***ENDOCRINE PRACTICE* Rapid Electronic Article in Press**
Rapid Electronic Articles in Press are preprinted manuscripts that have been reviewed and accepted for publication, but have yet to be edited, typeset and finalized. This version of the manuscript will be replaced with the final, published version after it has been published in the print edition of the journal. The final, published version may differ from this proof.
DOI:10.4158/EP171879.OR

Original Article EP171879.OR

EPIDEMIOLOGY OF GASTROINTESTINAL NEUROENDOCRINE TUMORS IN A US COMMERCIALLY INSURED POPULATION

Michael S. Broder, MD, MSHS[1]; Beilei Cai, PhD[2]; Eunice Chang, PhD[1];
Maureen P. Neary, PhD[2]

Running title: Epidemiology of GI NET

From: [1]Partnership for Health Analytic Research, LLC, Beverly Hills, CA, 90212, [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, 07936-1080.

Corresponding address: Michael S. Broder, MD, MSHS
Partnership for Health Analytic Research, LLC,
280 S. Beverly Drive, Suite 404,
Beverly Hills, CA, 90212, USA
Email: mbroder@pharllc.com

DOI:10.4158/EP171879.OR
© 2017 AACE

Word Counts: abstract 241; manuscript 2,704

Conflict-of-interest statement: Funding for this study was provided by Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080, United States. Beilei Cai and Maureen P. Neary are employees of Novartis Pharmaceuticals Corporation. Michael S. Broder and Eunice Chang are employees of Partnership for Health Analytic Research, LLC (PHAR, LLC), a health services research company paid by Novartis to conduct this research.

DOI:10.4158/EP171879.OR

Abstract

OBJECTIVE: To estimate incidence and prevalence of gastrointestinal neuroendocrine tumors (GI NET) in US commercially insured patients.

METHODS: Retrospective, cross-sectional study using 2009-2014 data from MarketScan and PharMetrics commercial claims databases. Patients were 18-64 years old, and had 1 inpatient or 2 outpatient claims with GI NET, identified by ICD-9-CM codes. Incidence was calculated as number of patients with NET who were disease-free for 2 years prior, divided by number of enrollees and reported as per million per-years (PMPY). Prevalence was calculated as number of GI NET patients divided by number of enrollees per year and reported as PMPY.

RESULTS: The annual number of patients with GI NET identified from 2009-2014 ranged from 2,014-3,413 in MarketScan and 1,436-2,336 in PharMetrics. Incidence increased from 2011-2014: 67.0 -79.1 PMPY in MarketScan and 47.4-58.2 PMPY in PharMetrics. Incidence increased 24.3% in females and 10.7% in males in MarketScan, 17.6% in females and 29.3% in males in PharMetrics. Incidence increased with age and was highest in 45-54 and 55-64 age groups. Prevalence increased from 77.9 to 131.2 PMPY (MarketScan) and 50.8 to 108.9 (PharMetrics) from 2009-2014. Prevalence was generally higher in females than males and highest in 55-64 year olds. These increases may be due to better diagnostics, increased awareness of NET among clinicians and pathologists, and/or actual increase in disease.

CONCLUSION: Clinicians may see GI NET with increasing frequency in the future and may need to become more familiar with its presentation and treatment.

DOI:10.4158/EP171879.OR

Keywords: Gastrointestinal neuroendocrine tumors; Epidemiology; Prevalence; Incidence; Insurance claims

ABBREVIATIONS:

CPT-4 = Current Procedural Terminology 4; **GI =** Gastrointestinal ; **GI NET =** Gastrointestinal neuroendocrine tumors; **ICD-9-CM =** International Classification of Diseases, 9th Revision, Clinical Modification; **ICD-O-3 =** International Classification of Diseases for Oncology; **NET =** Neuroendocrine tumors; **PMPY =** Per million per-years; **SEER US =** Surveillance Epidemiology and End Results.

DOI:10.4158/EP171879.OR

INTRODUCTION

Neuroendocrine tumors (NET) comprise a broad family of rare and often slow growing malignancies. NET can develop anywhere in the body and arise from neuroendocrine cells throughout the endocrine system (1,2). Approximately two-thirds of NET tumors occur in the gastrointestinal (GI) tract, specifically stomach, small intestine, appendix, colon and rectum (3). NET secrete peptides and neuroamines that may cause distinct syndromes (e.g., carcinoid syndrome, glucagonoma), in which case they are referred to as “functional” tumors. Clinical presentation depends on the site of the primary tumor and whether or not they are functional. Surgery may be curative in the early stages, but delayed diagnosis is typical.

While rare, the incidence and prevalence of NET appear to be increasing worldwide (4–8). In a 2008 study using the US Surveillance Epidemiology and End Results (SEER) database, the incidence of NET in the US increased from 10.9 cases per million person-years (PMPY) in 1973 to 52.5 PMPY in 2004 (4) to 69.8 PMPY in 2012 (9). Overall NET prevalence was 350 per 1 million in 2004 (4) and 480 per 1 million in 2012 (9). Only patients with malignant cancers are included in the SEER registries, and the separation of NET into clear-cut benign and malignant categories is not as straightforward as it is for most epithelial malignancies (10). NET that have not invaded adjacent organs or metastasized may not be immediately labeled as malignant. Thus, many small, benign-appearing tumors may not get included in SEER (4).

DOI:10.4158/EP171879.OR

The objective of this study was to update the incidence and prevalence information for GI NET with non-registry based data, specifically insurance claims, using an additional decade of data beyond what had previously been reported.

METHODS

Design and data source

This was a retrospective cohort study using insurance claims data from January 1, 2009 to December 31, 2014. The data were from two large US commercial claims databases: Truven Health MarketScan Commercial Claims and Encounters Database, and IMS Health PharMetrics. The analyses were performed separately using each database and results were compared to check the consistency. The database has information from more than 100 payers of private health insurance for employees and their dependents, covering more than 25 million lives annually. The PharMetrics database is a nonpayer owned integrated claims database of commercial insurers that includes medical and pharmacy claims for more than 70 million unique patients across the US. Both databases contain de-identified adjudicated medical claims (e.g., inpatient and outpatient services) and pharmacy claims (e.g., outpatient prescriptions) submitted for payment by providers, healthcare facilities, and pharmacies. For both data sources, claims include information on each physician visit, medical procedure, hospitalization, drug dispensed, date of service, number of days of medication supplied, test performed and complete payment information. These databases include information about diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnosis codes) and procedures (Current Procedural Terminology 4 [CPT-4] and ICD- 9-CM procedure codes) in the outpatient and inpatient settings. Available

DOI:10.4158/EP171879.OR

patient demographic information are limited to age, gender, and geographic region. Both databases contain a limited number of patients ≥ 65 years old, however, patients ≥ 65 who have commercial insurance are not representative of the broader age group. Therefore, the analysis was restricted to patients <65. The database complies with the Health Insurance Portability and Accountability Act. This study involved the analysis of existing data, and the subjects could not be identified by the investigator, directly or through identifiers linked to the subjects. It was thus exempt from human subjects review under 45 CFR 46 (11).

Cohort selection

Patients at least 18 years of age were identified if they had at least 1 inpatient or 2 outpatient claims with an ICD-9-CM diagnosis code for GI NET (209.0x-209.6x, excluding those codes that do not specify an anatomic site [209.29, 209.30, 209.69]) during any single calendar year from 2009 to 2014. A limitation of using claims data to estimate disease incidence is the inability to know with certainty that the first diagnosis seen in the data represents the first clinical diagnosis of the condition. Therefore, we required patients to have been continuously enrolled for 3 years: the specific calendar year of diagnosis and 2 years prior, with no evidence of disease in the prior 2 years. For example, a cohort of patients identified with GI NET in 2011 must have been enrolled during the entire 2009 to 2011 period, with their first GI NET diagnosis in 2011.

Statistical analysis

DOI:10.4158/EP171879.OR

For each calendar year, we reported the distribution of patient demographics, summarizing continuous variables with means and SDs and categorical variables with patient counts and percentages. Incidence rate was calculated as the number of patients in a particular year divided by the number of all patients who were continuously enrolled across the three year period (year of diagnosis and 2 prior disease-free years). Prevalence was calculated as the number of patients in a particular year divided by the total number of patients continuously enrolled for the entire calendar year. For both incidence and prevalence, rates were reported overall and by sex and age categories (18-24, 25-34, 45-54, and 55-64 years). Because each database had a different denominator, all results are reported separately by database. No statistical testing was performed. All calculations were performed using SAS® version 9.4 (SAS Institute, Cary, NC).

RESULTS

On average, in each year from 2009-2014, 2,767 patients were identified as having GI NET in the MarketScan database. The annual number ranged from 2,014 in 2009 to 3,413 in 2012. In the PharMetrics database, the range was 1,436 in 2009 to 2,336 in 2014, with a mean of 2,025. In both databases, 55% of cases were female (ranging from 54.0% to 56.3%). Nearly half of the cases (43.1 to 49.9%) were patients between 55 and 64 years old (Table 1).

In the MarketScan database, incidence increased from 67.0 PMPY in 2011 to 76.2 PMPY in 2012, before dropping slightly in 2013 to 76.0, and rising to 79.1 in 2014, an overall rise of 18.1% over the time period. In the PharMetrics database, incidence

DOI:10.4158/EP171879.OR

increased each year: from 47.4 PMPY in 2011, to 53.1 in 2012, to 56.0 in 2013, and to 58.2 in 2014, a rise of 22.8% overall (Figure 1, Table 2). The increase occurred in both men and women: 24.3% over the time period in women and 10.7% in men in the MarketScan database; and 17.6% in women and 29.3% in men in the PharMetrics database. With 3 exceptions (all with cell sample size <100), in every year and for both databases, incidence was higher for each successive age group. Incidence was highest in the two oldest groups: 83.3-124.1 PMPY (depending on year and gender) in patients aged 45-54 compared to 122.9-161.2 PMPY in patients 55-64 in MarketScan; and 54.9-78.8 PMPY in patients aged 45-54 compared to 75.5-111.0 PMPY in 55-64 year olds in PharMetrics (Table 2).

Prevalence increased from 77.9 per million per year in 2009 to 131.2 in 2014 in the MarketScan database, a 68.4% increase. The increase over the same period in the PharMetrics database was 114.4%: from 50.8 per million per year in 2009 to 108.9 in 2014 (Figure 2, Table 3). For every year and in both databases, prevalence was higher for each successive age group. Prevalence was highest in 55-64 year olds (between 104.4 to 281.5 per million per year, depending on year and data source). Prevalence was generally higher in females than in males in every age category (Table 3).

DISCUSSION

The incidence and prevalence of GI NET increased considerably over the study period. In the MarketScan database, incidence increased 18.1% from 2011 to 2014, reaching 79.1 PMPY. In the same database, prevalence increased 68.4% between 2009 and 2014, reaching 131.2 cases per million per year. In the PharMetrics database, the

DOI:10.4158/EP171879.OR

results were slightly more dramatic: incidence increased 22.8% from 2011 to 2014 and prevalence increased 114.4% from 2009 to 2014. In each age and gender category, the number of cases identified, incidence, and prevalence, were all higher in the MarketScan database than in the PharMetrics database.

We have no data with which to explain the differences between the two databases we studied, but we considered several possible reasons. MarketScan is sourced primarily from large employers, whereas PharMetrics data are derived from more than 100 health plans. This might lead to underlying differences in the patient population. Neither dataset provides the specific geographic reach of their data, but they might differ substantially. Finally, there may have been differential changes in enrollment over time (e.g., enrollment increased at the end of the year in one data set and mid-year in the other), but our denominators were based on enrollment at a single fixed point in time. This would have artificially lowered (or increased) the calculated incidence and prevalence.

There are many possible reasons for the observed increase in incidence noted in both databases, although determining which reason or reasons are most important was beyond the scope of this study. First, more tumors may be found incidentally over time. Rates of both CT and MRI use in the general population have been steadily increasing, as has the accuracy of these tests (12). Some patients may have their tumors detected simply because they had an abdominal imaging study for another reason. Second, screening colonoscopy rates in the US have been steadily rising, increasing almost 50% over the last decade (13). As screening for colorectal cancer improves, more lower GI NET may be detected. Survival of patients with rectal carcinoid disease has steadily

DOI:10.4158/EP171879.OR

increased in the United States, which would be consistent with both earlier diagnosis and better treatment of the disease (14). A recent analysis of pancreatic NET using SEER data found increases in both incidence and survival and concluded that stage migration, or an increased detection of localized disease, explained at least part of these observations (15). In an exploratory analysis, we investigated the yearly proportion of patients who had endoscopy, CT, ultrasound, or MRI and found no increase from 2010-2014. However, our data included only patients with a diagnosis of NET. A study of the use of these tests in the general population would be worth conducting, but was beyond the scope of the current study. Third, in the last decade, high sensitivity assays for 5-hydroxyindoleacetic acid and chromogranin A, both markers for certain NET, have come into more common use. Increased use of these tests may have improved identification of previously undetected tumors (16). Fourth, pathologists may be improving in their abilities to identify NET. Finally, the underlying rate of the development of NET may be increasing. The increased prevalence would be expected from the combination of increasing incidence (4,9) and improved survival (3,17).

Using data from SEER, the incidence rate for GI NET was reported as 35.3 PMPY for 2012 (9), whereas we estimated 58.2 PMPY in one database and 79.1 PMPY in the other in 2014. Although our results are consistent with a continued increase in incidence, comparing these findings directly to prior estimates presents several challenges. First, SEER, the source of data for the 2008 and 2016 studies, is a coordinated system of population-based cancer registries located across the US. The SEER Program collects cancer incidence and survival data from 18 geographic areas,

DOI:10.4158/EP171879.OR

together representing about 1/4 of the US population (18). The insurance claims used in the present study, in contrast, are a convenience sample, albeit an extremely large one. Based on information provided by MarketScan and PharMetrics, the combined databases have claims for a geographically dispersed sample representing about 1/3 of the US population. Second, we were able to use data through 2012, 2 years more recent than SEER. Third, SEER includes patients of all ages, the current study only included patients 18-64 years of age. About 95% of individuals ≥ 65 are covered by Medicare (19). A small number of patients in this age group would have been available for inclusion in our study (e.g. they had commercial insurance as the primary payer, and therefore, their data were included in our databases), but they do not represent typical Medicare-age patients, and thus were excluded from analysis. Fourth, SEER registrars are trained and provided with software to improve their ability to accurately code reportable cancers. Claims coding is performed by a mix of care providers and professional coders. A study of ICD-9-CM codes for 32 conditions (not including NET) found a median PPV of 80.7%, a mean of 77%, and a range of 23% to 100% (20). We found no published studies reporting similar statistics related to ICD-9-CM codes for NET. The only data available to indicate diagnosis are contained in ICD-9-CM codes; there are no test results included. An important limitation of the databases used in this study is that privacy restrictions prohibited us from attempting to identify the patients in our study, which would be a necessary first step in linking the claims data to histopathology results. We are not aware of any formal validation of the codes we used against a gold standard like pathology reports. Fifth, the coding systems differ between SEER and insurance claims. SEER currently uses the International Classification of

DOI:10.4158/EP171879.OR

Diseases for Oncology system (ICD-O-3), whereas claims use ICD-9-CM (and, since 2015, ICD-10). While the systems can be mapped to each other, the mapping is not one-to-one. NET represent an unusual tumor type for which the traditional labels of benign and malignant are a poor fit. While classification has evolved considerably in the last several decades, NET are now generally described by their anatomic locations (e.g., GI or lung), degree of differentiation (either “well” or “poorly”), and proliferative index (mitotic activity). Small, well differentiated NET may thus have been overlooked for inclusion into SEER (4).

ICD-9-CM codes provide information on the specific anatomic location of the tumors we studied (e.g., 209.11 is malignant neuroendocrine carcinoma of the appendix), but this location information is contained in the last digit of the 5-digit code. Insurance payment is rarely contingent on this level of specificity, so 5th digit codes are often omitted entirely or are inaccurate (ICD-10-CM coding is expected to improve this problem). In an exploratory analysis, we found the distribution of anatomic locations coded by this 5th digit were significantly different from what would be expected based on clinical data. A further limitation of claims data is the inability to identify with certainty whether a case is truly incident or represents a patient who simply did not present for care for a prolonged period. We required continuous enrollment for 2 years before the first NET claim to reduce this source of uncertainty. Prevalent patients would have to have had no care for their condition for more than 2 years to have been incorrectly counted as incident cases.

Despite these differences, both the prior SEER study and the current study have identified an increasing incidence of GI NET. The consistent pattern in 3 databases over more than 4 decades strongly suggests the increase in GI NET cases is not an artifact

DOI:10.4158/EP171879.OR

of the database chosen, the method used, or changes in patient enrollment over time. Recent increases in other cancer types have a variety of explanations. At least some portion of the recent increases in thyroid cancer appears to result from improved screening (21), but there also appears to be an underlying increase in disease incidence as well (22). In NET, multiple mechanisms may be operating, and studies using other sources of data will be required to determine the extent to which each contributes to the observed rise. Prevalence is also increasing, which may be explained both by the increase in incidence and an increase in survival as a result of new therapies (9).

CONCLUSION

Regardless of the underlying cause, comparing our data with prior data suggest the incidence of GI NET has increased between 66% and 216% over the last ten years. Gastroenterologists, oncologists, and other physicians may see patients with these tumors with increasing frequency in years to come and may thus need to become more familiar with the presentation and treatment of this disease. Health plans will also see an increase in this previously rare disease and should consider ways to effectively manage this population. Finally, because higher incidence brings higher costs, studies assessing the increasing economic burden of this disease are warranted.

DOI:10.4158/EP171879.OR

Acknowledgements

Funding: This study was supported by Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080, United States.

DOI:10.4158/EP171879.OR

References

1. **Korse CM, Taal BG, van Velthuysen MLF, Visser O.** Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: Experience of two decades of cancer registry. *Eur J Cancer*. 2013;49:1975–1983.
2. **Modlin IM, Oberg K, Chung DC, et al.** Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. 2008;9:61–72.
3. **Tsikitis VL, Wertheim BC, Guerrero MA.** Trends of Incidence and Survival of Gastrointestinal Neuroendocrine Tumors in the United States: A Seer Analysis. *J Cancer*. 2012;3:292–302.
4. **Yao JC, Hassan M, Phan A, et al.** One Hundred Years After 'Carcinoid': Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. *J Clin Oncol*. 2008;26:3063–3072.
5. **Ito T, Igarashi H, Nakamura K, et al.** Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. *J Gastroenterol*. 2015;50:58–64.
6. **Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S**. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer*. 2015;121:589–597.
7. **Tsai YC, Ho CH, Tai HC, Chung SD, Chueh SC.** Laparoendoscopic single-site versus conventional laparoscopic total extraperitoneal hernia repair: a prospective randomized clinical trial. *Surg Endosc*. 2013;27:4684–4692.

DOI:10.4158/EP171879.OR

8. **Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD.** Knowledge NETwork. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. *Endocr Relat Cancer*. 2014;21:R153–R163.
9. **Dasari A, Shen C, Halperin D, et al**. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.* Forthcoming 2017.
10. **Boudreaux JP, Klimstra DS, Hassan MM, et al.** North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. *Pancreas*. 2010;39:753–766.
11. US Department of Health and Human Services. Protection of Human Subjects. *Federal Register.* 1991;56:28012,28022.
12. **Smith-Bindman R, Miglioretti DL, Johnson E, et al.** Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996-2010. *JAMA*. 2012;307:2400–2409.
13. **National Center for Health Statistics**. Health, United States, 2014: With Special Feature on Adults Aged 55–64. Hyattsville, MD. 2015.
14. **Scherübl H.** Rectal carcinoids are on the rise: early detection by screening endoscopy. *Endoscopy*. 2009;41:162–165.
15. **Alsidawi S, Westin GF, Hobday TJ, Halfdanarson TR.** Pancreatic Neuroendocrine Tumors: A Population-based Analysis of Epidemiology and Outcomes. Gastrointestinal Cancers Symposium; 2017; San Francisco, CA.

DOI:10.4158/EP171879.OR

16. **Bajetta E, Ferrari L, Martinetti A, et al.** Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. *Cancer*. 1999;86:858–865.
17. **Modlin IM, Lye KD, Kidd MA.** 50-year analysis of 562 gastric carcinoids: small tumor or larger problem? *Am J Gastroenterol*. 2004;99:23–32.
18. **National Cancer Institute**. SEER as a Research Resource. Available at: http://seer.cancer.gov/about/factsheets/SEER_Research_Brochure.pdf.
19. **Smith JC, Medalia C,** U.S. Census Bureau, Current Population Reports, P60-253, Health Insurance Coverage in the United States: 2014, U.S. Government Printing Office, Washington, DC, 2015.
20. **Quan H, Li B, Saunders LD, et al.** Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res*. 2008;43:1424e1441.
21. **Davies L, Welch HG.** Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA*. 2006;295:2164–2167.
22. National Cancer Institute. A Snapshot of Thyroid Cancer. 2014. Available at: https://www.cancer.gov/research/progress/snapshots/thyroid. Accessed Nov 9, 2016.

DOI:10.4158/EP171879.OR

Tables and Figures

Table 1a. Patients with GI NET in MarketScan Database, N[a]

	2009	2010	2011	2012	2013	2014
N	2,014	2,334	3,018	3,413	2,915	2,910
Age, year, n (%)						
18-24	52 (2.6)	53 (2.3)	73 (2.4)	76 (2.2)	60 (2.1)	57 (2.0)
25-34	120 (6.0)	142 (6.1)	155 (5.1)	181 (5.3)	167 (5.7)	138 (4.7)
35-44	265 (13.2)	294 (12.6)	376 (12.5)	399 (11.7)	370 (12.7)	359 (12.3)
45-54	709 (35.2)	808 (34.6)	1,036 (34.3)	1,147 (33.6)	944 (32.4)	966 (33.2)
55-64	868 (43.1)	1,037 (44.4)	1,378 (45.7)	1,610 (47.2)	1,374 (47.1)	1,390 (47.8)
Female	1,108 (55.0)	1,272 (54.5)	1,658 (54.9)	1,863 (54.6)	1,641 (56.3)	1,622 (55.7)

[a] Adult patients (age 18 years or older) with ≥ 1 inpatient or ≥ 2 outpatient claims for GI NET in a calendar year. Patients may have been identified in multiple calendar years. Continuous enrollment not required.

DOI:10.4158/EP171879.OR

Table 1b. Patients with GI NET in PharMetrics Database, N[a]

	2009	2010	2011	2012	2013	2014
N	1,436	1,836	2,077	2,207	2,260	2,336
Age, year, n (%)						
18-24	44 (3.1)	50 (2.7)	53 (2.6)	57 (2.6)	42 (1.9)	54 (2.3)
25-34	84 (5.8)	114 (6.2)	119 (5.7)	124 (5.6)	144 (6.4)	114 (4.9)
35-44	163 (11.4)	197 (10.7)	239 (11.5)	267 (12.1)	265 (11.7)	272 (11.6)
45-54	503 (35.0)	610 (33.2)	721 (34.7)	735 (33.3)	695 (30.8)	730 (31.3)
55-64	642 (44.7)	865 (47.1)	945 (45.5)	1,024 (46.4)	1,114 (49.3)	1,166 (49.9)
Female	800 (55.7)	991 (54.0)	1,171 (56.4)	1,196 (54.2)	1,255 (55.5)	1,299 (55.6)

[a] Adult patients (age 18 years or older) with ≥ 1 inpatient or ≥ 2 outpatient claims for GI NET in a calendar year. Patients may have been identified in multiple calendar years. Continuous enrollment not required.

DOI:10.4158/EP171879.OR

Table 2a. GI NET Incidence Rate in MarketScan Database, Cases Per Million Person-Years[a]

		2011	2012	2013	2014
Gender	**Age**				
Female	18-24	17.5	15.7	16.1	16.4
	25-34	15.2	34.2	43.9	23.9
	35-44	33.1	43.1	54.6	54.0
	45-54	91.1	105.8	97.8	124.1
	55-64	122.9	123.9	129.3	135.5
	All Female	68.2	76.8	79.0	84.8
Male	18-24	9.5	13.0	16.9	11.1
	25-34	14.8	23.2	21.6	27.1
	35-44	32.7	37.1	37.5	39.4
	45-54	87.0	83.3	94.0	94.5
	55-64	124.6	161.2	139.0	140.0
	All Male	65.7	75.4	72.6	72.7
All Patients		**67.0**	**76.2**	**76.0**	**79.1**

[a] Cases of adults with ≥ 1 inpatient or ≥ 2 outpatient claims for GI NET in listed year and continuous enrollment in year listed and two years prior) ÷ number of members with continuous enrollment in same period.

DOI:10.4158/EP171879.OR

Table 2b. GI NET Incidence Rate in PharMetrics Database, Cases Per Million Person-Years[a]

		2011	2012	2013	2014
Gender	**Age**				
Female	18-24	8.6	7.5	8.3	16.4
	25-34	18.6	16.5	30.5	21.2
	35-44	29.5	35.9	38.4	38.0
	45-54	69.9	69.8	74.6	78.8
	55-64	85.1	75.5	101.9	103.1
	All Female	51.6	49.6	60.0	60.7
Male	18-24	4.8	10.9	5.7	10.0
	25-34	16.7	10.0	3.7	19.6
	35-44	20.5	28.7	22.3	33.1
	45-54	54.9	76.3	68.7	63.2
	55-64	80.6	106.9	108.3	111.0
	All Male	43.0	56.9	51.8	55.6
All Patients		**47.4**	**53.1**	**56.0**	**58.2**

[a] Cases of adults with ≥ 1 inpatient or ≥ 2 outpatient claims for GI NET in listed year and continuous enrollment in year listed and two years prior) ÷ number of members with continuous enrollment in same period.

DOI:10.4158/EP171879.OR

Table 3a. GI NET Prevalence in MarketScan Database, Cases Per Million Per Year[a]

		2009	2010	2011	2012	2013	2014
Gender	**Age**						
Female	18-24	20.0	21.2	23.4	25.8	19.2	20.9
	25-34	33.5	28.5	39.5	42.6	52.4	35.2
	35-44	59.2	65.1	68.1	75.2	88.1	95.7
	45-54	107.1	124.4	152.9	179.7	182.3	204.5
	55-64	146.0	170.5	213.8	236.9	265.2	274.7
	All Female	81.6	93.0	111.7	125.5	135.8	141.6
Male	18-24	12.2	11.5	14.2	14.7	18.9	16.8
	25-34	18.7	29.4	22.4	27.6	25.8	25.2
	35-44	30.5	40.4	52.1	54.5	57.9	57.0
	45-54	95.9	114.9	138.1	147.5	150.7	159.2
	55-64	173.0	193.6	219.5	272.0	269.8	289.3
	All Male	73.7	88.2	99.6	113.3	114.9	119.7
All Gender	18-24	16.2	16.5	18.8	20.2	19.0	18.8
	25-34	26.6	28.9	31.5	35.5	40.0	30.5
	35-44	45.6	53.5	60.5	65.4	73.8	77.4
	45-54	101.9	120.0	146.0	164.6	167.5	183.2
	55-64	158.7	181.2	216.4	253.3	267.3	281.5
All Patients		**77.9**	**90.8**	**106.0**	**119.7**	**125.9**	**131.2**

[a] Cases of adults with ≥ 1 inpatient or ≥ 2 outpatient claims for GI NET in listed year and continuous enrollment in year listed ÷ number of members with continuous enrollment in same period

DOI:10.4158/EP171879.OR

Table 3b. GI NET Prevalence in PharMetrics Database, Cases Per Million Per Year[a]

		2009	2010	2011	2012	2013	2014
Gender	**Age**						
Female	18-24	18.0	19.0	21.0	18.4	21.0	21.0
	25-34	23.5	29.2	34.6	36.3	46.9	33.5
	35-44	31.5	41.5	50.7	61.3	70.6	77.2
	45-54	74.9	101.4	125.2	127.0	137.5	145.0
	55-64	99.1	133.5	154.1	177.1	210.8	243.3
	All Female	55.6	74.3	87.8	95.4	109.6	117.7
Male	18-24	5.8	7.6	8.9	14.2	5.8	10.0
	25-34	10.2	17.4	19.0	15.5	18.1	20.4
	35-44	17.4	28.9	35.3	39.9	42.4	40.5
	45-54	55.1	78.7	93.7	119.1	115.1	128.7
	55-64	110.3	160.8	162.1	184.9	213.7	243.4
	All Male	45.6	67.7	72.7	84.8	89.7	99.9
All Gender	18-24	11.9	13.3	14.9	16.3	13.2	15.4
	25-34	17.2	23.6	27.1	26.2	32.8	27.0
	35-44	24.7	35.5	43.3	51.0	56.9	59.2
	45-54	65.5	90.6	110.2	123.2	126.7	137.1
	55-64	104.4	146.5	157.9	180.8	212.2	243.4
All Patients		**50.8**	**71.1**	**80.5**	**90.3**	**99.9**	**108.9**

[a] Cases of adults with ≥ 1 inpatient or ≥ 2 outpatient claims for GI NET in listed year and continuous enrollment in year listed ÷ number of members with continuous enrollment in same period

DOI:10.4158/EP171879.OR

Figure 1 GI NET Incidence Rate, Cases Per Million Person-Years. In the MarketScan database, incidence increased from 67.0 PMPY in 2011 to 76.2 PMPY in 2012, before dropping slightly in 2013 to 76.0, and rising to 79.1 in 2014, an overall rise of 18.1% over the time period. In the PharMetrics database, incidence increased each year: from 47.4 PMPY in 2011, to 53.1 in 2012, to 56.0 in 2013, and to 58.2 in 2014, a rise of 22.8% overall.

Figure 2 GI Net Prevalence Rate, Cases Per Million Per Year. Prevalence increased from 77.9 per million per year in 2009 to 131.2 in 2014 in the MarketScan database, a 68.4% increase. The increase over the same period in the PharMetrics database was 114.4%: from 50.8 per million per year in 2009 to 108.9 in 2014.

DOI:10.4158/EP171879.OR

Figure 1 GI NET Incidence Rate, Cases Per Million Person-Years

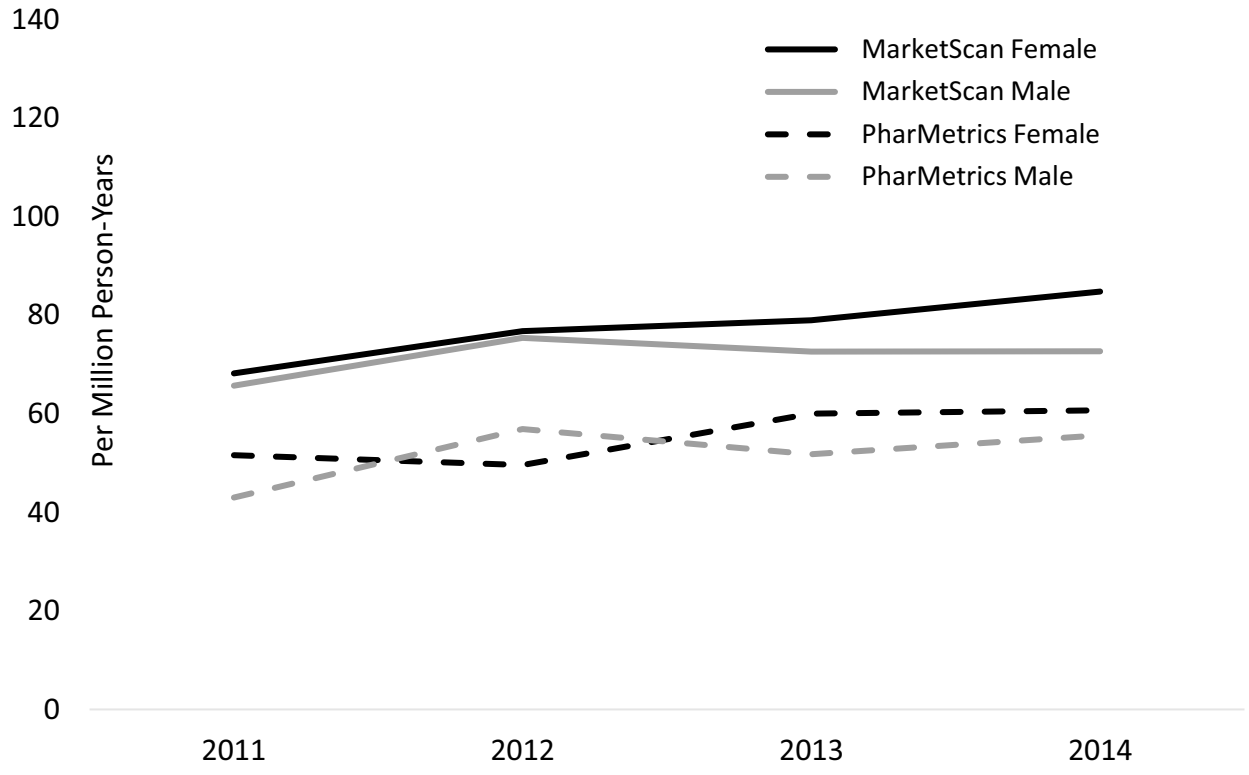

Figure 2 GI Net Prevalence Rate, Cases Per Million Per Year