Improving Time-to-Diagnosis for Neuroendocrine Tumours

Report for the Canadian Neuroendocrine Tumour Society (CNETS)

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1. Introduction

1.1. What are Neuroendocrine Tumours?

Neuroendocrine Tumors (NETs) represent a spectrum of rare, highly heterogenous, slow growing tumors that arise from neuroendocrine cells in a multitude of organs [1]–[3]. The most common sitesfor NETs are the gastrointestinal system and the lungs, accounting for 65% and 25% of all cases respectively [4]. However, NETs are not limited to these two regions, they can also arise in areas such as the pituitary, thyroid, pancreas, ovaries and adrenal glands [5]–[7]. NETs usually occur in late adulthood but can occur in children and adolescents as well, where aggressive forms lead to both higher morbidity and mortality [4], [8].

Previously considered rare tumours, recent statistics paint a different picture: Prevalence and incidence of NETs are on the rise, with a doubling of the incidence in Canada between 1994 and 2009 [5], [9]. The current incidence rate in Canada is 5.86 per 100,000 [9]. Moreover, this increase in incidence of NETs has been reported worldwide [5], [9], [10], with a seemingly upward trend [9], [11], [12]. Today, due to prolonged survival of patients with active disease, there are currently more people living with NETs than there are people living with some non-neuroendocrine tumours such as esophageal, gastric and pancreatic cancer [9], [10], [13].

The vast majority of NETs occur sporadically, but some can be associated with underlying genetic conditions such as von Hippel-Lindau (VHL) or Types 1 and 2 Multiple Endocrine Neoplasia (MEN 1 & MEN2), which can affect families [4], [14].

The delay in diagnosis of NETs has serious implications for patients and the healthcare system. So, what happens following a delayed diagnosis? Population-based studies and retrospective chart reviews depict an unfortunate reality. When patients are finally diagnosed, many will show metastases. About 20% by some accounts, and in excess of 60% by others [5], [9], [15]–[17]. During this long diagnostic journey, patients will see multiple specialists and make many doctor visits [17]. Furthermore, patients are likely to be misdiagnosed with common conditions such as irritable bowel syndrome and menopause [17].

In addition to the risk of deteriorating health, patients can suffer NET symptoms for years before a diagnosis is made, taking a toll on their lives, their mental health and their personal relationships [17], [18]. This is unnecessary suffering when treatments do exist and are effective at controlling symptoms [19], but how is a patient supposed to get the treatment they need if they haven’t been diagnosed yet? Research that explores the causes for the delay in diagnosis can pave the way for mitigating those delays. Once the sources contributing to the delay are identified, targeted actions can be taken to reduce the delay and achieve faster diagnoses for NETs. This will have a tremendous impact on NET patient care.

1.2. How are NETs diagnosed?

NETs are associated with common and non-specific symptoms, or symptoms that do not appear until more advanced stages of the disease, which often leads to delays in diagnosis [18], [20], [21]. NETs may be discovered incidentally or following suspicion from clinical symptoms. Some NETs can secrete biologically active hormones that lead to hormone-related symptoms, while others do not. Symptoms of gastrointestinal and pancreatic NETs can include abdominal pain, diarrhea, gastrointestinal bleeding, bowel obstruction and skin flushing. Lung NETs can cause symptoms such as cough, hemoptysis and recurring infections [15], [16], [22]–[25]. More extreme manifestations can occur when NETs lead to debilitating syndromes such as Carcinoid Syndrome, Zollinger-Ellison, Whipple Triad, 4D Syndrome, Somatostatinoma Syndrome and Verner-Morrison, and Cushing Syndrome [23]–[26].

Establishing a NET diagnosis requires a multidisciplinary effort from specialists and is based on results from pathology testing, biochemical testing and diagnostic imaging [27]. When hormone-related symptoms lead to a suspicion of a NET, a patient will undergo a 24-hour urine 5HIAA test. Another lab test used for NETs is Chromogranin A [27]. In terms of imaging, there are multiple modalities that can be used, which range from MRI and CT scans, to NET-specific imaging techniques which exploit unique characteristics of the tumour. Some NET-specific imaging modalities are currently of limited availability in Canada and are reserved to subspecialty centres [27]. However, pathology testing of a tissue sample remains essential for a NET diagnosis [28], [29].

1.3. What are we trying to do?

One of the biggest problems affecting NET patients is the frequent delay in reaching a diagnosis. This is currently believed to happen because NET symptoms are not very specific, and the disease is perceived to be rare [17], [30]. In fact, the delay is often substantial: A recent international survey has shown that the mean reported delay time from first symptom to confirmed diagnosis was 52 months – or just over 4 years – but can be as long as 9 years [17], [18]. This has severe consequences, leading to increased suffering for patients, and putting a pressure on our health care system [17]

The aim of this project is to determine why these long delays occur in the diagnosis of Neuroendocrine tumours by determining where in their diagnostic journeys do patients face the delay and identifying the factors that lead to diagnostic delays.

Research Questions:

1. In which phase/s of the diagnostic journey do patients experience delays (pre-suspicion, suspicion and undergoing medical tests, medical imaging)
2. What are the factors that contribute to a delayed diagnosis?

1.4. Impact Statement

This study is the starting point for designing interventions to improve NET diagnosis, and ultimately NET

patient care. Reducing the delay and improving NET diagnosis will likely lead to improved patient outcomes. The findings of this research highlight two main points:

- There are steps that can be taken immediately that may improve diagnostic time for NET patients
- There are specific areas warranting further investigation, that may ultimately lead to the improvement of NET patient care.

2. Methods

The target population in this study was current and past Neuroendocrine Tumour (NET) patients that are on the mailing list of the Canadian Neuroendocrine Tumour Society (CNETS). The survey was entirely voluntary, no personal information or contact information was collected, and the participant was fulling informed about the study objectives and the measures in place to protect their data. A question asking for consent was used at the end of the survey to collect participant consent. Answering "yes" to the consent question was mandatory to start the survey. No information was collected until the participant clicked submit at the end of the survey, that way, the participant had the option to change their mind at any time about participating in the study.

Inclusion Criteria:

- Participant age over 18 years
- History of any type of Neuroendocrine Tumour

Exclusion Criteria:

- No history of a Neuroendocrine Tumour
- Participant under 18 years of age

Questions about the participant's history with Neuroendocrine Tumours were adapted from a question bank from the International Neuroendocrine Cancer Alliance (INCA). Questions about the diagnostic journey and patient experience were developed by the researcher in consultation with the Translational Research Program advisor, Dr. Edyta Marcon and the members of the project's advisory committee: Jackie Herman (CNETS President) and Dr. Gregory Fairn (Scientist, Unity Health). The survey was tested with a patient collaborator to ensure inclusiveness and diversity of response options. The final survey contained 35 questions and took around 15 minutes to complete. The study along with all its material was approved by the University of Toronto's Research Ethics Board (Protocol #39302).

2.1. Data Collection and Analysis

The link to the anonymous survey was disseminated through CNETS' email list, Facebook page and Twitter account on July 9, 2020. The survey was closed on August 24, 2020 at which point 106 participants had completed the survey. Multiple choice data coding and analysis was performed using

SPSS® and Microsoft® Excel®. Descriptive statistics were used due to the lack of counterfactual. Free text responses were coded using Quirkos® (Quirkos Limited, Version 2.3), which was used to generate quotes. Data coding was done in consultation with Dr. Radhika Yelamanchili (Medical Oncologist, Niagara Health), a member of the project's advisory board.

3. Results & Discussion

3.1. Patient Characteristics

Among the 106 respondents, 83 completed both the multiple-choice and the short answer portions of the survey. The average time to completion was 18 minutes. Most respondents were female (69/106). Most participants identified as White or Caucasian (99/106). Respondent age was collected as an age-range. Most respondents were between ages 55-64 (41 respondents), with some 65+ (36 respondents), 45-54 (22 respondents), 35-44 (6 respondents), and 1 respondent was under the age of 25.

The mean age at diagnosis of survey participants was 52. A similar survey-based study out of the UK in 2018 reported a mean age at diagnosis of 51.6 years [31]. Large scale epidemiological studies have reported a mean age at diagnosis of 62 years in the United States [5] and 60.9 years in Ontario, Canada [9]. In this respect, our results follow closely previously reported studies. Survey participants came mainly from Ontario, Canada, but other provinces were represented as well. In addition, 8 participants lived in the United States, 1 lived in Germany, and 1 participant lived in Canada for part of their diagnostic journey and outside of Canada (location not specified) for the other part (**Figure 1**).

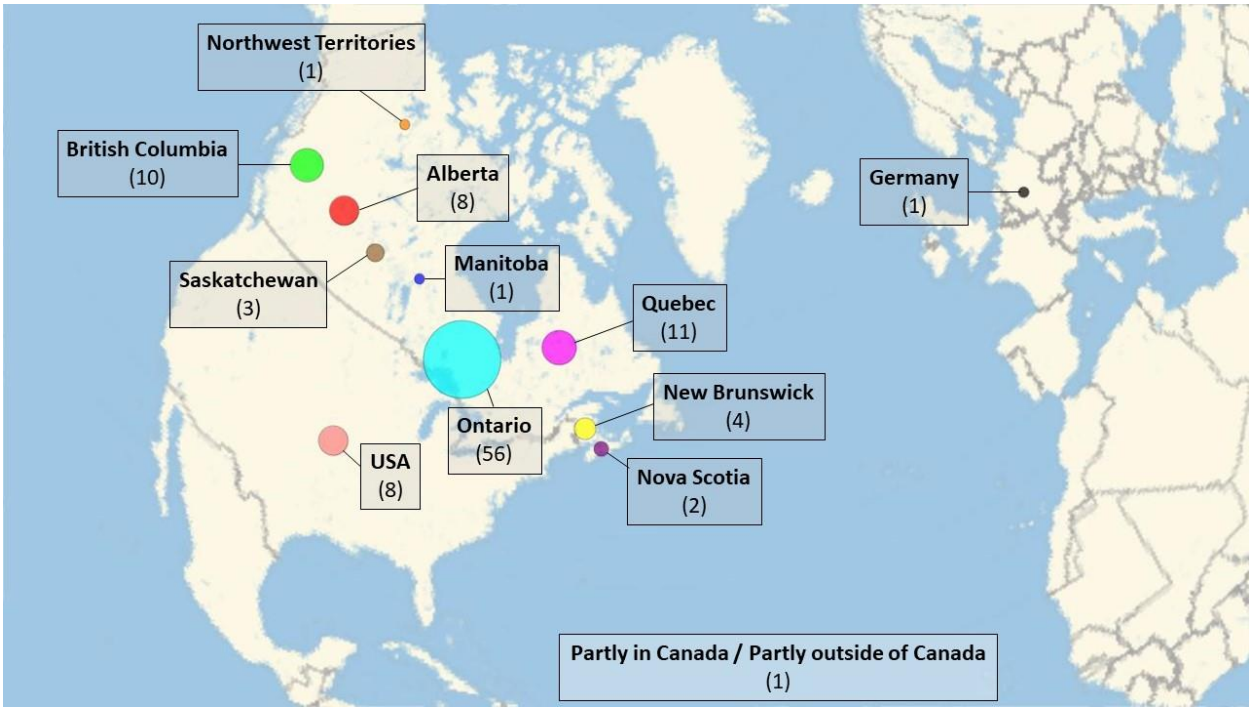


Figure 1. Geographical distribution of survey participants. The location signifies where the participants lived during the pre-diagnosis period.

3.2. Disease Characteristics

The most common primary sites for NETs were found to be small intestine, pancreatic, and lung (**Table 1**). In previous studies from US (1973 to 2004, SEER 9 registry) [5], and Ontario (OHIP) from 1994 to 2009 [9] it was shown that lung NETS are the most common. Similarly, a UK study on delays and routes to diagnosis reported the most common primary sites as small intestine, pancreas, and lung respectively [31]. Our findings agree with the previous studies.

Table 1. Primary NET site at the time of diagnosis. Summary table with number of cases, gender distribution, mean age at diagnosis and mean symptom severity stratified by primary site of NET. Ranges are presented next to mean values in brackets. Severity of symptoms is measured on a scale of 0 to 10, with 0 being no symptoms at all, and 10 being very severe symptoms.

		Count by Gender			
Primary Site	**No.**	**Males**	**Females**	**Mean severity of symptoms**	**Mean age at diagnosis**
Small Intestine (Duodenal, Jejunal, Ileal)	45	13	32	5.4 (0 – 10)	54.8 (33 – 74)
Pancreatic	19	6	13	5.2 (0 – 10)	49.3 (10 – 75)
Lung	14	3	11	6.6 (0 – 10)	46.1 (10 – 65)
Colon	5	3	2	4.6 (0 – 10)	55.8 (45 – 71)
NET of unknown origin	4	1	3	5.5 (0 – 10)	57.3 (42 – 66)
Appendix	3	2	1	4 (0 – 7)	52.7 (43 – 59)
Cecum	3	1	2	7.3 (6 – 10)	54 (50 – 60)
Genetic/Inherited NET Syndrome	3	3	0	6.3 (0 – 10)	44.7 (30 – 55)
Rectum	2	0	2	8.5 (7 – 10)	51.5 (45 – 58)
Thymic	1	1	0	0 (0)	63 (63)
Other - Liver	1	1	0	5 (5)	65 (65)
Other - Mesentery	1	0	1	10 (10)	49 (49)
Other - "Bowel"	2	0	2	6.5 (6 – 7)	46 (45 – 47)
Other - "Small bowel mesentery"	1	1	0	4 (4)	70 (70)
Other - "Pheochromocytoma and Neurofibromatosis"	1	1	0	7 (7)	31 (31)
I do not know	1	1	0	3 (3)	61 (61)

3.3. Incidental Cases

Incidental findings are extra discoveries found by a medical test that is unrelated to the reason the test was ordered in the first place [32]. There were multiple questions on the survey that gave participants the option to indicate that their NET was discovered incidentally. This option choice – the "NET discovered incidentally" choice – was mutually exclusive to the other option choices in the question. A careful examination of individual level data revealed many instances in which the diagnosis was misidentified as

incidental. In order to overcome that, each case was sorted by the researcher as incidental or non-incidental based on the definition of "incidental finding" described above.

Following this sorting, 30 out of 106 participants were identified as having been diagnosed with NETs as a result of an incidental finding. This represents a substantial proportion of the total sample, and given the unique dynamic of an incidental diagnosis, these 30 cases were subjected to a discrete analysis separate from the 76 non-incidental cases. The results from these analyses can be found under **Section 3.11. An Analysis of Incidental Findings.**

3.4. Delay in Diagnosis

The time to diagnosis in this study was measured as the time from the appearance of the first symptom until confirmed diagnosis. The majority of survey participants experienced a long time to diagnosis (**Figure 2**). This is in agreement with the delay reported by a UK survey study which reported an average time to diagnosis of about 4.5 years [31].

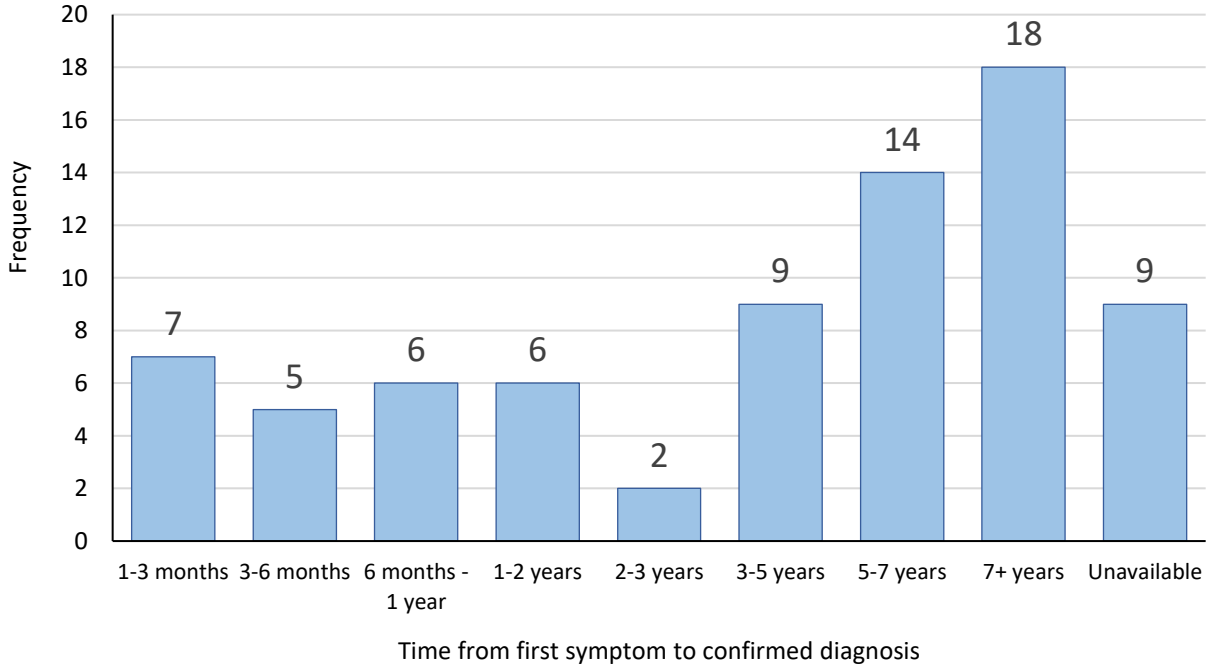


Figure 2. Time-to-Diagnosis. Time from the first symptom to confirmed diagnosis for non-incidental cases (n=76). "Unavailable" means that the participant chose an answer choice that does not denote time. There were two such answer choices: "I did not experience symptoms" and "NET discovered incidentally."

In this study, a timely diagnosis is defined by a time to diagnosis of 6 months or less. A diagnosis that took over 6 months will be defined as a delayed diagnosis. Given these definitions, most participants from this study experienced a delay in diagnosis (55 participants) – excluding those for which time-to-diagnosis information is unavailable and excluding incidental cases. Additionally, it appears most participants experienced a delay in diagnosis regardless of whether they lived in an urban, suburban, or rural area (**Table 2**).

Table 2. Delay in diagnosis based on type of residence. Delay in diagnosis is tabulated against the type of residence indicated by participants. Table is based non-incidental cases (n=76).

	Type of Residence				
Delay Status	**Urban**	**Suburban**	**Rural**	**Missing**	**Total**
Delay (over 6 months)	19	28	8	-	55
Timely (under 6 months)	5	4	3	-	12
Unknown	1	4	3	1	9
Grand Total	**25**	**36**	**14**	**1**	**76**

3.5. Time to suspicion is a major contributor to the delay in diagnosis

While similar studies have examined the delay to diagnosis, no study has so far deconstructed this delay in diagnosis into distinct phases to assess which phase contributes the most to the diagnosis. In this study survey participants were asked about how long it took until their doctor suspected they may have NETs, and how long it took from when they started being tested for NETs until they've received a diagnosis. Here, two peaks – one at "less than 6 months," and one at "3+ years" can be seen (**Figure 3**). It seems that for most participants time to suspicion is either short or very long. As for the participants who indicated "NET was discovered incidentally" – but were determined not to be truly incidental findings – a case-by-case analysis revealed that participants used this answer choice because their NETs were never suspected at all. The same applies to the one participant who indicated "this does not apply to me." This case-by-case analysis is presented in **Tables S1** and **S2** in **Appendix A: Supplementary Information**. Therefore "NET discovered incidentally" can be considered as "NETs were never suspected" instead (**Figure 3**). This further supports the idea that time to suspicion is situated at two extremes – NETs are either suspected early, extremely late, or never suspected at all. On the other hand, it seems like most participants spent less than 6 months getting tested for NETs (**Figure 4**). This shows that once a suspicion has been made, testing time is reasonably short and does not contribute substantially to the delay in diagnosis.

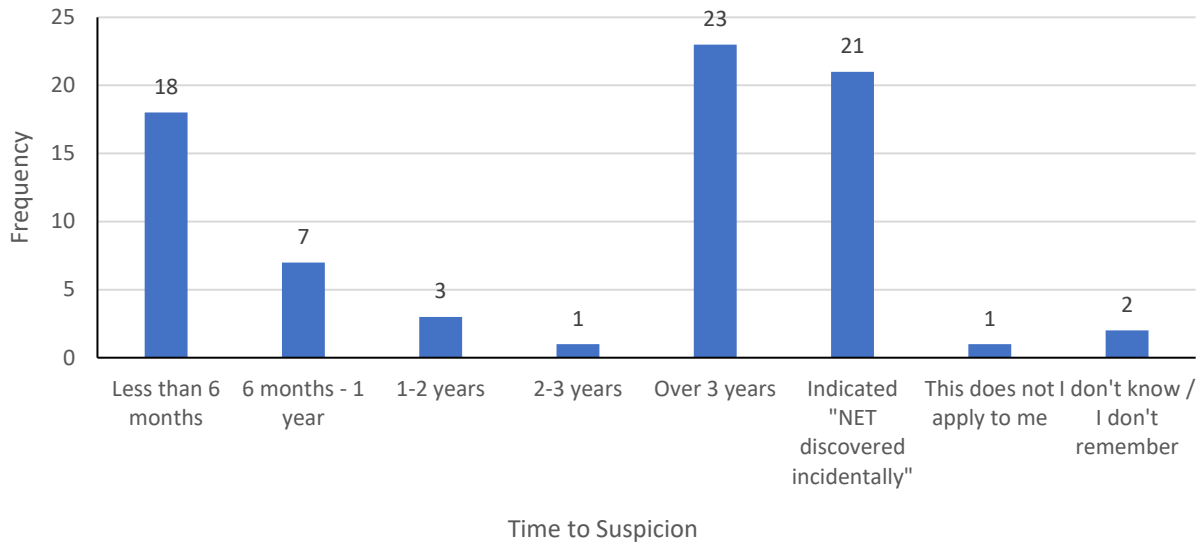


Figure 3. Time to suspicion of NETs for non-incidental cases. The time to suspicion was collected in the survey using the question: *"Approximately how long did it take until your doctor suspected you might have NETs?"* A choice was given to indicate if the NET was discovered incidentally, but given that this data is from a non-incidental subset, further analyses showed that the *"NET discovered incidentally"* field can be thought of as *"NETs were never suspected."* Figure is based non-incidental cases (n=76).

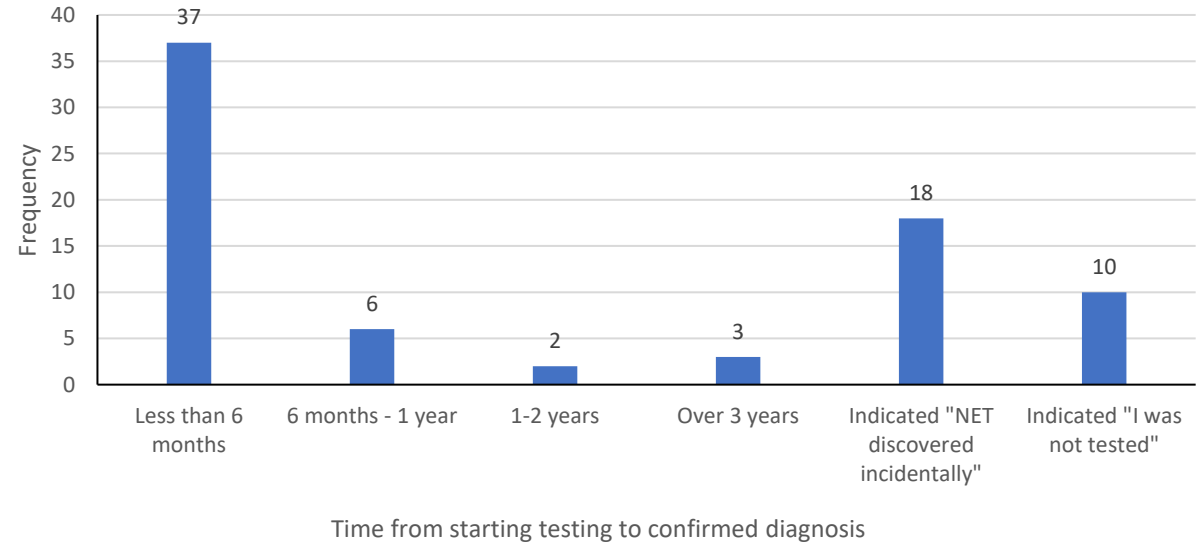


Figure 4. Time from starting testing for NETs, until confirmed diagnosis. Time from testing to diagnosis was collected using the question: *"Approximately how long did it take from when you started being tested for NETs until you received a final diagnosis?"* A choice was given to indicate if the NET was discovered incidentally, but given that this data is from a non-incidental subset, further analyses showed that the *"NET discovered incidentally"* field was chosen by participants who were diagnosed after finding the tumour on a scope/imaging, following surgery, or after ER admission (see **Table S3**). Participants who indicated they were not tested were given the option to comment on why they were not tested. The responses are documented in **Table S4** in **Appendix B: Supplemental**

Information. These responses echo the reasons described above for those who indicated an incidental discovery. Figure is based non-incidental cases (n=76).

Furthermore, those who were diagnosed in a timely manner experienced shorter time to suspicion, while those who had a severely delayed diagnosis experienced a suspicion period of over 3 years (**Table 3**). However, both sets of participants, those with timely and those with delayed diagnosis periods shared a short testing time of less than 6 months (**Table 4**).

Table 3. Delay severity and the time to suspicion. This table shows the relationship between the delay in diagnosis and time to suspicion. Delay severity is ranked based on the time to diagnosis from first symptom: Timely = less than 6 months; Slight Delay = 6 months – 1 year; Delayed Diagnosis = 1 – 5 years; Severe Delay = 5+ years. Numbers displayed are counts of participants. Table is based non-incidental cases (n=76).

		Time to suspicion							
		Less than 6 months	6 months - 1 year	1-2 years	2-3 years	Over 3 years	Indicated "NET discovered incidentally"	This does not apply to me	I don't know / I don't remember
Delay Severity	Timely	9	1	0	0	0	2	0	0
	Slight Delay	1	4	0	0	0	0	0	1
	Delayed Diagnosis	3	1	3	1	4	5	0	0
	Severe Delay	3	1	0	0	18	9	1	0
	Unknown	2	0	0	0	1	5	0	1
	Total	18	7	3	1	23	21	1	2

Table 4. Delay severity and time from testing to diagnosis. This table shows the relationship between the delay in diagnosis and testing time. Delay severity is ranked based on the time to diagnosis from first symptom: Timely = less than 6 months; Slight Delay = 6 months – 1 year; Delayed Diagnosis = 1 – 5 years; Severe Delay = 5+ years. Numbers displayed are counts of participants. Table is based non-incidental cases (n=76).

		Time from starting testing until diagnosis							
		Less than 6 months	6 months - 1 year	1-2 years	2-3 years	Over 3 years	Indicated "NET discovered incidentally"	Indicated "I was not tested"	I don't know / I don't remember
Delay Severity	Timely	10	1	0	0	0	1	0	0
	Slight Delay	4	2	0	0	0	0	0	0
	Delayed Diagnosis	7	0	1	0	1	6	2	0
	Severe Delay	14	2	1	0	2	7	6	0
	Unknown	2	1	0	0	0	4	2	0
	Total	37	6	2	0	3	18	10	0

3.6. Health-seeking by patients is not a contributor to the delay in diagnosis

Time to suspicion is the major time contributor to a delayed diagnosis but it is unclear if the health-seeking behaviour of the survey participants plays a role during the time to suspicion period. To check whether the delay in diagnosis may be partly a result of patients not seeking medical attention early enough, the reported time to seeking medical attention after first experiencing symptoms, and the severity of the delay were examined (**Figure 5)**. Participants who reported the most severe delay in diagnosis have sought medical attention both early and late. Therefore, it is possible that a fraction of the time to confirmed diagnosis could have come from seeking medical attention late. However, given that those who reported a delay in diagnosis have mostly reported a severe delay (5+ years; **Figure 2**), a long time to seeking medical attention has minimal effect on the total time from first symptom to confirmed diagnosis.

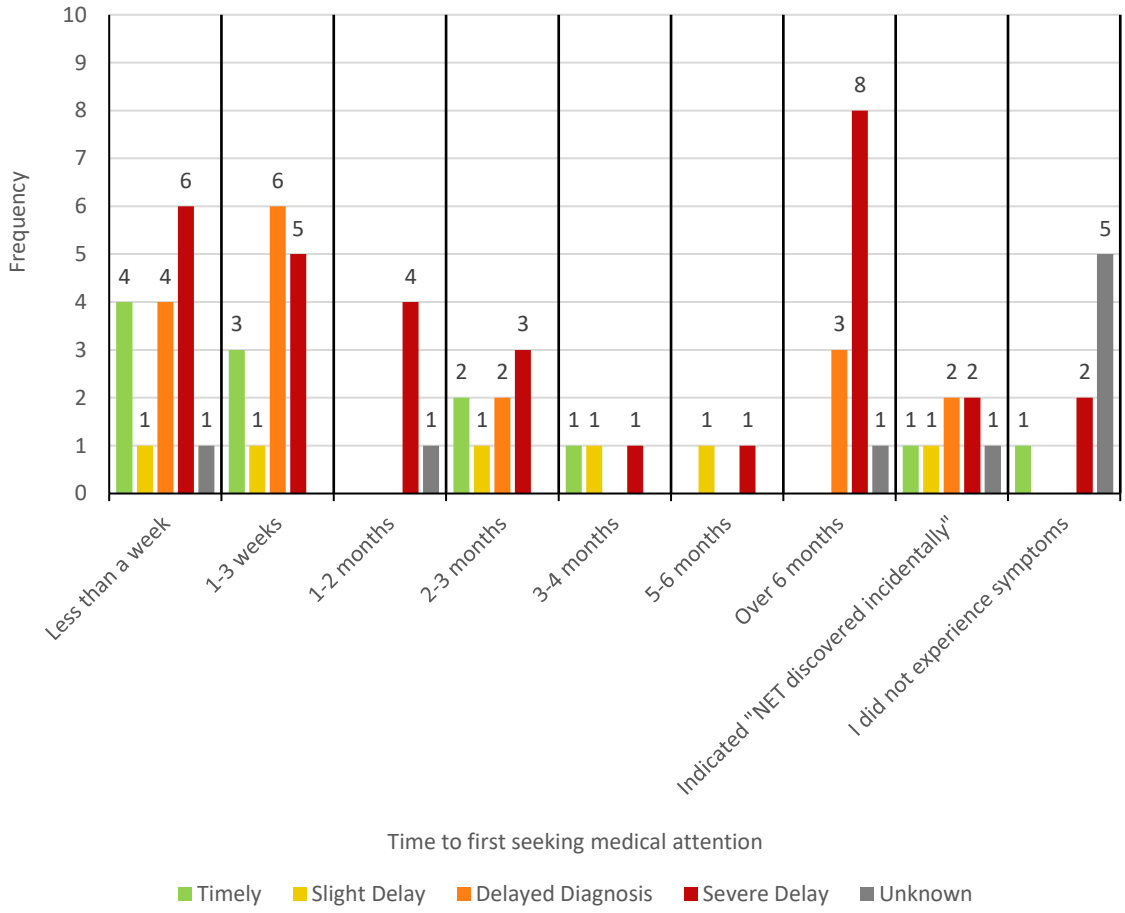


Figure 5. Delay in diagnosis and time to seeking medical attention after first experiencing symptoms. This figure shows the relationship between time to seeking medical attention, and the severity of the delay in diagnosis experienced. Figure is based non-incidental cases (n=76).

3.7. Symptom profile and severity do not affect time to suspicion of NETs

Symptom profile does not vary dramatically between those who have had their NETs suspected early compared to those who had a late suspicion or no suspicion at all **(Figure 6)**. The most common symptoms just increase in frequency the longer the suspicion period simply because there are more participants who experienced a long time to suspicion. Less common symptoms appear sporadically across the vertical stacks. This shows that time to suspicion did not seem to be affected by what kind of symptoms the patient presented with when they sought medical attention. Furthermore, symptom severity does not seem to affect time to suspicion as both, short and long suspicion times can be seen across various degrees of symptom severity (**Figure 7**).

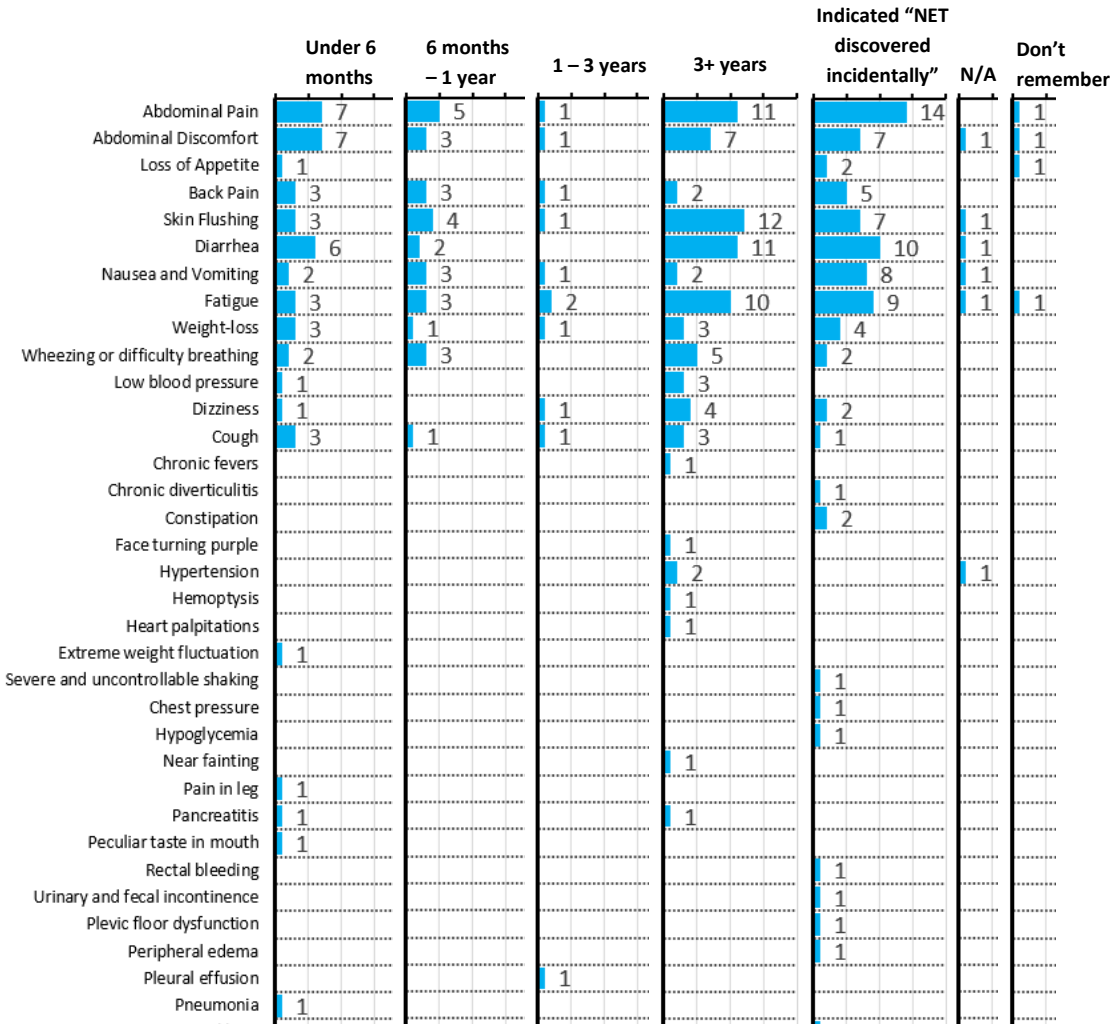


Figure 6. Symptom profile and time to suspicion of NETs. The different symptoms that led to participants first seeking medical attention are displayed to the left of the compound graph, and each vertical stack represents the different time to suspicion ranges. For example, vertical stack "Under 6 months" shows the symptoms reported by participants whose NETs were suspected by their doctor in less than 6 months. As explained in **Figure 3**, "NET discovered incidentally" can be thought of as "NETs were never suspected." Those who indicated this question does not apply to them are shown under the label "N/A." Figure is based non-incidental cases (n=76).

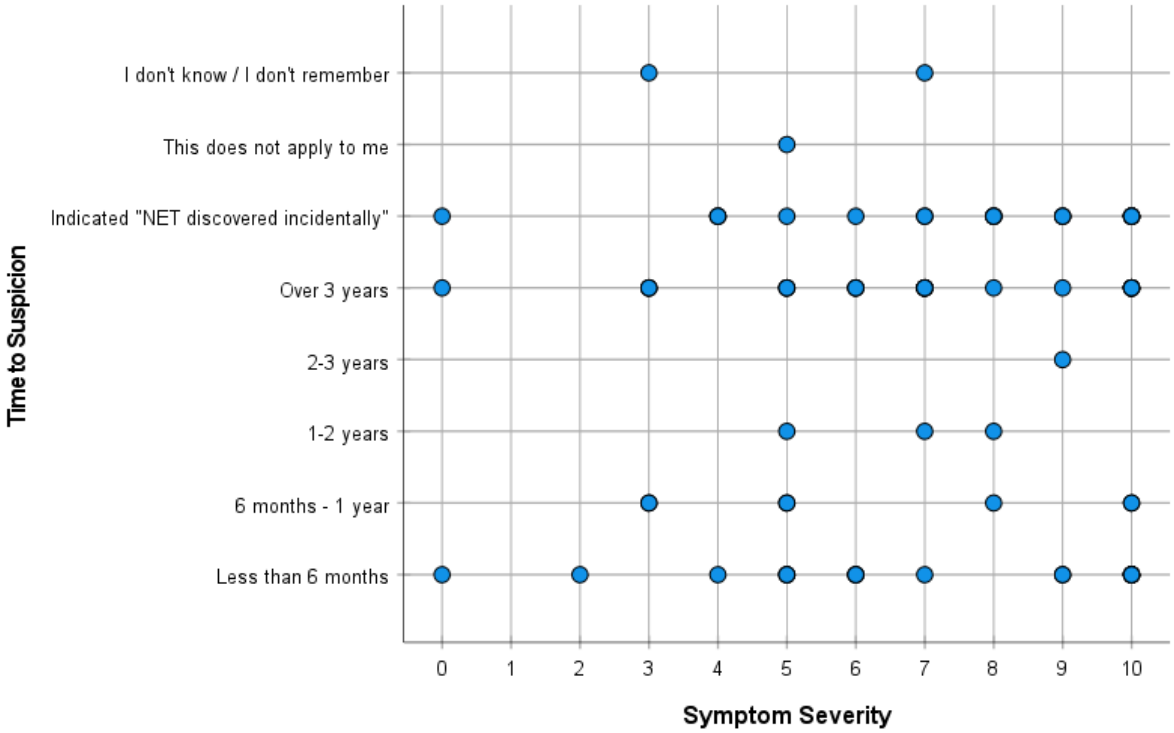


Figure 7. Symptom severity by time to suspicion of NETs. Symptom severity was captured in the survey using the question: *"How severe were the symptoms that first led you to seeking medical attention? (0 being no symptoms at all, 10 being very severe symptoms)."* The "NET discovered incidentally" response can be thought of as "NETs were never suspected." Figure is based on non-incidental cases (n=76).

1.1. The delay in diagnosis is likely a result of physician dependent factors

It is important to examine where the participants went for medical attention after first experiencing symptoms. For most respondents, the primary point of contact when seeking medical attention following the onset of symptoms was either a family doctor/GP or the emergency room. The majority of the participants, both, those with a timely and delayed diagnosis, first saw their family doctor (**Figure 8**).

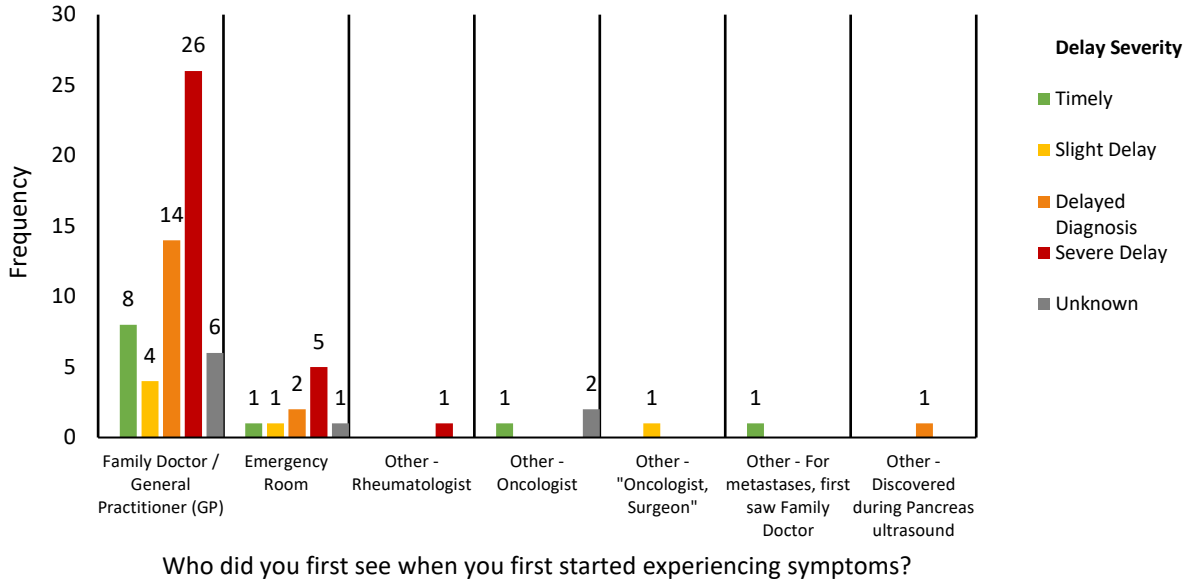


Figure 8. Participants' primary contact with health professionals. This figure shows the relationship between delay severity experienced and who the patient first saw after experiencing symptoms. Figure is based non-incidental cases (n=76).

Among the most common NETs represented in the survey, both timely and delayed diagnoses have been made (**Table 5**). Pancreatic NETs are more frequent among the delayed groups than the timely group, and the less common NETs are more frequent among the delay groups. Therefore, it is likely that the delay in diagnosis is not so much dependent on patient-related factors but is rather dependent on physician-related factors. The same patient, with the same symptoms and the same primary site, is likely to have a different diagnosis time simply because they saw one family doctor instead of another.

Table 5. Time from first symptom to confirmed diagnosis by primary site of NET. This table shows the relationship between the primary site of NET and the severity of the delay in diagnosis. Numbers displayed as counts. Table is based non-incidental cases (n=76).

	Delay Severity				
Primary Site Reported	**Timely**	**Slight Delay**	**Delayed Diagnosis**	**Severe Delay**	**Unknown**
Small Intestine (Duodenal, Jejunal, Ileal)	7	3	8	10	6
Pancreatic	1		3	6	
Lung	2	1	2	6	
NET of unknown origin	1			2	
Appendix				2	1
Cecum			1	1	
Colon				1	1
Rectum	1			1	
Genetic/Inherited NET Syndrome			2		

Other - "Bowel"				2	
Other - Liver			1		
Other - Mesentery		1			
Other - "Small bowel mesentery"					1
Other - "Pheochromocytoma and Neurofibromatosis"				1	
I do not know		1			

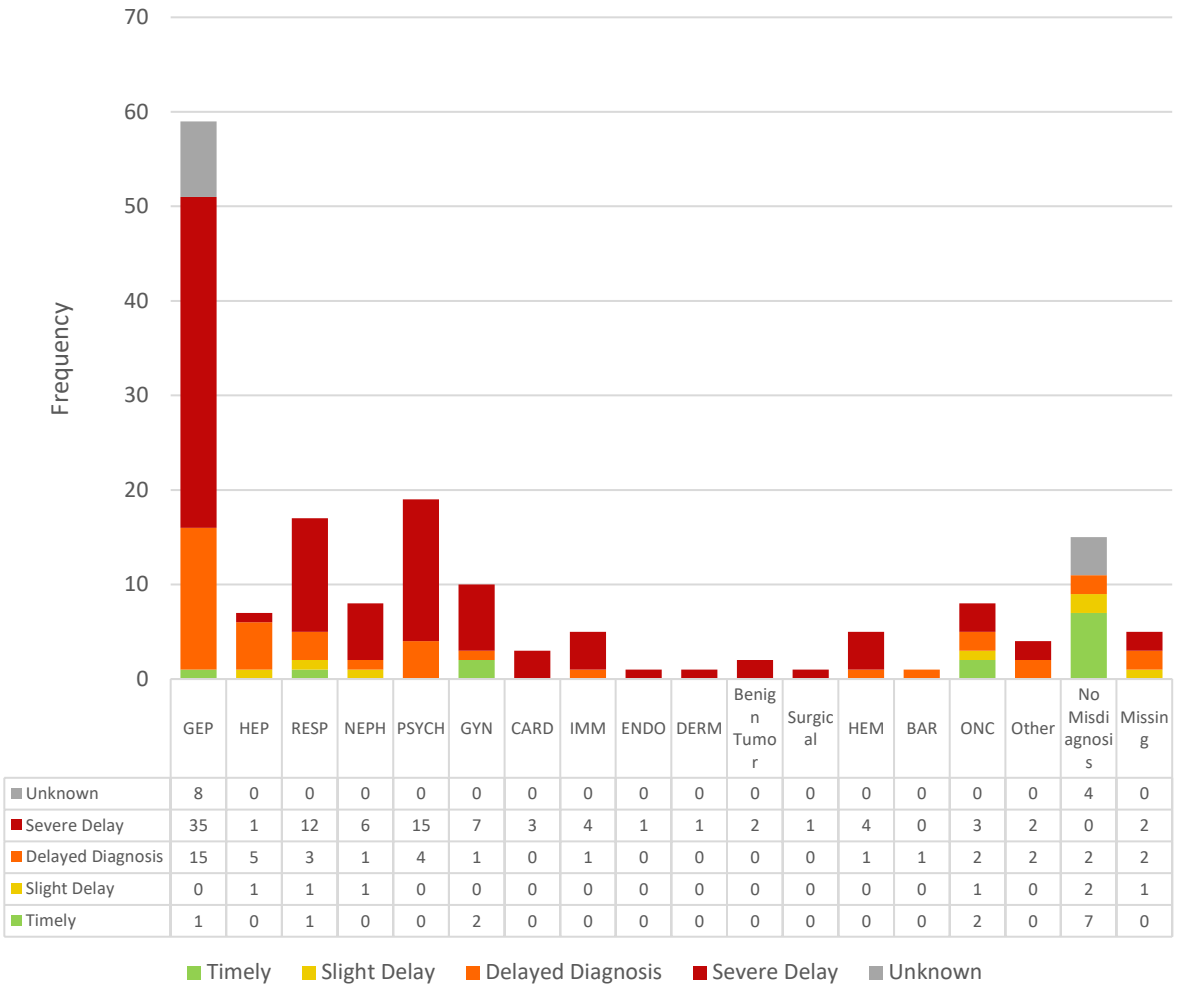
1.2. Where does this leave us?

The importance of suspicion in the diagnosis of NETs cannot be understated. If a physician does not consider NETs, the appropriate tests are simply not performed [33]. This study found that the major contributing factor to a delayed diagnosis is a delay in suspicion of NETs. Furthermore, symptom profile and severity do not seem to play a role in reducing suspicion time. On the other hand, physician-related factors likely play a role. Given the fact that the first point of contact for many patients is their family doctor or the emergency room, there is a need for increased awareness about NETs among family and emergency doctors. If more doctors are aware of NETs and their manifestation, the delay in suspicion could be reduced. This can translate to a faster diagnosis since testing is done relatively quickly (**Figure 4**).

While increased awareness by primary care physicians can put patients on a shorter diagnostic journey from the outset, what about those who have been already committed to a long diagnostic journey? In order to gain insights into the struggles of these patients, one can examine the reported misdiagnoses that patients received during their diagnostic journey.

1.3. Psychiatric misdiagnosis is a key factor among those who experienced a delayed diagnosis

The majority of participants diagnosed in a timely manner received no misdiagnoses, while those with long diagnostic journeys received several misdiagnoses including gastroenteropancreatic, respiratory or gynecological in nature **(Figure 9**). In fact, among the participants who reported a delay in diagnosis, the most prevalent misdiagnoses are gastroenteropancreatic, respiratory and psychiatric. Most notable here is the high frequency of reported psychiatric misdiagnoses. There are multiple explanations for that observation. It could be the case that receiving a psychiatric misdiagnosis is associated with a subsequent delay in diagnosis. An equally plausible explanation is that the distress experienced during a lengthy diagnostic journey is enough to affect the mental health of patients. The experiences shared by participants who received a psychiatric misdiagnosis hints to the former explanation. Some participants who indicated a psychiatric misdiagnosis provided text responses throughout the survey that highlight their experiences. These quotes and associated contextual information are provided in **Table 6.** Interestingly, it seems that female patients experienced psychiatric misdiagnosis more often than male patients (**Table 7**).



	GEP	HEP	RESP	NEPH	PSYCH	GYN	CARD	IMM	ENDO	DERM	Benign Tumor	Surgical	HEM	BAR	ONC	Other	No Misdiagnosis	Missing
Unknown	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0
Severe Delay	35	1	12	6	15	7	3	4	1	1	2	1	4	0	3	2	0	2
Delayed Diagnosis	15	5	3	1	4	1	0	1	0	0	0	0	1	1	2	2	2	2
Slight Delay	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	2	1
Timely	1	0	1	0	0	2	0	0	0	0	0	0	0	0	2	0	7	0

Figure 9. Misdiagnoses reports and delay in diagnosis of NETs. There were many misdiagnoses reported by participants. For simplicity, these misdiagnoses were grouped into categories based on a rough general area of medicine that they fall into: **GEP** – Gastroenteropancreatic, **HEP** – Hepatobiliary, **RESP** – Respiratory, **NEPH** – Nephrological, **PSYCH** – Psychiatric, **GYN** – OB/GYN, **CARD** – Cardiological, **IMM** – Immunological, **ENDO** – Endocrine, **DERM** – Dermatological, **HEM** – Hematological, **BAR** – Bariatric, **ONC** – Oncological. The exact list of misdiagnoses in each category can be found in **Table S5.** Figure is based non-incidental cases (n=76).

Table 6. Quotes by participants who have received a misdiagnosis of a mental health condition. The quotes displayed in this table serve to complement the findings from **Figure 9** and provide some possible explanations for why a psychiatric misdiagnosis may be associated with a delay in diagnosis.

Quote	Contextual Information
"My symptoms were attributed to an ulcer, gall bladder, then I was told it was all in my head and referred for a psychiatric evaluation." Question Source: Why were you not tested?	**Gender:** Female **Age at diagnosis:** 39 **Area of residence during diagnosis:** Quebec **Primary Site:** Small Intestine (Duodenal, Jejunal, Ileal) **Incidental / Non-incidental:** Not Incidental **Indicated Mental Health misdiagnosis:** Yes

	Symptom severity: 9 **Time from first symptom to diagnosis:** 3-5 years **Tumour Grade:** My physician did not provide a NET grade **Tumour Stage:** Stage IV **Metastasis at diagnosis:** Yes **Quality of care rating:** Good
"My symptoms where generally ignored and attributed to mostly to stress and anxiety and other mental health issues. The doctors brushed my concerns aside for so long that I started to ignore the growing problem until my bowel became ischemic and I was vomiting so badly and for so long that I needed to go to emergency." Question Source: With respect to NET diagnosis, did you experience any major issues, and if so, what were the issues?	**Gender: Female** **Age at diagnosis:** 47 **Area of residence during diagnosis:** British Columbia **Primary Site:** Small Intestine (Duodenal, Jejunal, Ileal) **Incidental / Non-incidental:** Not incidental **Indicated Mental Health misdiagnosis:** Yes **Symptom severity:** 8 **Time from first symptom to diagnosis:** 5-7 years **Tumour Grade:** My physician did not provide a NET grade **Tumour Stage:** Stage IV **Metastasis at diagnosis:** Yes **Quality of care rating:** Very Poor
"A radiologist missed the tumour on a scan early soon after symptoms started. Therefore my family doctor started to blame my symptoms on emotional issues." Question Source: With respect to NET diagnosis, did you experience any major issues, and if so, what were the issues?	**Gender:** Female **Age at diagnosis:** 48 **Area of residence during diagnosis:** New Brunswick **Primary Site:** Pancreatic (Insulinoma, Glucagonoma, VIPoma, Somatostatinoma, etc.) **Incidental / Non-incidental:** Not incidental **Indicated Mental Health misdiagnosis:** Yes **Symptom severity:** 6 **Time from first symptom to diagnosis:** 7+ years **Tumour Grade:** My physician did not provide a NET grade **Tumour Stage:** No, I do not know the stage **Metastasis at diagnosis:** Yes **Quality of care rating:** Very Poor
"Mental health unit admittance for suicide ideation from pain and being misunderstood by all health individuals about what is happening with my body" Question Source: With respect to NET diagnosis, did you experience any major issues, and if so, what were the issues?	**Gender:** Female **Age at diagnosis:** 34 **Area of residence during diagnosis:** Alberta **Primary Site:** Pancreatic (Insulinoma, Glucagonoma, VIPoma, Somatostatinoma, etc.) **Incidental / Non-incidental:** Not incidental **Indicated Mental Health misdiagnosis:** Yes **Symptom severity:** 9 **Time from first symptom to diagnosis:**

	Tumour Grade: *Grade 1: NETs are relatively slow growing* **Tumour Stage:** Stage I **Metastasis at diagnosis:** No **Quality of care rating:** Poor
"I had multiple symptoms over a 6-year period prior to diagnosis.... I was treated as crazy and sent to several psychiatrists." Question Source: With respect to NET treatment, did you experience any major issues, and if so, what were the issues?	**Gender:** Female **Age at diagnosis:** 43 **Area of residence during diagnosis:** Ontario **Primary Site:** Appendix **Incidental / Non-incidental:** Not incidental **Indicated Mental Health misdiagnosis:** Yes **Symptom severity:** 7 **Time from first symptom to diagnosis:** "Diagnosed with NET after surgery" **Tumour Grade:** Grade 1: NETs are relatively slow growing **Tumour Stage:** Stage III **Metastasis at diagnosis:** No **Quality of care rating:** Poor

Table 7. **Gender and psychiatric misdiagnosis.** Given that all the quotes in **Table 6** came from female participants, the gender distribution for participants who reported getting a mental health misdiagnosis is shown here. Table is based on all participants (n=106).

	Psychiatric Misdiagnosis	
	No	**Yes**
Male	34	3
Female	54	15

Patient experiences highlighted by these quotes indicate that their symptoms were attributed to mental, rather than their physical well-being. It is likely that a psychiatric misdiagnosis contributes to lengthening the time to diagnosis, possibly due to the anchoring heuristic in clinical decision making. The anchoring heuristic is a cognitive shortcut that leads physicians to sticking to their initial impression once it has been formed [34]. In addition to anchoring bias, a psychiatric misdiagnosis has the capacity to "overshadow" physical illness, leading to the misattribution of symptoms to mental illness [35].

While increasing awareness of NETs is recommended across all clinical disciplines, it is conceivable that special focus should be given to psychiatrists for the reasons described above. One must also consider the fact that NETs have been reported to have both neurologic [36] and psychiatric effects [37]–[41]. This could magnify the probability of symptom misattribution. Psychiatrists should be made aware about NETs and their manifestations so that they can re-refer a NET patient to the appropriate specialist, putting the patient back on the right diagnostic track.

All considered, there are likely numerous NET patients currently stuck with a misdiagnosis, anchored, unable to move ahead. A general awareness strategy for various specialties with a special focus on psychiatry may help many patients who are beyond the point of primary care.

1.4. An Analysis of Incidental Findings

A total of 30 incidental cases were identified in the sample population in this study (30/106). Since the survey was not designed to accommodate such a high proportion of incidental findings, there is no clear definition of what time-to-diagnosis is in such cases. Furthermore, other elements of the survey would not apply to these patients, for example, time to suspicion, because in an incidental finding, there was was no suspicion. For that reason, incidental findings have been excluded from the analyses and were subjected to separate analyses presented below.

In the incidental cases, the most common primary NETs – small intestine, pancreas and lung – recapitulate those from the non-incidental group (**Table 8 & Table 1**). Diverse events in patients lives led to the discovery of these NETS (**Table 9**). Because NETS were discovered accidentally, there is a lot of information missing about the diagnostic journey of these patients. More research is needed into how NET incidental findings are investigated, and what a delay in diagnosis (if any) looks like in that subset of patients.

Table 8. Primary site of incidentally discovered NETs. This table shows the frequency of NETs by primary site for the group of participants who have had their NET discovered incidentally.

Primary Site	Count
Small Intestine	11
Pancreatic	9
Lung	3
Colon	3
Cecum	1
Thymic	1
NET of unknown origin	1
Genetic/Inherited NET Syndrome	1

Table 9. Incidents that led to incidental findings. A tabulation of all incidental findings in the study showing the primary site of the tumour and the incident that led to their discovery, as well as whether there was metastasis at diagnosis. The incidental events have been categorized for ease of viewing. Some respondents did not provide enough information, hence were tabulated as "Unavailable."

Incident Category	Incident that led to discovery	NET Primary Site	Metastases at diagnosis
Colonoscopy	Routine Colonoscopy	Colon	Yes
	Routine Colonoscopy	Small Intestine (Duodenal, Jejunal, Ileal)	No

	Routine Colonoscopy	Small Intestine (Duodenal, Jejunal, Ileal)	No
	Routine Colonoscopy	Small Intestine (Duodenal, Jejunal, Ileal)	Yes
	Routine Mammogram	Small Intestine (Duodenal, Jejunal, Ileal)	Yes
	Colonoscopy	Colon	Yes
	Patient-demanded colonoscopy	Small Intestine (Duodenal, Jejunal, Ileal)	Yes
Accident	Accident (cracked ribs)	Thymic	Yes
	Fall accident	Pancreatic (Insulinoma, Glucagonoma, VIPoma, Somatostatinoma, etc…)	No
Follow-ups	Annual check-up following lung lobectomy	Lung	Yes
	Annual check-up following prostate surgery	Colon	Yes
	Annual CT following melanoma treatment	Small Intestine (Duodenal, Jejunal, Ileal)	No
CT	CT investigating polynephritis	Small Intestine (Duodenal, Jejunal, Ileal)	Yes
	Mandatory CT for travel purposes	Cecum	Yes
Unique	"Cushings"	Pancreatic (Insulinoma, Glucagonoma, VIPoma, Somatostatinoma, etc…)	Yes
	Mentioned abdominal discomfort during routine checkup	Small Intestine (Duodenal, Jejunal, Ileal)	Yes
	Elevated liver enzyme lead to an ultrasound which found what was misdiagnosed as a hemangioma. Five years later a CT found a NET.	Small Intestine (Duodenal, Jejunal, Ileal)	Yes
	Adverse drug reaction to blood thinners	Small Intestine (Duodenal, Jejunal, Ileal)	Yes
	Abdominal Ultrasound	Pancreatic	No
	"Unrelated scan of abdomen"	Pancreatic	Yes
	"Low Ferritin"	Genetic/Inherited NET Syndrome	No
Unavailable	Unavailable	Lung	No
	Unavailable	Pancreatic	Yes
	Unavailable	NET of unknown origin	Yes
	Unavailable	Pancreatic	No
	Unavailable	Pancreatic	No
	Unavailable	Small Intestine (Duodenal, Jejunal, Ileal)	Yes
	Unavailable	Lung	No
	Unavailable	Pancreatic	No
	Unavailable	Pancreatic	No

1.4.1. Incidental Findings about Incidental Findings?

When looking at incidental findings, an interesting observation emerged. Out of the 6 reported colonoscopies, 4 led to the diagnosis of a NET with a primary site in the small intestine (**Table 9**). In Canada, colonoscopies are sometimes extended to reach the cecum and the distal ileum (**Figure 10**) [42], which can explain how these NETs were found. This raises questions about the prevalence of ileal NETs and the likelihood of their incidental discovery in colonoscopies, and whether that can serve as a screening procedure for NETs, similar to what is done in colorectal cancer screening [43]. Indeed, there is evidence that suggests that small bowel NETs are most common in the distal ileum [44].

In the United States, a routine colonoscopy is recommended every 10 years for every adult between the ages of 50 and 75 [45], whereas in Canada only a flexible sigmoidoscopy is done for adults between the ages of 50 and 74 – if they choose to be screened [46]. Flexible sigmoidoscopy does not extend past the lower third of the colon and cannot find NETs in the distal ileum or the cecum [47].

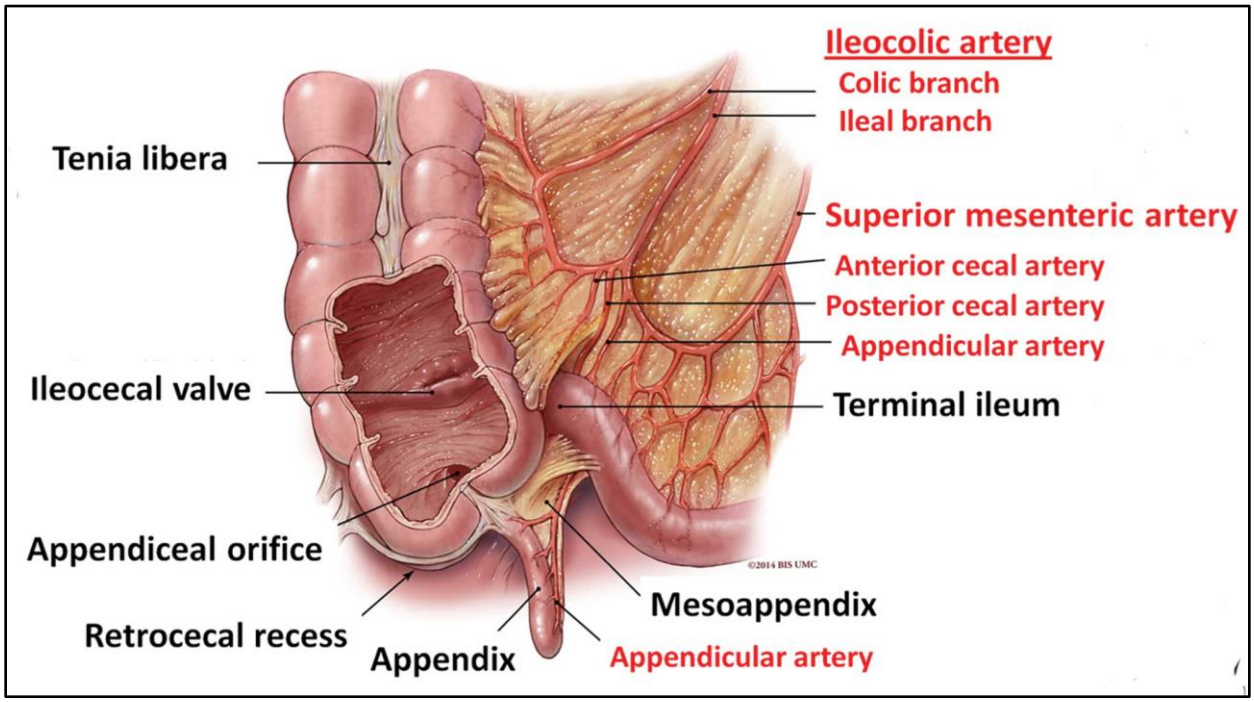


Figure 10. The Terminal Ileum. An illustration of the Ilececum Anatomy showing the location of the terminal ileum [48].

Considering that the small bowel NETs are among the most prevalent types of NETs, and the mean age at diagnosis is over 50 – based on this study as well as previous studies [5], [9] – there might be an argument to be made for expanding colonoscopy screening in Canada to everyone between the ages of 50 and 75. Afterall, ileal intubation with colonoscopy is achievable in the majority of cases [49]. This presents an interesting possibility for screening small bowel NETs and warrants further research into cost-effectiveness and feasibility of this intervention.

2. Limitations

As discussed earlier in this report, the biggest limitation to this study is recall and selection bias. Most participants were diagnosed over 3 years ago and the recollection of their diagnostic journey might not be entirely accurate. The survey was conducted entirely online, disseminated through CNETS' mailing list and social media pages, which could have led to selection bias and selecting a more informed group of NET patients. The responses in this survey may not be representative of all NET patients in Canada.

Furthermore, the survey was not designed to accommodate incidental findings. It was expected that very few cases will be incidental, in which an option to choose "NET discovered incidentally" was given to participants in multiple questions. However, the goal of these option choices was only to quantify and classify incidental cases, but not to elucidate how a delay in diagnosis can occur in those cases. The problem was that what is considered an "incidental finding" was not defined to the survey participants, which left it open to the participant's judgement. This was circumvented by the researcher to a limited degree by reviewing and reclassifying participants' responses by looking at other entries in the survey, particularly, open ended questions. Cases were re-classified in consultation with Dr. Yelamanchili, but this classification was not conducted in a systematic way. This opened a new limitation in that there was only one researcher, and hence this classification lacked inter-rater reliability.

Another limitiation is that the survey was not designed to accommodate incidental findings, very little information could be collected from the 30 truly incidental cases of NET diagnosis. Finally, the multiple-choice portion of the survey failed to account for more complex cases. The rigid structure did not allow for the clear collection of data about patients who have had multiple primary NETs, or those who have had a recurrence, or those who have experienced a delay in diagnosis for both the primary and at recurrence.

3. Knowledge Translation

3.1. Recommendations for CNETS

Recommendation #1: Physician Awareness

CNETS is currently partnered with Endeavour Scientific to launch a NET awareness campaign. An important question for CNETS is who to target during this campaign. Based on this study, A NET awareness campaign is needed across various physician specialties, but special focus should be given to family doctors, emergency doctors and psychiatrists for the reasons outlined in **sections 3.9** and **3.10** of this report. In addition, more effort on patient awareness will also be helpful. In this study, seven participants were the initiators who suggested the diagnostic test that led to their NET diagnosis **(Table 10)**. In a paradigm where time to suspicion is leads to a delay in diagnosis, an informed patient suggesting the possibility of NETs and advocating for themselves is a step in the right direction.

Table 10. Who suggested the diagnostic tests that led to a NET diagnosis for survey participants?

Who suggested the diagnostic test(s) that led to your NET diagnosis?	Count
Your General Practitioner (GP)	16

An Emergency Doctor	14
A Nurse	0
A Dermatologist	1
A Rheumatologist	0
A Medical Oncologist	6
An Endocrinologist	7
A Gastroenterologist	11
A Hematologist	0
A Nuclear Medicine Specialist	0
A Nutritionist / a Dietitian	0
A Pathologist	1
A Physician Assistant	0
A Respirologist	4
A Radiation Oncologist / Radiotherapist	2
A Radiologist	3
A Surgeon	17
You suggested the test(s)	7
I don't know / I don't remember	2
Somebody else: Allergist	1
Somebody else: Found during Colonoscopy	3
Somebody else: A Surgeon and an Oncologist	1
Somebody else: Liver specialist	1
Somebody else: Pulmonologist	1
Somebody else: Internist	2
Somebody else: "I asked for my X-ray follow-up"	1
Somebody else: Diagnosed after surgery	1
Somebody else: Surgical Oncology Fellow	1
Somebody else: Diagnostic Imaging Technician	1
Somebody else: Endocrinologist (friend)	1
Somebody else: Hepatobiliary Surgeon	1

Recommendation #2: Expanding support to Alberta and Saskatchewan

Based on the answers to the question “With respect to NET diagnosis, did you experience any major issues, and if so, what were the issues?”, there appears to be a problem with access to resources based on the geographical location of NET patients. One patient said: “Was tested the day before hospitals shutdown due to COVID-19, received diagnosis 10 days later, and was completely forgotten amidst the chaos. The local cancer clinic refused to see me due to the rarity of neuroendocrine cancer and no treatments available in Saskatchewan.” Another patient said: “Was not provided with much information. Other provinces have support groups. I feel all alone in Saskatchewan in this journey.” And yet another mentioned: “Delays due to living in Northern AB and doctors there having no experience with NET.

Referral process was slow." These quotes point to a lack of expertise and support in Saskatchewan, and a lack of expertise in northern Alberta. While three quotes may not present an accurate view of the state of affairs in Saskatchewan and Alberta, there do point to the need of further research in these provinces but also other provinces. The data from this study comes mainly from Ontario although there are other provinces represented. It is recommended that CNETS look into expanding their support to those two areas and other areas as well. If CNET support is already available, then it is worth looking into the ways the presence of such support could be disseminated to patients and the physicians. In addition, it is worth to examine the patients' needs in terms of support required in provinces other than Ontario.

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Appendix A: Supplemental Information

Table S1. Investigating potential reasons behind why participants chose "NET discovered incidentally" option when reporting the time to suspicion of NETs by their doctor.

Potential reason why "NET discovered incidentally" was chosen	**Number**	**Explanation**
NETs were never suspected	1	Colon primary. Patient reported that they suggested the ultrasound that led to finding tumours on the liver after suffering years of abdominal pain. A liver specialist then ordered a biopsy which diagnosed the NET. Hence there was no suspicion of NET.
Insufficient Information	2	Insufficient information provided. Unclear why participant chose "NET discovered incidentally" option. Small Intestine primary. Severe peripheral edema reported as only symptom.
NETs were never suspected	3	Not a lot of information provided. Primary site in small intestine Patient reported strong symptoms: abdominal pain, diarrhea, and back pain. First saw GP for symptoms and received multiple misdiagnoses (diverticulosis, inflamed bowel, possible allergic reaction). Among the tests received, patient reported to have undergone a biopsy, colonoscopy, ultrasound and CT scan. It is likely that the abdominal symptoms prompted investigation through colonoscopy or CT that found the NET. The biopsy then was what diagnosed the NET. Hence, NETs were never suspected.
NETs were never suspected	4	I had been treated continuously for diverticulitis with antibiotics after multiple trips to the ER. Developed an allergic reaction to cypro/flagyl so had to have surgery to remove damaged part of intestine. Had CT and colonoscopy before bowel resection. Pathology from resection showed neuroendocrine tumor on part of colon removed. Hence no suspicion of NETs.
NETs were never suspected	5	Cysts on pancreas seen on CT. Surgery to resect mass and pathology of mass showed pNET
NETs were never suspected	6	Not enough information provided. But among other symptoms reported were rectal bleeding and incontinence. This may have led to a scope or imaging that found the tumour, followed by testing for NETs. Hence there was no suspicion of NETs.
NETs were never suspected	7	Not enough information provided. However, patient reported extensive surgery in small bowel and large intestine. Primary site is appendix. Patient also indicated Biopsy as the only test for NETs undertaken. It could be the case that there was never suspicion of NETs by a doctor, but rather a surgery for complications from NETs followed by a diagnosis.
NETs were never suspected	8	Not enough information provided. However, patient reported colonoscopy as the only testing procedure undergone, symptoms of skin flushing and diarrhea with a severity of 10, and misdiagnosis with Irritable Bowel Disease. Primary site is the Cecum. It's likely that this patient had undergone colonoscopy to investigate abdominal symptoms and NET was discovered then. Hence there was no suspicion of NETs.

NETs were never suspected	9	Not enough information provided. However, patient indicated that diagnosis was made following surgery. Primary site was Small Intestine and symptoms reported were abdominal pain and nausea with vomiting. Diagnostic tests reported were CT, Colonoscopy and Endoscopy. Therefore, it is likely that an investigation of abdominal complaints led to the discovery of a tumour which was shown to be a NET in pathology. Hence there was no suspicion of NETs.
NETs were never suspected	10	Lung primary. Patient reported the NET was discovered on a bronchoscope and a respirologist recommended the test for NETs. While the patient did not indicate any respiratory symptoms experienced that led to seeking medical attention, they did report pneumonia as a misdiagnosis they have received. This hints that that the patient has experienced some respiratory symptoms that prompted the bronchoscope and the subsequent detection and diagnosis of NET. Hence there was no NET suspicion.
NETs were never suspected	11	Patient indicated reported first seeing a GP with severe abdominal symptoms, and that it was a colonoscopy and subsequent pathology that diagnosed the NET. Hence there was no NET suspicion.
NETs were never suspected	12	Not a lot of information provided. Small Intestine primary. Patient reported strong abdominal symptoms like pain, diarrhea and nausea with vomiting. It was indicated that a GP was first seen for those symptoms and a CT scan was the only test undergone that the patient has reported in the survey. It is likely that the abdominal symptoms have prompted the CT and a diagnosis was made from there. Hence there as no NET suspicion.
NETs were never suspected	13	Lung primary. Patient reported respiratory symptoms and a history of Sjogren's prompted an X-ray that showed a growth. Growth was determined to be benign but upon a patient requested X-ray years later, multiple tumours were found and were misdiagnosed as lung cancer. Further investigation showed the tumour to be a NET. Hence there was never a suspicion of NET.
NETs were never suspected	14	Small Intestine primary. Severe symptoms reported: Abdominal symptoms and skin flushing. After years of misdiagnosis, patient kept going to their doctor asking for more tests until an ultrasound showed something on the liver. Testing was done for months until a biopsy identified the NET. Hence there was never a suspicion of NETs.
NETs were never suspected	15	Pancreatic primary. Patient reported that after going to doctors with symptoms and complaints, there was never a suspicion of NETs. Patient did the research and demanded a CT through a walk-in clinic which led to the diagnosis. Patient indicated that "NETs discovered incidentally" was chosen because the doctors never suspected NETs, and it was the patient who did and the patient who suggested the test to find NETs. After a hospital referral and further testing, NETs were diagnosed.
NETs were never suspected	16	Appendix primary. Patient reported experiencing multiple symptoms for years that were misattributed to be psychiatric of origin. After going to the ER for severe lower back flank pain, only mild swelling in the appendix was found with no fever or vomiting. After patient demanded a surgery be done, the on-call surgeon identified the NET. Hence there was never a suspicion of NETs.

NETs were never suspected	17	Not a lot of information provided. Small Intestine primary. Patient reported being diagnosed with NET after surgery. Severe symptoms reported: Abdominal pain, fatigue and constipation. Patient also reported seeking medical attention 1-2 months after the appearance of symptoms and seeing a GP/Family Doctor. Among the tests undergone for NETs, patient reported a CT scan. It is therefore likely that the patient went to a GP with severe abdominal symptoms which prompted imaging that found the growth. Surgery and subsequent pathology revealed it to be a NET. Hence there was no suspicion of NETs.
NETs were never suspected	18	Double primary: Appendix and pancreas as part of MEN1. Patient reported severe abdominal pain as the only symptom and that within the first day of symptoms, they had a CT and an ultrasound. Results ruled out appendicitis but a shadow on the pancreas was found. An MRI followed by an endoscopic ultrasound and biopsy confirmed that there was no cancer. Follow-up MRI over a 3-year period found nothing. After the final MRI 2 years later, tumours were found. NETs were diagnosed following surgery. Hence there was never a suspicion of NETs.
NETs were never suspected	19	Small intestine primary. Multiple severe symptoms (abdominal pain, abdominal discomfort, skin flushing, diarrhea, nausea with vomiting, wheezing or difficulty breathing, dizziness, shaking, chest pressure and hypoglycemia) ignored by doctors for years and attributed to stress. ER admission after severe bout of vomiting. Emergency CT showed tumour in bowels with metastases to the liver and peritoneal cavity. Surgeon did a biopsy later that diagnosed the NET. Hence NETs were never suspected.
NETs were never suspected	20	Bowel obstruction. Diagnosed after surgery. Hence no suspicion of NETs.
NETs were never suspected	21	Pain was seasonal, mainly winter and spring, and related to sleep, extended periods of laying down, it had persisted for several years and was at times significant enough to disturb sleeping. Investigate moderate abdominal pain via CT scan. Radiological report identified an item that was suggested to be a carcinoid. Hence no suspicion of NETs.

Table S2. Investigating potential reasons behind why participants chose "This does not apply to me" option when reporting the time to suspicion of NETs by their doctor.

NETs were never suspected	Small intestine primary. Patient reported moderately severe symptoms: abdominal discomfort, skin flushing, diarrhea, nausea with vomiting, fatigue and hypertension. Patient indicated that they were not tested and mentioned vomiting and a suspicion that it was a gall bladder problem. Among tests received were biopsy, CT scan and ultrasound. Patient reported that an emergency doctor suggested the test that led to the NET diagnosis. Given that information, it is likely that a bout of vomiting led to ER admission where the emergency doctor investigated with CT and ultrasound which detected what was later confirmed with a biopsy to be a NET. Hence NETs were not suspected. And this is probably why the patient selected that this does not apply to them.

Table S3. Investigating potential reasons behind why participants chose "NET discovered incidentally" option when reporting the time from testing to diagnosis of NETs

Potential reason why "NET discovered incidentally" was chosen	**No.**	**Explanation**
Diagnosed after surgery	1	I had been treated continuously for diverticulitis with antibiotics after multiple trips to the ER. Developed an allergic reaction to cypro/flagyl so had to have surgery to remove damaged part of intestine. Had CT and colonoscopy before bowel resection. Pathology from resection showed neuroendocrine tumor on part of colon removed. Hence no suspicion of NETs.
Diagnosed after surgery	2	Cysts on pancreas seen on CT. Surgery to resect mass and pathology of mass showed pNET
Likely found on imaging/scope	3	Not enough information provided. But among other symptoms reported were rectal bleeding and incontinence. This may have led to a scope or imaging that found the tumour, followed by testing for NETs. Participant likely thought it was found incidentally and not tested simply because it was caught on imaging or through scope.
Diagnosed after surgery	4	Not enough information provided. However, patient reported extensive surgery in small bowel and large intestine. Primary site is appendix. Patient also indicated Biopsy as the only test for NETs undertaken. It could be the case that there was never suspicion of NETs by a doctor, but rather a surgery for complications from NETs followed by a diagnosis.
Likely found on imaging/scope	5	Not enough information provided. However, patient reported colonoscopy as the only testing procedure undergone, symptoms of skin flushing and diarrhea with a severity of 10, and misdiagnosis with Irritable Bowel Disease. Primary site is the Cecum. It's likely that this patient had undergone colonoscopy to investigate abdominal symptoms and NET was discovered then. Hence there was no suspicion of NETs.
Diagnosed after surgery	6	Not enough information provided. However, patient indicated that diagnosis was made following surgery. Primary site was Small Intestine and symptoms reported were abdominal pain and nausea with vomiting. Diagnostic tests reported were CT, Colonoscopy and Endoscopy. Therefore, it is likely that an investigation of abdominal complaints led to the discovery of a tumour which was shown to be a NET in pathology. Hence there was no suspicion of NETs.

Likely found on imaging/scope	7	Lung primary. Patient reported the NET was discovered on a bronchoscope and a respirologist recommended the test for NETs. While the patient did not indicate any respiratory symptoms experienced that led to seeking medical attention, they did report pneumonia as a misdiagnosis they have received. This hints that that the patient has experienced some respiratory symptoms that prompted the bronchoscope and the subsequent detection and diagnosis of NET. Hence there was no NET suspicion.
Likely found on imaging/scope	8	Patient indicated reported first seeing a GP with severe abdominal symptoms, and that it was a colonoscopy and subsequent pathology that diagnosed the NET. Hence there was no NET suspicion.
Likely found on imaging/scope	9	Not a lot of information provided. Small Intestine primary. Patient reported strong abdominal symptoms like pain, diarrhea and nausea with vomiting. It was indicated that a GP was first seen for those symptoms and a CT scan was the only test undergone that the patient has reported in the survey. It is likely that the abdominal symptoms have prompted the CT and a diagnosis was made from there. Hence there as no NET suspicion.
Likely found on imaging/scope	10	Lung primary. Patient reported respiratory symptoms and a history of Sjogren's prompted an X-ray that showed a growth. Growth was determined to be benign but upon a patient requested X-ray years later, multiple tumours were found and were misdiagnosed as lung cancer. Further investigation showed the tumour to be a NET. Hence there was never a suspicion of NET.
Likely found on imaging/scope	11	Small Intestine primary. Severe symptoms reported: Abdominal symptoms and skin flushing. After years of misdiagnosis, patient kept going to their doctor asking for more tests until an ultrasound showed something on the liver. Testing was done for months until a biopsy identified the NET. Hence there was never a suspicion of NETs.
Likely found on imaging/scope	12	Pancreatic primary. Patient reported that after going to doctors with symptoms and complaints, there was never a suspicion of NETs. Patient did the research and demanded a CT through a walk-in clinic which led to the diagnosis. Patient indicated that "NETs discovered incidentally" was chosen because the doctors never suspected NETs, and it was the patient who did and the patient who suggested the test to find NETs. After a hospital referral and further testing, NETs were diagnosed.
Diagnosed after surgery	13	Appendix primary. Patient reported experiencing multiple symptoms for years that were misattributed to be psychiatric of

		origin. After going to the ER for severe lower back flank pain, only mild swelling in the appendix was found with no fever or vomiting. After patient demanded a surgery be done, the on-call surgeon identified the NET. Hence there was never a suspicion of NETs.
Likely found on imaging/scope	14	Not a lot of information provided. Small Intestine primary. Patient reported being diagnosed with NET after surgery. Severe symptoms reported: Abdominal pain, fatigue and constipation. Patient also reported seeking medical attention 1-2 months after the appearance of symptoms and seeing a GP/Family Doctor. Among the tests undergone for NETs, patient reported a CT scan. It is therefore likely that the patient went to a GP with severe abdominal symptoms which prompted imaging that found the growth. Surgery and subsequent pathology revealed it to be a NET. Hence there was no suspicion of NETs.
Likely found on imaging/scope	15	Double primary: Appendix and pancreas as part of MEN1. Patient reported severe abdominal pain as the only symptom and that within the first day of symptoms, they had a CT and an ultrasound. Results ruled out appendicitis but a shadow on the pancreas was found. An MRI followed by an endoscopic ultrasound and biopsy confirmed that there was no cancer. Follow-up MRI over a 3-year period found nothing. After the final MRI 2 years later, tumours were found. NETs were diagnosed following surgery. Hence there was never a suspicion of NETs.
Found tumour during ER admission, Diagnosed after surgery	16	Small intestine primary. Multiple severe symptoms (abdominal pain, abdominal discomfort, skin flushing, diarrhea, nausea with vomiting, wheezing or difficulty breathing, dizziness, shaking, chest pressure and hypoglycemia) ignored by doctors for years and attributed to stress. ER admission after severe bout of vomiting. Emergency CT showed tumour in bowels with metastases to the liver and peritoneal cavity. Surgeon did a biopsy later that diagnosed the NET. Hence NETs were never suspected.
Likely found on imaging/scope	17	Small intestine primary. Reported strong symptoms: abdominal discomfort, skin flushing, diarrhea and fatigue and hypertension. Only indicated CT scan as test received. It is likely that the NET was first seen on a CT done to address the abdominal complaints. This is why patient indicated "NET discovered incidentally", mistaking a finding on a CT as an incidental finding.
Diagnosed following ER admission	18	Small intestine primary. Patient indicated that NET was diagnosed following an emergency admission and that a surgeon suggested the test that led to NET diagnosis. It is likely that patient chose "NET discovered incidentally" because they were

		never tested traditionally, but rather investigated during the ER visit.

Table S4. Responses to "Why were you not tested"

Number	Comment provided by participant
1	Started vomiting thought it was gallbladder. But I had been sick for at least 5-7 years .
2	Discovered during biopsy
3	My family doctor had never had a case before. Finally after two trips to emergency I was given a CT scan. The Timor was blocking 95% of my small intestine
4	We thought it was diverticulitis
5	Diagnosed after surgery
6	I was told I had Crohn's
7	My symptoms were attributed to an ulcer, gall bladder, then I was told it was all in my head and referred for a psychiatric evaluation. My neuroendocrine diagnosis was diagnosed (4 years into my symptoms) by the Dr. during a colonoscopy. Im sure many of us have our stories to tell.
8	I complained about all the pain I had with bloating etc. My primary family doctor sent me for ultrasound. This found rumours in mynliver. Went to liver specialists and that's when NETs was suspected. I was even in hospital for pain w years earlier and it wasnt suspected. WTF
9	I was finally diagnosed during surgery to have tumor removed.
10	Bronchoscopy was done and biopsy advised NET. There was never any suspicion of NET and it wasn’t until pathology came back I was finally diagnosed.

Table S5. Misdiagnosis comprising each clinical category

Clinical Category	Reported Misdiagnoses
Gastroenteropancreatic (GEP)	Irritable Bowel Disease
	Inflammatory Bowel Disease (Crohn's, Ulcerative Colitis)
	Constipation
	Hemorrhoids
	Appendicitis
	Diverticulitis
	Diverticulosis
	Inflamed bowel
	Chronic Ascending Cholangitis
	Twisted Bowel Syndrome
	Partial Small Bowel obstruction
	Dyspepsia
	Stomach ulcer
	Acid Reflux
	Heartburn
	GERD
	Barrett's esophagus
	Pancreatitis
Hepatobiliary (HEP)	Gall Stones
	"Underwent Cholecystectomy"
Respiratory (RESP)	Pneumonia
	Chest Infection
	Asthma
	Flu
	Bronchitis
	Sleep apnea
	Lung cancer
Nephrological (NEPH)	Kidney Stones
	Urinary Tract Infection (UTI)
Psychiatric (PSYCH)	Mental Health Condition (Anxiety, Depression, Bipolar, PTSD, Other)
	Stress
	Panic attacks
OB/GYN (GYN)	Menopause
	Polycystic Ovary Syndrome (PCOS)
	Uterine fibroids
	Fibroma

Cardiovascular (CARD)	Hypertension
	Tachycardia
	Transient heart palpitations
Immunological (IMM)	Allergy
	Food allergies
	Ehlers-Danlos Syndrome (EDS)
Endocrine (ENDO)	Diabetes
Dermatological (DERM)	Rosacea
Benign Tumours	Hemangioma
	"Other benign tumor"
Surgical	"Complication from Gall Bladder surgery"
Hematological (HEM)	Anemia
Bariatric (BAR)	Obesity
Oncological (ONC)	Other Tumour / Cancer
Other	Magnesium deficiency
	Throat irritation
	"Lesion that causes high blood pressure"
	"Possible Abuse"