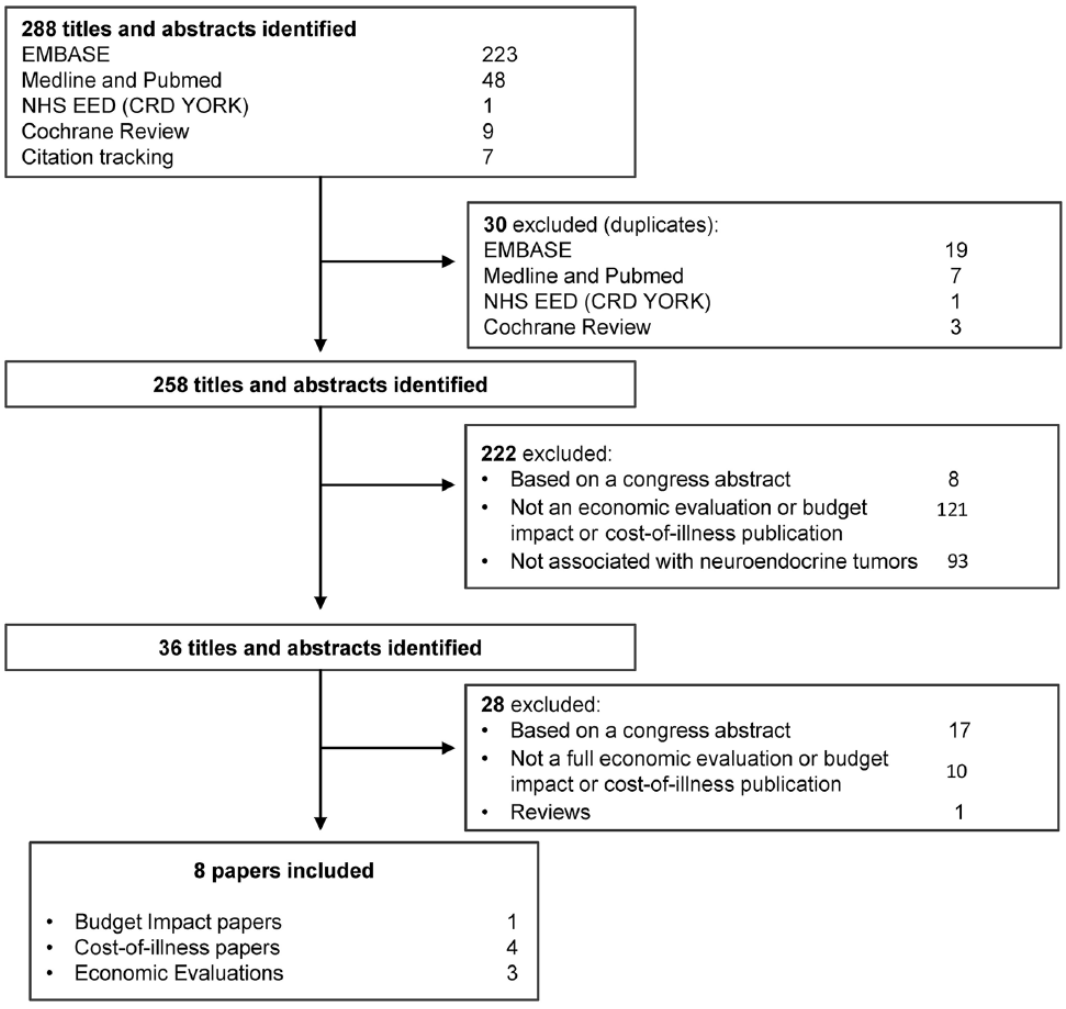

Figure 1. Flow chart search strategy.

to hospitalizations, surgeries, imaging and lab tests, chemotherapy and somatostatin analogs (SSAs). The authors also suggested that more research was necessary to elucidate differences in adverse event reporting between patients receiving chemotherapy *versus* targeted agents. Chuang and colleagues[13] highlighted the existence of economic impact among individuals with NETs and pointed out the importance of investigating the economic burden of patients with longer follow up in the future.

Of the two studies that examined resource utilization associated with adverse events in patients treated for NETs,[14,15] neither used a decision analysis to estimate the costs generated. Broder and colleagues[14] evaluated a retrospective database with a time horizon of 10 years and Huynh and colleagues[15] analyzed data for a 1-year follow up. The latter study also conducted a deterministic sensitivity analysis. Both studies included costs on medication, outpatient visits and hospitalizations; it was concluded that adverse events, such as diarrhea associated with CS, accounted for higher total healthcare spending compared with no adverse events. In addition to these savings, the improvement of quality of life should be also taken into account. Therefore, healthcare costs could be reduced if effective preventive treatment for adverse events associated with pharmacological treatments for NETs could be used.

Table 1. Summary of cost-of-illness studies ($n = 4$).

Reference (authors)	Publication year	Average age	Country of author	Country of study	Study design	Perspective	Cost typology	Analysis method
Strosberg and colleagues[12]	2013	NS	United States	United States	Prospective	Provider	Direct healthcare costs	Multivariate analysis
Chuang and colleagues[13]	2015	54.2 years (medical group) 51.3 years (surgical group)	United States	United States	Retrospective	Provider	Direct healthcare costs	Statistical analysis (descriptive analysis; nonparametric Wilcoxon test to detect differences analysis; etc.)
Broder and colleagues[14]	2016	51.5	United States	United States	Retrospective	Provider (insured population)	Direct healthcare costs	Statistical analysis (descriptive analysis; multivariate analysis to compare the risk of overall and carcinoid syndrome-related hospitalizations)
Huynh and colleagues[15]	2017	NS	United States	United States	Retrospective	Commercial payer (healthcare and patients related costs)	Direct healthcare costs and health-related productivity losses	Statistical analysis (descriptive analysis; two-sample Student's *t*-test with unequal variance, Satterthwaite's method)

NS, not stated.

Economic evaluation

Of eight economic evaluations, seven were on pharmacological treatment.[16,17,19–22] The remaining study analyzed a surgical strategy (Table 2).[18] Only one study compared pharmacological therapies with equivalent doses.[16] Most studies that evaluated pharmacological treatment provided dosing information of the intervention group, with the exception of Hallet and colleagues.[20] Cost-effectiveness was evaluated in all analyses, except those conducted by Hallet[20] and Ayyagari and colleagues,[22] which used cost analysis. A total of four studies used a Markov model to estimate costs and health outcomes.[16–18,21] The time horizons were established as 5 years,[22] 10 years,[16,17,19] and a lifetime[18,21] or were not specified.[20] Overall survival and quality adjusted life years (QALYs) were used across six studies. Overall, four studies used the National Health System perspective,[16,17,21,22] whereas two studies used the provider perspective.[18,19] All costs and outcomes were discounted according to the recommended rate in each country. All studies included costs such as medication; outpatient visits hospitalizations, check-ups and tests. These costs were the same as those included in studies of economic burden. The incremental cost-effectiveness or cost-utility ratios were specified in seven studies[16–22] and were all below the cost-utility threshold recommended for that particular country, which indicated the cost-effectiveness of the intervention. A probabilistic and deterministic sensitivity analysis was performed in all studies, although the acceptability curve was detailed in only four studies.[17–19,21]

Budget impact

Rose and colleagues[23] assessed the budget impact of everolimus for the treatment of GI-NETs and advanced or metastatic lung NETs and established the total population using prevalence data, although no data was provided regarding the percentage of

Table 2. Summary of economic evaluations ($n = 7$).

Reference (authors)	Publication year	Average age	Control		Treatment		Perspective	Results measure	Costs	Conclusions
			Therapeutic strategy	Dose	Therapeutic strategy	Dose				
Casciano and colleagues[16]	2012	NS	Sunitinib	37.5 mg/day	Everolimus	10 mg/day	Payer	LYG/QALYs	Everolimus: US$221/dose; US$5768/monthly cycle SUNI: US$230/dose; US$6374/monthly cycle	ICER (everolimus *versus* sunitinib): US$28,281/LYG and US$41,702/QALYs
Ortega and colleagues[17]	2012	NS	Placebo +BSC	NS	Sunitinib + BSC	37.5 mg/day	Payer	PFS, OS, QALYs	Sunitinib+BSC increases direct costs in US$20,854.5 (*versus* placebo+BSC)	ICER (sunitinib+BSC *versus* placebo+BSC): US$17,661.7/OS US$42,157.2/PFS US$29,807.9/QALY
Spolverato and colleagues[18]	2015	57 years	IAT	NS	HR	NA	Provider	QALYs	HR: $25,086 lifetime cost IAT: US$61,252 lifetime cost	ICER (HR *versus* IAT) (man with metachronous symptomatic NELM that involved <25% of the liver in absence of extrahepatic disease): US$8,427/QALY
Chua and colleagues[19]	2018	NS	BSC	NS	Everolimus + BSC	10 mg/day	Provider	Cost per LYG/QALYs	Everolimus + BSC: CA$146,137. BSC alone: CA$56,342	ICER: CA$145,670/QALY CA$109,166/LYG

Table 2. (Continued)

Reference (authors)	Publication year	Average age	Control		Treatment		Perspective	Results measure	Costs	Conclusions
			Therapeutic strategy	Dose	Therapeutic strategy	Dose				
Hallet and colleagues[20]	2017	This cost analysis compared the cost of NET management with CC management in four phases of care (pre-diagnosis, diagnosis, post-diagnosis and prolonged post-diagnosis). The pre-diagnostic mean NET costs were higher than the CC costs (US$5877 *versus* US$5368) but was lower in the diagnostic and post-diagnostic phases. In the prolonged post-diagnostic stage, the drug costs were higher for NETs, compared with CC (US$26,788 *versus* US$7827).								
Joish and colleagues[21]	2018	NS	Octreotide	24.32 mg / month average	TE + octreotide	TE dose = 21,000 mg/ month average	Payer	Costs and QALYs		QALYs: 1.67 (octreotide), 2.33 (TE + octreotide) Costs: US$495,125 (octreotide), US$590,087 (TE + octreotide)
Ayyagari and colleagues[22]	2017	NS	Octreotide (long-acting)	30 mg	Lanreotide	120 mg	Payer	Cost analysis (treatment and adverse events)	Octreotide was associated with lower costs by US$10,290 (1 year), US$25,480 (3 years) and US$37,323 (5 years), compared with lanreotide	The cost of treatment with octreotide 30 mg is lower than lanreotide 120 mg for patients with metastatic GI-NETs

BSC, best supportive care; CA, Canadian dollars; CC, colon cancer; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; GI, gastrointestinal; HR, hepatic resection; IAT, intraarterial therapy; ICER, incremental cost-effectiveness ratio; LYG, life year gained; NELM, neuroendocrine liver metastases; NET, neuroendocrine tumor; NS, not stated; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life years; TE, telotristat ethyl.

Table 3. Summary of budget impact evaluations ($n = 3$).

Reference (authors)	Publication year	Average age	Treatment	Dose	Current scenario	Potential scenario	Perspective	Time horizon
Rose and colleagues[23]	2017	NS	Everolimus	10 mg/day	Budget without everolimus	Budget with everolimus	Payer (total US managed care health plan and pharmacy budget)	3 years
Joish and colleagues[24]	2017	NS	TE	250 mg	Budget per current treatment (somatostatin analog LAR)	Budget with TE (+ SSA LAR)	Payer	1, 2 and 3 years
Ortendahl and colleagues[25]	2018	NS	Somatostatin analog (octreotide and lanreotide)	120 mg lanreotide and 30 mg octreotide	Baseline utilization of lanreotide or octreotide	Hypothetical shift in utilization of lanreotide or octreotide	Provider	1 year

LAR, long-acting release; NS, not stated; SSA, somatostatin analog; TE, telotristat ethyl; US, United States.

patients diagnosed and treated (Table 3). The authors established a clear comparison between the current scenario without everolimus on the market for GI-NETs and the potential scenario with everolimus on the market. The same scenarios were built for lung NETs. The total budget impact on a US managed healthcare plan and a pharmacy budget was evaluated. The time horizon for both perspectives was 3 years. In the first perspective, costs included drug therapies, other cost of treatment, treatment administration, hospitalizations, physician visits and monitoring/management of adverse events. Costs included in the second perspective only included the drug therapy costs. The total budget impact and the impact on pharmacy budget were expected to increase in GI-NETs and lung NETs with the introduction of everolimus, although the changes were minimal. For GI-NETs, in the first 3 years, the difference between having everolimus on the market or not was 0.0568 and 0.1443 cents per member per month (PMPM), resulting in a −0.0875 cent PMPM difference, and for lung NETs 0.0181 cents and 0.0355 cents PMPM, resulting in a −0.0174 cent PMPM difference. A deterministic univariate sensitivity analysis was carried out in order to study the impact of a 10% variation in drug costs, treatment duration, number of patients eligible for treatment, and new treatment market share. The most significant impact was caused by drug price and treatment duration, which were expected to alter the budget impact by a magnitude of 2.04 cents PMPM and 0.79 cents PMPM in the third year after launch for GI-NETs and lung NETs, respectively. According to the sensitivity analysis of the budget impact model, the impact of drug costs and treatment duration is greater for GI-NETs, compared with lung NETs.[23]

In the evaluation of the short-term affordability of reimbursing telotristat ethyl for CS diarrhea in patients who were not controlled with long-acting release SSAs, the net budget impact of was found to be minimal to a US health plan. The incremental cost PMPM of reimbursing telotristat ethyl was US$0.013, US$0.019 and US$0.025 for 1, 2 and 3 years, respectively.[24]

Furthermore, a model-predicted per-patient cost for SSAs was US$83,473 and US$89,673, for lanreotide and octreotide, respectively, for patients with locally advanced or metastatic GEP-NETs.[25]

Discussion

Despite new treatment approvals, representing important therapeutic advances, there are substantial gaps in the published literature in the understanding of several key domains relevant to

the economics of NETs, particularly with respect to cost-of-illness, economic evaluation and budget impact. The present systematic review highlights the scarcity of data on resource utilization in patients with GEP-NETs.

A previous systematic review on resource utilization in NETs was performed to review available data in advanced NETs for cost-of-illness/resource utilization, economic studies/health technology assessment and quality of life.[26] Chau and colleagues found a lack of consistent and comprehensive documentation of resource utilization in the management of NETs.[26] It could be argued that diagnosis and surgical resection (primary treatment) and therapeutics should be treated as separate categories. However, despite the relevance of separating these categories the lack of evidence on the economic burden of NETs still remains a problem.

There is a lack of studies that quantify the potential cost reduction associated with CS symptom resolution or improvement, following treatment of patients with NETs. In addition, patients with NETs have significantly higher rates of mortality and hepatic and gastrointestinal morbidities, compared with patients without NETs.[27] There is a need to quantify this burden economically in order to have a clear picture of the total economic burden.

Due to the limited number of studies, robust conclusions could not be drawn in terms of effectiveness of pharmacological therapies. Further cost savings may be achieved by reducing adverse events, however, there is currently not enough evidence on the cost of adverse events and more studies are required in this field. The conclusions from the economic evaluations in this review highlight the lack of data on the estimated utilities of different health states among patients with NETs. While it is optimal to compare pharmacological therapies in head-to-head trials, due to data restrictions, indirect comparisons may still provide useful information.

Since 2009, pharmacological treatments of NETs[28–32] have demonstrated improvements, in progression-free survival and overall survival, compared with placebo,[33–35] although some patients had drug-related adverse events, such as diarrhea, fatigue and respiratory infections. The use of lanreotide[30] and telotristat ethyl[31,32] can improve symptoms of CS in NETs. This review showed that there was enough published evidence to conduct further research into the effectiveness of these treatments taking in account direct healthcare costs, such as the drug-related events, direct nonhealthcare related costs and productivity losses. The latter two are important for this type of disease due to the high degree of dependency on family members and impact on caregivers, which contributes to the cost of illness from a societal perspective.[36] If the differences in terms of additional health benefits between available treatments are not significant, this implies that the end differences on drug price are going to be relevant in order to convince decision-makers to publicly fund these types of treatments. In this sense, studies on the treatment costs for different options[37,38] are useful in clarifying the direct healthcare costs of these treatment options.

Some research concluded that surgical therapy is the only curative treatment in individuals with NETs and when adequately indicated, no further treatment is need, thereby reducing future healthcare resource use and costs.[39] However, with innovative pharmacological treatments, more evidence of resource utilization with longer follow up is needed to evaluate and compare healthcare resource utilization and the economic burden of surgery and pharmacological treatments. Other costs such as productivity losses have also not been evaluated.[13] Therefore, more research is required to evaluate the overall impact on the economic burden of NETs.

Regarding the limitations of the present review, its main weaknesses are due to the limited available data included in the identified literature. However, the review of existing international data has resulted in a clearer picture of the current burden of the disease that can be useful to inform clinical and healthcare policy decisions. The limitation of the budget impact study was the availability of data found only in the US. Costs and prices may not be generalizable to other countries or health systems. Another limitation included uncertainty surrounding some of the most important inputs used in this analysis. Prevalence estimates were not accurate enough in order to do fair approximations of the real number of patients diagnosed with NETs. The number of patients with progressive tumors is not available in the published literature and there is no available information from real-world studies. Moreover, there was a lack of evidence on the estimation of

treatment market share and treatment duration. Specific estimates of healthcare resource utilization associated with each therapy were not available; therefore, the results might be affected by the uncertainty of these parameters. The lack of real estimates and data might indicate that the 10% of variation used to run a deterministic sensitivity analysis might be not enough in order to estimate the potential uncertainty around these model results.

In conclusion, management of advanced GEP-NETs has changed substantially in the past few decades due to improved diagnostic tests and increased availability of targeted treatments; further economic evaluations are required to inform healthcare decision-making.

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Supplemental material

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