1. Title page

Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature

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On behalf of the Knowledge NETwork

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Short title
Epidemiology of gastroenteropancreatic neuroendocrine tumours

Key words
Neuroendocrine tumour, Carcinoid, Epidemiology, Incidence

Word count (excl. references and figures): 5,432
2. **Abstract**

Based on the current medical literature, the worldwide incidence of neuroendocrine tumours (NETs) has seemed to increase; however, a systematic literature overview is lacking. This review aimed to collect all available data on the incidence of gastroenteropancreatic (GEP) NETs and population characteristics in order to establish their epidemiology. A sensitive MEDLINE search was performed. The papers were selected via a cascade process which restricted the initial pool of 7,991 articles to 33, using predefined inclusion and exclusion criteria. Original articles evaluating the incidence of sporadic GEP-NETs in regional, institutional and national registries were considered. The majority of data originates from the USA National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database and from national cancer registries in Western Europe. Generally the retrospective nature of existing databases and outcomes might be biased hindering firm conclusions. Age-adjusted incidence of GEP-NETs has steadily increased over the past four decades (1973–2007), increasing 3.65-fold in the USA and 3.8–4.8-fold in the UK. Incidence has changed variably from one anatomic site to another. The greatest increase in incidence occurred for gastric and rectal NETs, while the smallest increase was for NETs of the small intestine. There were gender and racial differences, which differed site by site and, in some cases, changed over time. Incidence rates of GEP-NETs have significantly increased in the last 40 years. Data are only available from North America, Western Europe and Japan. A site-by-site analysis revealed that for some NETs the incidence rate increased more than others.
3. Introduction

 Neuroendocrine tumours (NETs) are heterogeneous neoplasms, arising from different cells distributed in many organs and tissues which share a common neuroendocrine phenotype. NETs have been recognised as biologically different from classical carcinomas since the first description of a ‘karzinoid’ by Oberndorfer at the beginning of the 20th century [Oberndorfer 1907]. However, only in recent years have well-defined histological and immunohistochemical criteria allowed clinicians to reliably identify NETs and differentiate them from other types of tumours. The World Health Organization (WHO) classification criteria of NETs, which have been recently revised by an international pathological board, are basic instruments which have superseded all previous NET classifications and terms, such as APUDoma, argentaffinoma or carcinoid [Klimstra et al. 2010; Klöppel et al. 2010].

The most recent 2010 WHO system renders all neuroendocrine tumours as neoplasms with a malignant potential and the acronym NEN is recommended corresponding to the term NeuroEndocrine Neoplasia [Klimstra et al. 2010a,b; Klöppel 2011].

Nowadays, more and more NETs are diagnosed on surgical samples or biopsy, in the absence of classical clinical picture suggestive of NET. Furthermore, highly sensitive and specific imaging techniques, such as computed tomography (CT), SPECT with In-Pentetretotide and Positron Emission Tomography (PET) with Ga-DOTATATE, C 5-HTP and F-DOPA, multidetector-row CT, endoscopic ultrasound and videocapsule endoscopy are now available to help detect and localise symptomatic and asymptomatic NETs [Kwekkeboom et al. 2009; Sundin et al. 2009].

Despite several recent articles from monocentric and multicentric national studies, we are still lacking adequate epidemiological information on NETs. This lack of data only partially explains the strong discrepancy between the estimated incidence of GEP-NETs and the
higher frequency of these tumours found in autopsy series [Berge & Linell 1976].

The aim of this study was to perform a systematic literature review in order to collect all available data on the worldwide epidemiology, and specifically incidence, of GEP-NETs and to identify potential trends in the incidence rates of these tumours.
4. Materials and methods

Prospective and retrospective epidemiologic studies that evaluated the incidence and/or prevalence of GEP-NETs in people at any age were considered. Studies were included if they presented incidence and/or prevalence of GEP-NETs. Autopsy series were excluded. Only original articles were included; review articles and abstracts were excluded. Studies on patients with multiple endocrine neoplasia (MEN1) and other familial NETs were excluded. A search strategy was defined which included search terms on study design, patient group, clinical problem and outcome of interest using the Medline database (1966–07/2011). Search terms were "Incidence"[Mesh] OR "Data Collection"[Mesh]] OR "Prevalence"[Mesh]) AND (("Neuroendocrine Tumors"[Mesh] OR "Carcinoma, Neuroendocrine"[Mesh] OR "Gastro-enteropancreatic neuroendocrine tumor"[Supplementary Concept]) OR ((neuroendocrine AND (tumors OR tumour)) OR (neuro-endocrine AND (tumors OR tumour)) OR (neuro endocrine AND (tumors OR tumour)) OR (neuroendocrine carcinoma) OR (neuro-endocrine carcinoma) OR (neuro endocrine carcinoma) OR (gastro entero pancreatic neuroendocrine tumors) OR (gastroenteropancreatic neuroendocrine tumor) OR (gastro entero pancreatic neuroendocrine tumours) OR (gastroenteropancreatic neuroendocrine tumours) OR (gep tumor) OR (gep tumour) OR (gep net) OR (gep neuroendocrine tumor) OR (gep neuroendocrine tumours) OR carcinoid* OR insulinoma* OR gastrinoma*

There were no language restrictions. Studies reporting on regional, institutional and national registries were included if they reported annual incidence rates. The bibliographies of all retrieved and relevant publications identified by the search were investigated for further relevant studies. All identified references were assessed by title and abstract to determine possible eligibility if these met the inclusion criteria: concerning patient group: patients with
GEP-NETs, outcomes reported: incidence and/or prevalence and type of registry (i.e. national, regional or institutional). Full-paper copies of the subsequent identified articles were retrieved and each was assessed for eligibility using pre-defined data extraction sheets. Studies were excluded if they reported incidence rates of all NETs with no specific data on GEP-NETs separately. Each paper included was further assessed and information was extracted using standard data extraction sheets. Data were collected concerning the country or region, type of registry, patient identification procedure, patient population (location of primary tumour and type of tumour), reported time period and outcomes (incidence and/or prevalence figures). In case of doubt the papers were discussed in teams of at least two reviewers and a consensus opinion achieved. Particularly in the United States where the SEER database is publicly available, different groups had used the same data and reported similar incidences over similar time periods. In the majority of cases, we included all papers as many incidences used different inclusion criteria or were reported in different ways (e.g. annually vs. 5-year incidence). When the same group published updated data in the same way these reports were grouped together. Extracted data were summarised in evidence tables on a study-by-study narrative basis (for full data tables see the Supplementary appendix). Because of the heterogeneity of study designs, type of registries, follow-up and outcomes, no attempt was made to pool the results. The evidence tables were compiled following collective discussion by the working party. IRs were reported as number of cases per 100,000 persons in the population studied per year (unless otherwise stated). In cases where age-adjusted IRs were reported these figures were used.
5. Results

Of the 7,991 publications that came up in our initial search, 199 papers were judged to be potentially eligible based on their title and abstract and were reassessed on a full-text basis. A total of 33 papers fulfilled all specified inclusion and exclusion criteria. These publications covered IRs of GEP-NETs at different time periods between the years of 1958–2007 in different parts of the world (see figure 1). None of the reports included data on GEP-NET prevalence by anatomic location in the gastrointestinal tract. Yao et al. reported an estimated 29-year limited-duration prevalence of NETs on January 1, 2004, in the United States of 103,312 cases or 35/100,000 [Yao et al. 2008]. Reports on IRs of GEP-NETs were mainly from North America and Western Europe with one report from Japan (also reporting prevalence rates) (Figure 1). The majority of data from North America originated from the USA SEER database. Incidence was usually reported as annual age-adjusted incidence per 100,000 population. In some cases, incidence was reported separately for males and females and by race; in others, incidence was reported for the whole population without separating the genders or race.

Methods of patient identification for national and regional registries included in this review are listed in table 1.

Data from the USA

Numerous cancer registries exist in the United States on a national, state, and institutional level. The majority of, and most robust, epidemiologic studies have been performed using the national registries. The End Results Group (ERG) reflected cancer cases from 1950–1969. The Third National Cancer Survey (TNCS) was a more short-lived registry including patients from 1969–1971. More recently, the most prominent studies have been performed using the
SEER cancer registry. The most up-to-date SEER data represents approximately 28% of the population of the United States and includes information on 7,262,696 cancer patients diagnosed from 1973 to 2009. The SEER database is considered to be roughly representative of the US population with respect to features such as socioeconomic status, education, and urban/rural residence (seer.cancer.gov website).

Data outside the USA

In Europe, data on the incidence of GEP-NETs, separated by anatomic location, arise from national and regional registries. The countries in Europe for which there were IRs specifically for GEP-NETs (fulfilling our inclusion criteria) included: the UK, Sweden, Norway, France, Switzerland, Austria and Italy. In some of the countries, IRs have been published several times for different time periods allowing some insights into trends in the incidence of GEP-NETs (UK, France, Switzerland, Norway and Sweden). Some countries reported large series of GEP-NET patients but were not population based and therefore could not report on annual IRs [Lombard-Bohas et al. 2009; Garcia-Carbonero et al. 2010; Ploeckinger et al. 2009; Younes et al. 2008; Li et al. 2008]. Some registries reported IRs of all GEP-NETs or all NETs, including lung NETs, with no site-specific incidence rates (Scotland, Netherlands, Denmark and early reports from England and Ireland), and therefore were not included in this review [Westergaard et al. 1995; Newton et al. 1994; Buchanan et al. 1986; Watson et al. 1989; Quaedvlieg et al. 2001]. There was only one study outside of the US and Europe that qualified for our review, originating in Japan [Ito et al. 2010].

Overall GEP-NET incidence

Several registries published data on all site NETs incidences, but since these IRs included non-GEP sites (mainly lung) and were not solely dedicated to GEP-NETs they were not
In the US, the incidence of GEP-NETs has steadily increased over the past four decades. In the most recent epidemiologic study 29,664 patients with GEP-NETs were identified from the SEER database from 1973 to 2007. Between 1973 and 1977, the age-adjusted incidence rate (IR) for all GEP-NETs was 1.00, increasing to 3.65 between 2003 and 2007 [Lawrence et al. 2011]. In the UK, the IR of gastrointestinal (GI) NETs (excluding pancreas) increased by 4.8 times in males and 3.8 times in females from the 1970s to the years between 2000 and 2006 (from 0.27 to 1.32 in males and from 0.35 to 1.33 in females) [Ellis et al. 2010]. The absolute rate of GEP-NETs in the UK was significantly lower compared to that in the USA over similar time periods. While possibly explained by true variations in incidence, influenced by local genetic and environmental conditions, these discrepancies mainly raise major concerns on the validity of method of patient identification in the different registries and in the same registry throughout time.

**Gastric NETs**

Incidence rates of Gastric NETs are particularly difficult to assess as registers did not differentiate between type I, II, and III gastric NETs. Moreover, Registration of these tumours in different cancer registries is variable, with some only documenting malignant while others documenting benign and malignant tumours. In the SEER database up to 1986 only malignant gastric NETs were registered. The differentiation between benign and malignant gastric NETs is not acceptable any more, as all types have various grades of malignant potential [Klimstra et al. 2010a].

In the 1970s incidence was low: 0.01 both in the US and the UK [Maggard et al. 2004, Ellis et al. 2010] for details see Supplementary appendix Table 1.

Most recently, the highest IRs of gastric NETs have been reported in the USA [Lawrence et
al. 2011], and somewhat lower in Norway [Hauso et al. 2008], UK [Ellis et al. 2010] and Austria [Niederle et al. 2010], figure 2A.

There has been an increase in IRs over time in the UK, US, Switzerland, and Norway [Ellis et al. 2010; Yao et al. 2008; Lawrence et al. 2011; Levi et al. 2000; Hauso et al. 2008]. The most dramatic increases were in the UK (15-fold increase) and in the US (11-fold increase) [Ellis et al. 2010; Yao et al. 2008; Lawrence et al. 2011; Maggard et al. 2004; Modlin et al. 2004; Modlin et al. 1997; Hodgson et al. 2005; Modlin & Sandor 1997; Modlin et al. 2003]. It remains unclear whether this represents a true increase in incidence or reflects increased awareness, changes in method of registration ('malignant' vs 'benign' and 'malignant tumours') and mainly the raise in availability and usage of upper endoscopy.

In the US, there was initially a suggestion that female gender could be protective [Modlin et al. 2004]; however this no longer holds true as males and females now tend to have similar incidence rates of gastric NETs [Yao et al. 2008]. In the US, over the past 30 years, gastric carcinoids have consistently been more common in blacks, as compared to whites [Lawrence et al. 2011; Modlin et al. 2004; Modlin et al. 1997; Crocetti et al. 2003; Modlin & Sandor 1997; Modlin et al. 2003].

Small bowel (SI) NETs

In older classification systems the duodenum was classified as foregut carcinoids. In most recent classifications NETs of the duodenum are considered a distinct entity [Klimstra et al. 2010a; Klöppel 2011].

Despite this, many of the reports summarized in this review included duodenum with and without the jejunum/ileum as a group of SI NETs, while others reported all three sites combined.
SI NETS have been the most common GEP NET in the western world for many years [Lawrence et al. 2011; Ellis et al. 2010], and only recently have they been surpassed by rectal NETS in the US [Lawrence et al. 2011].

In the 1970s, the lowest IR was recorded in the UK (0.11–0.12) [Ellis et al. 2010]. During the same period, IRs in the US were higher, 0.28 to 0.82 (lowest in white females and highest in black males) [Godwin 1975; Maggard et al. 2004; Gustafsson et al. 2008] for details see table 2 in the supplementary appendix.

Data from different time periods shows a clear increase in IRs of small bowel NETs over time. Between 1971 and 2006 the increase in IR in the UK was approximately 3.8-fold in men and 2.9-fold in women [Ellis et al. 2010], and in the latest report from the SEER database, a 2.8-fold increase was demonstrated comparing the early 1970s to the mid-2000s [Lawrence et al. 2011; Bilimoria et al. 2009]. Smaller increases with different trends in males and females were seen in Sweden, [Hemminki & Li. 2001; Landerholm et al. 2010], Burgundy, France [Lepage et al. 2004], Vaud, Switzerland, [Levi et al. 2000], and Norway [Hauso et al. 2008].

While increase in "incidental" tumours due to increased imaging and awareness can explain the rise in IR of other GEP NET's, this is less relevant to SI NET's which are usually not amenable to luminal imaging with endoscopy techniques.

In recent years, significantly higher incidences have been recorded (presented in figure 2B). The highest IR of these tumours has been reported in the US with similarly high IR reported over similar time frames in Norway and Jonkoping County, Sweden [Lawrence et al. 2011; Hauso et al. 2008; Landerholm et al. 2010]. Lower IR have been recorded in the latest reports from the UK [Ellis et al. 2010] and in Austria [Niederle et al. 2010] (see figure 2B).

Of note this more than 2 fold variation in IR of SI NET in the US compared to the UK and some other western European countries (see Fig 2B) raises some major concerns as to the validity of the various registries and reflects the variation in methods of patient identification in
each country.

In the SEER registry from the US jejunal/ileal NETs were the most common among small intestine NETs [Yao et al. 2008; Lawrence et al. 2011] they are more common in African-Americans compared to whites (for details see Supplementary appendix Table 2) [Yao et al. 2008; Modlin et al. 2009; Godwin 1975; Modlin & Sandor 1997; Modlin et al. 2003; Chow et al. 1996; Severson et al. 1996]. Male predominance has been reported in most of the countries reporting IR’s of SI NET’s.

Pancreatic NETs

The most recent IRs of pancreatic NETs is presented in figure 2C (and in more detail in Supplementary appendix Table 3).

In Europe, few reports on the incidence of pancreatic NETs fulfilled our selection criteria.

In the US, the IR of pancreatic NETs increased with time as apparent from several reports [Hauso et al. 2008; Modlin et al. 2003; Halfdanarson et al. 2008], with the most recent one showing an increase from 0.17 in 1973–1977 to 0.43 in 2003–2007 [Lawrence et al. 2011]. Surprisingly there were major differences in IRs in the different reports based on the SEER database which may be explained by differences in ICD code selection. For example, Yao et al. looking specifically at the IR of islet cell carcinoma found a decrease in IRs with time between 1973 and 2003 [Yao et al. 2007]. In Norway IR of pancreatic NETs doubled from 0.15 to 0.3 between the mid 90’s to the early 2000’s [Hauso et al. 2008].

In general, IRs in the US seemed slightly higher than in Europe, with a male predominance in France, US and Norway, but a female predominance noted in Italy. In the US SEER population pancreatic NETs were more common in whites and African Americans (0.32 and 0.36 respectively), as compared to Asian Americans and American Indians (0.25 and 0.20 respectively) [Yao et al. 2008].
Colorectal NETs

NET incidence at these anatomic sites is difficult to assess, as registries variably reported incidence rates for colorectal, colon, or rectal NETs. In addition, some reports included appendiceal NETs with colorectal NETs. Comparisons between geographic areas were especially challenging because of these differences in classification. The incidence of colorectal NETs has risen over the last forty years. It remains unclear whether this reflects a true increase in incidence or increased availability and usage of flexible sigmoidoscopy and colonoscopy.

Colon NETs

Most recent incidence rates of colon NETs are reported in figure 2D (for more details see table 4 of the supplementary appendix). Within the colon, right-sided NETs have generally predominated [Yao et al. 2008; Lawrence et al. 2011; Ellis et al. 2010; Crocetti & Paci 2003; Modlin et al. 2003; Ballantyne et al. 1992].

In the 1970s, the IRs of colon NETs in the UK were as low as 0.05 [Ellis et al. 2010]. From the 1970s to the mid-2000s, IRs increased approximately 4-fold in the UK and more than doubled in the US SEER population [Lawrence et al. 2011; Ellis et al. 2010; Hauso et al. 2008; Maggard et al. 2004; Modlin & Sandor 1997; Modlin et al. 2003; Gustafsson et al. 2008]. Smaller increases in IR have been observed in Norway [Hauso et al. 2008]. Interestingly, a recent report from Austria demonstrated a particularly low colon NET IR of 0.06 in the mid-2000s [Niederle et al. 2010].

Racial and gender differences in IRs have also been visualized. Colon NET IRs remained highest in African Americans (0.38), with lower incidences in American Indians (0.22), whites (0.18), and the lowest incidence in Asians (0.12) [Yao et al., 2008]. With gender, IRs of colon
NETs were higher in males in the US [Yao et al. 2008; Hauso et al. 2008; Godwin 1975] but the opposite was true in Italy, Norway, and Sweden [Caldarella et al. 2011; Hauso et al. 2008; Hemminki & Li 2001].

Rectal NETs

The most recent IRs of rectal NETs are presented in figure 2E and in more detail in table 5 of the supplementary appendix. In the early 1970s, IRs for rectal NETs were ten times lower in the UK than in the US (0.01 and 0.1 per 100,000, respectively) [Lawrence et al. 2011, Ellis et al. 2010; Godwin 1975; Modlin & Sandor 1997; Modlin et al. 2003]. From the 1970s to the mid-2000s, IRs rose approximately 10-fold in both countries, reaching a maximum IR of only 0.12 in the UK as compared to 1.05 in the US SEER population [Lawrence et al. 2011; Ellis et al. 2010]. The lowest IR of rectal NETs has been reported in Austria which was 0.03 in the mid-2000s [Niederle et al. 2010]. Modest increases in rectal NET IRs are reported from other European countries such as Norway [Hauso et al. 2008].

Racial and gender differences in incidence of rectal NETs have been reported. In the US racial differences in the incidence of rectal NETs have been demonstrated, with highest frequency in African Americans (1.80), followed by Asian Americans (1.25) and American Indians (1.0), and lowest frequency in whites (0.66) [Yao et al. 2008; Godwin 1975; Modlin & Sandor 1997; Modlin et al. 2003]. In the UK and Norway the IRs of rectal NETs were only slightly higher in males compared to females, and in Italy and Sweden there were no gender differences [Ellis et al. 2010; Caldarella et al. 2011; Hauso et al. 2008; Hemminki & Li 2001].

Appendiceal NETs

The most recent IRs of appendiceal NETs are presented in figure 2F (and in more detail in Supplementary appendix Table 6).
Registration of NETs of the appendix has changed over time, depending on whether only malignant tumours or both benign and malignant ones were included. In the 1970s, the lowest IRs were recorded in the UK and were 0.03 in males and 0.05 in females respectively [21, Ellis]. During the same period, IRs in the US were slightly higher at 0.07–0.12 [Lawrence et al. 2011; Maggard et al. 2004; Gustafsson et al. 2008]. [Godwin 1975; Modlin & Sandor 1997; Modlin et al. 2003].

IR of ANETs has increased over time in all countries. Interpreting this raise in incidence is complex due to the differences in registration mentioned earlier [Ellis et al. 2010; Caldarella et al. 2011; Hemminki & Li 2000]. Another source of error to the incidence of appendiceal NETs is the fact that it is often an incidental finding, and removed appendices are sent for pathology with a frequency that may vary between countries and over time. The most dramatic rise in IR was in the UK the (10-fold) between 1979 and 2006, largely explained by the change of ICD-O coding, which from 1995 onwards included both benign and malignant appendiceal NETs [Ellis et al. 2010]. In Norway and the US incidence rates increased much more mildly (about 2) fold over various time periods [Hauso et al. 2008; Lawrence et al. 2011].

In recent years, significantly higher IRs have been recorded: highest in the UK [Ellis et al. 2010] and significantly lower over similar time frames in the US, [Yao et al. 2008; Lawrence et al. 2011], Norway [Hauso et al. 2008] and Austria, [Niederle et al. 2010], see fig 2F.

IR of ANETs are higher in females than males in all countries reporting incidence by gender, and as of the 1990s, ANETs are the most common GI NET in women in the UK [Ellis et al. 2010]. In the US SEER registry incidence rates of appendiceal NETs are several fold higher in whites and African Americans, as compared to Asian Americans and American Indians (see appendix table 6) [Yao et al. 2008].
Data from Japan

The report by Ito et al., (Table 7 in the supplementary appendix), reporting on the incidence of GEP-NETs in Japan is unique in several aspects. It is one of the few which reports on prevalence as opposed to just incidence. Calculation of incidence rates was not done by identifying patients according to ICD-O codes in cancer registries. Rather, a nationwide survey of GEP-NET patients in Japan who received treatment from January 1 to December 31, 2005 was conducted in a sample of hospitals and departments that were chosen using stratified random sampling. This study is unique using the old classification of NETs: foregut, midgut and hindgut. For these reasons it is difficult to make comparisons between Japan and other parts of the world [Ito et al. 2010].

6. Discussion

By reviewing all published articles concerning the epidemiology of GEP-NETs, we found that 33 were population-based studies providing information about incidence per year of these tumours. Our findings are briefly summarised as follows:

Data source

Incidence rates of GEP-NETs are available from national and regional cancer registries in North America, Western Europe and Japan but not from other parts of the world. Most published data on the epidemiology of NETs is based on small and heterogeneous series, where the real incidence of these tumours for most sites is not completely known and probably not reliably estimated. In this review we included only publications that strictly fulfilled our inclusion criteria in order to present only true incidence rates, at the national or regional level. Table 1 presents the heterogeneity of the data sources and means of
registration which were used by the different sources of data in this review, and thus explains why pooling of data in the form of a meta-analysis was not possible. This also may explain part of the differences seen in IR's of GEP NETs between the US and Europe, which to our opinion cannot be completely attributed to true variation in incidence rates.

Major changes have been made in the classification of NETs from their original identification by Oberndorfer in the early 1900s, who coined the name ‘Karzinoide’ [Oberndorfer 1907]. Consistency of nomenclature and classification of NET is the major limitation in elucidating the precise epidemiology of GEP-NETs. This is reflected in the International Classification of Disease for Oncology coding system (ICD-O) that used one of several names to describe the same tumour: apudoma/ carcinoid tumour/enterochromaffin cell carcinoid and so on [Lawrence et al. 2011]. Another source of error as to the true incidence of GEP NETs is that older cancer registries included only ‘malignant carcinoids’ while ‘benign’ tumours were not included. At the same time other registries reported both ‘benign’ and ‘malignant’ tumours. This has changed, with the new ICD-O 10 coding already including 'benign' NETs, and may explain some of the rise in incidence of GEP-NETs around the world. Furthermore, current NET classification (WHO and ENETS) does not discriminate between benign and malignant NETs, rather classification relies on histologic grade and differentiation, rendering all NETs as neoplasia with a malignant potential [Klimstra et al. 2010a,b; Klöppel et al. 2009].

**Trends in Incidence rates**

The age-adjusted incidence of all GEP-NETs has steadily increased in the last four decades, increasing in the time interval 1973–2007 by 3.6-fold in the US and by 3.8–4.8-fold in Europe. The small intestine and rectum are currently the most common primary sites for GEP-NETs. The highest increase in IR in recent years/decades has been observed for gastric and rectal NETs, whereas the IR for SI-NETs have changed least among the various sites/locations.
There are gender and racial differences, which differ site-by-site and, in some cases, change over time and are different between countries and continents.

**Limitations of the available data**

Our findings were limited by the heterogeneity of data reporting and presentation, and by the fact that some of the reports were not population based and therefore did not report annual incidence rates, with very little data on prevalence rates. Heterogeneity was apparent in several aspects including: different countries and study populations; different manners of identification of patients (see table1); different time intervals from which incidence data has been calculated; variations in the way data was presented (age, gender and race); site of origin of the tumour; and grade of malignancy. Only one study used the 2000 WHO classification (Austria), and no studies used the 2010 WHO classification. Most reports had a retrospective study design with only one prospective study (Austria) in which incidence rates have been established taking into account all diagnoses of NETs performed in that country in 1 year. Multiple reports for the same population, e.g. the numerous SEER-based publications, were not always consistent with each other. As of the second decade of the 21st century, data on incidence rates of GEP-NET is still lacking from many parts of the world, including Australia, the Far East and Africa.

Assessing trends in the IRs of GEP-NETs is confounded by multiple factors. Classification of GEP-NETs has changed with time. Benign tumours were not included in some of the older studies, while today we know that all NETs have a malignant potential. In addition, increased awareness of NETs by clinicians and pathologists and the use of NETs classifications in more recent years might at least partly explain the rise in incidence of NETs. Awareness of NETs by clinicians and pathologists, and rise in clinical use of luminal and anatomic imaging have
both likely contributed significantly to the increase in IRs of GEP-NETs, while the precise
collection of pathology reports, using a
	identifying all NET cases on the base of standardized collection of pathology reports, using a
	uniform classification system, preferably based on the most updated WHO classification,
	should be performed to study possible topographic differences and changes in incidence with
time. These studies should be conducted in different parts of the world. Together this
	information may promote our understanding of the genetic and environmental factors which

collect and report annual age-adjusted incidence and prevalence rates. Population-based studies, ideally whole countries,
7. Declaration of interest

MF, MKK, AF and GDV have no conflict of interest. WDH has been on advisory boards organised by Novartis and Ipsen.

8. Funding

See Acknowledgments below.

9. Author contributions

All authors screened the search results and compiled data sheets with incidence rates of the study population. All authors participated in writing the manuscript and reviewed the final version.

10. Acknowledgments

The authors wish to thank the participants of the Knowledge Network.

The authors would like to thank Alex Coulthard of echo Communications, UK for editorial assistance, funded by Ipsen, in the preparation of this manuscript.”

This article was developed independently by members of a working group of the Knowledge Network. This program involved meetings and collaboration between clinicians working in the field of NET around the world, which was organized and funded by Ipsen. The authors were fully responsible for the concept and all content, for all editorial decisions, and for approval of the final version.
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Figure 1
Figure 2

A. Gastric NETs

- Highest IR was in the USA, lowest in Austria
- Increase in IR over time in all countries reporting data
- 16- and 15-fold increase in males and females respectively in the UK between 1971 and 2006

B. Small intestine NETs

- Highest IR was in the USA, lowest in France and Austria
- Increase in IR over time in all countries reporting data

C. Pancreatic NETs

- Little data on IR of pancreatic NETs in Europe
- In general, IRs in the USA seemed higher than in Europe

D. Colon NETs

- In the UK and USA IRs rose approximately 10-fold between the 1970s and the 2000s
- Difficult to ascertain patterns due to different coding of appendiceal NET over time and across the countries
- Highest IRs in Sweden and the UK, lowest in Austria

E. Rectal NETs

- The highest IR was in the USA, lowest in Austria
- In the UK and USA IRs rose approximately 10-fold between the 1970s and the 2000s

F. Appendiceal NETs
<table>
<thead>
<tr>
<th>Country</th>
<th>Method of patient identification for national/regional registry</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norway</td>
<td>Physicians and pathology departments reporting to national registry with check by Norwegian registry of cancer</td>
<td>Hauso et al, 2008</td>
</tr>
<tr>
<td>UK</td>
<td>Regional registries based on ICD-O codes</td>
<td>Ellis et al, 2010</td>
</tr>
<tr>
<td>Switzerland (Vaud)</td>
<td>Voluntary agreement between recording medical institutions and the registry. Unclear how patients are identified</td>
<td>Levi et al, 1993, 2000</td>
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<tr>
<td>Sweden</td>
<td>National registry based on ICD-7 codes</td>
<td>Hemminki &amp; Li, 2001</td>
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<td>Landerholm et al, 2010</td>
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<tr>
<td>Italy (Tuscany)</td>
<td>Regional cancer registry based on ICD-O codes</td>
<td>Crocetti et al. 1997</td>
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<td>Caldarella et al, 2011</td>
</tr>
<tr>
<td>Austria</td>
<td>Registry based on reports from 40/41 pathology departments</td>
<td>Niederle et al, 2010</td>
</tr>
<tr>
<td>France (Burgundy)</td>
<td>Data collected by cancer registry staff using multiple databases: pathology laboratories, university hospitals, local hospitals, private surgeons, oncologists, gastroenterologists, general practitioners, and monthly reviews of death certificates</td>
<td>Lepage et al, 2004, 2006</td>
</tr>
<tr>
<td>Japan</td>
<td>Questionnaire to heads of departments about number of patients with GEP NET</td>
<td>Ito et al, 2010</td>
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</tbody>
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*Surveillance, Epidemiology and End Results

ICD-O: International Classification of Diseases for Oncology,