Pheochromocytoma in Denmark during 1977–2016: validating diagnosis codes and creating a national cohort using patterns of health registrations

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Background: Pheochromocytoma and catecholamine-secreting paraganglioma (PPGL) are rare but potentially life-threatening tumors. We aimed to validate diagnosis codes for PPGL in the Danish National Patient Registry, the Danish National Pathology Registry, and the Danish Registry of Causes of Death and to create a national cohort of incident PPGL patients by linking these three registries.

Patients and methods: We obtained data from the three abovementioned registries for all individuals registered with pheochromocytoma or catecholamine hypersecretion in Denmark during 1977–2016 (average population 5.30 million). We then reviewed health records for all individuals living in the North Denmark Region and Central Denmark Region (average population 1.75 million) to validate the diagnosis of PPGL. We tested a number of algorithms for accurately identifying true cases of PPGL to maximize positive predictive values (PPVs) and completeness. The best algorithm was subsequently validated in an external sample.

Results: We identified 2626 individuals with a PPGL diagnosis code in Denmark, including 787 (30.0%) in the North Denmark Region and Central Denmark Region. In this subsample, we retrieved the health records of 771/787 (98.0%) individuals and confirmed 198 incident PPGL patients (25.3%). The PPV of PPGL diagnosis codes was 21.7% in the Danish National Patient Registry, 50.0% in the Danish Registry of Causes of Death, and 79.5% in the Danish National Pathology Registry. By combining patterns of registrations in the three registries, we could increase the PPV to 93.1% (95% confidence interval [CI]: 88.5–96.3) and completeness to 88.9% (95% CI: 83.7–92.9), thus creating a national PPGL cohort of 588 patients. PPV for the optimal algorithm was 95.3% (95% CI: 88.5–98.7) in the external validation sample.

Conclusion: Diagnosis codes for pheochromocytoma had low PPV in several individual health registries. However, with a combination of registries we were able to identify a near-complete national cohort of PPGL patients in Denmark, as a valuable source for epidemiological research.

Keywords: registry-based research, International Classification of Diseases, ICD, Systematized Nomenclature of Medicine, SNOMED, hospital register diagnoses, pathology register, cause of death register

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Introduction

Pheochromocytoma and catecholamine-secreting paraganglioma (PPGL) are rare but potentially fatal catecholamine-secreting tumors.¹ During recent years, improvements in imaging techniques have led to increasing number of patients being incidentally diagnosed with adrenal tumors and evaluated for catecholamine hypersecretion.^{2,3}

Whether this has led to an increase in the incidence of PPGL, or changes in its prognosis, remains unknown. Due to the rarity of the disease, large-scale studies of incidence and clinical outcomes of PPGL are scarce and most previous studies have been limited to tertiary centers with the potential risk of referral bias and substantial loss to follow-up.^{4–7}

Health care databases are a valuable source for epidemiological research in rare diseases provided diagnoses are valid. Since 1967, the unique civil registration number in the Civil Registration System has been used to register all individuals living or working in Denmark with a complete follow-up history of birth, addresses, migration, and death.⁸ The civil registration number enables exact linkage of all data routinely collected in national health registries in Denmark, which makes it possible to rapidly identify a complete nationwide cohort of individuals with a disease diagnosis.^{9,10} However, as shown in previous Danish studies on certain rare tumors¹⁰ and endocrine diseases,^{11,12} the validity of diagnosis codes of rare diseases may be relatively low, with positive predictive values (PPVs) of true presence of disease ranging from 30% to 55%. Applying algorithms restricting to patients hospitalized at specialized departments or undergoing certain treatment regimens may improve PPV of diagnosis codes with a limited loss of cases.^{10–12} To our knowledge, no studies have yet validated the accuracy of PPGL registrations.

Therefore, we aimed to validate PPGL diagnosis codes and to create an algorithm that can accurately identify incident cases of PPGL in Denmark by combining data from three registries: the Danish National Patient Registry, the Danish Registry of Causes of Death, and the Danish National Pathology Registry. This would allow us to create a nationwide, population-based PPGL cohort as a source for future research on trends in the incidence, morbidity, and mortality of PPGL.

Patients and methods

Health registries, International Classification of Diseases (ICD), and Systematized Nomenclature of Medicine (SNOMED)

In Denmark, MDs report the primary cause of a contact at a Danish hospital to the Danish National Patient Registry for all in- and outpatient contacts with up to 20 secondary diagnoses.⁹ Likewise, for all deaths in Denmark, an MD will complete a death certificate and report one or more causes of death to the Danish Registry of Causes of Death.¹³ In both registries, diagnoses have been registered using the

ICD 8th edition (ICD-8) until 1994, and thereafter using the 10th edition (ICD-10).^{9,13} For all pathological examinations performed in Denmark, the pathologist registers the diagnosis, the origin of tissue, and performed examinations in the SNOMED.¹⁴ Reporting to the three registries is mandatory in all of Denmark.

Generally, the coverage or completeness of the registries are internationally considered excellent and have not undergone any major structural changes in the last 20 years (see Table S1).^{9,13–16}

Identification of potential PPGL cases

In order to identify all individuals with potential PPGL, we obtained data from the Danish Health Authority for individuals registered with at least one diagnosis code related to pheochromocytoma or catecholamine hypersecretion in the Danish National Patient Registry, Danish National Pathology Registry, or Danish Registry of Causes of Death (Table 1).

The primary eligibility criterion was a PPGL diagnosis code at an in- or outpatient contact (as either primary, secondary, supplementary, or referral diagnosis code), as a cause of death, or as a diagnostic conclusion of a pathological examination. We included only patients who had their first PPGL diagnosis code from January 1, 1977, to December 31, 2016, whilst living in Denmark. PPGL diagnosis codes included 255.29 (ICD8), D350A, E275, R825A (ICD10), M8700, and S29740 (SNOMED).

Validation of PPGL diagnosis codes was limited to eligible individuals living in the North Denmark Region and Central Denmark Region at the time of first PPGL diagnosis: the validation cohort. These two out of five Danish regions had an average population during the study period of 1.75 million inhabitants, corresponding to 33% of the total Danish population (average population 5.30 million, calculations based on data from public institutions).^{17–20}

Completeness of PPGL registrations

To assess if our eligibility criteria completely identified all PPGL cases, that is, if all diagnosed PPGL patients had been registered with a PPGL diagnosis code, we introduced expanded eligibility criteria. We included individuals registered with one of 31 possibly PPGL-related diagnosis codes in the Danish National Patient Registry between January 1, 1990 and February 28, 2015 (Table 2). Validation of this group was restricted to individuals registered at the Department of Endocrinology and Internal Medicine at Aarhus University Hospital, the largest endocrine center in Central Region Denmark: the expanded validation cohort.

Table 1 Eligibility criteria

	Danish National Patient Registry	Danish Registry of Causes of Death	Danish National Pathology Registry
Registration date	Date of start of in- or outpatient contact	Date of death or found dead	Date of requisition of pathological examination
Type of diagnosis code	Diagnosis code for primary, secondary, or supplementary cause of contact or referral	Diagnosis code for immediate, contributing, or other cause of death	Pathology code for diagnostic conclusion of pathological examination
PPGL diagnosis codes	ICD-8 255.29 Pheochromocytoma ICD-10 D350A Pheochromocytoma E275x ^a Catecholamine hypersecretion R825A Elevated urine levels of catecholamines SNOMED ^b ZM8700x ^a Pheochromocytoma	ICD-8 ^c 255.2 Pheochromocytoma ICD-10 ^c D350 Benign neoplasm of adrenal gland E275 Catecholamine hypersecretion R825 Elevated urine levels of drugs, medicaments, and biological substances	SNOMED M8700x ^a Pheochromocytoma S29740 Pheochromocytoma syndrome

Notes: Individuals were considered eligible if they had a PPGL diagnosis code as the specified type of diagnosis code in a registry, and the date of their first registered diagnosis code was between January 1, 1977, and December 31, 2017, and while they lived in Denmark. Only individuals living in the North Denmark Region and Central Denmark Region at time of first registration were included in the validation cohort. ^aIncluding underlying diagnosis codes. ^bIn the Danish National Patient Registry, SNOMED diagnosis codes can only be used as optional supplementary diagnosis codes. ^cDiagnosis codes in the Danish Registry of Causes of Death have a maximum length of four characters making them less detailed than in ICD-8 and ICD-10 codes in the Danish National Patient Registry.

Abbreviations: ICD-8, International Classification of Diseases 8th edition; ICD-10, International Classification of Disease 10th edition; PPGL, pheochromocytoma and catecholamine-secreting paraganglioma; SNOMED, Systematized Nomenclature of Medicine.

Further, we asked specialists in adrenal diseases from the two major endocrine centers in the validation area (Department of Endocrinology and Internal Medicine at Aarhus University Hospital and Department of Endocrinology at Aalborg University Hospital) to contribute with any additional PPGL patients who might not have been initially identified.

Thus, the final PPGL cohort in our validation area consisted of confirmed PPGL patients found in the validation cohort, the expanded validation cohort, or additionally reported by endocrine specialists (Figure 1).

Validation of PPGL diagnosis

One researcher (ALE) located and reviewed health records from hospitals for all individuals in the validation cohort. Electronic health records were reviewed, if available. Paper health records and/or records from hospitals outside the validation area were located if no electronic records existed or if necessary to definitively confirm or refute PPGL.

The researcher confirmed or refuted PPGL based on agreement among lab tests of catecholamines, vanillylmandelic acid, and metanephrines in blood or urine; imaging studies and pathological examinations; as well as the diagnostic conclusion made by treating clinician as noted in health records. Diagnostic criteria for confirming or refuting PPGL are listed in Table 3.

Individuals who had ambiguous results or incomplete diagnostic workup were considered cases of doubt and presented to an expert panel consisting of two specialists (PLP and ES) in endocrinology and adrenal diseases (see Table 3

for examples). Based on available information on performed tests, examinations, and imaging studies as well as medical history and presentation, the expert panel decided if PPGL was the most likely diagnosis and there was sufficient evidence to confirm it. If not, PPGL was considered refuted.

For confirmed PPGL patients, we defined the date of clinical diagnosis as the first date of a positive pathological examination, an at fivefold elevated lab test for PPGL, or the date the treating clinician confirmed PPGL according to the health records.

Data were recorded in a database designed using EpiData Manager 4.2.0.0 (EpiData Association, Odense, Denmark).

Development of algorithm to identify true PPGL patients

After reviewing health records and confirming or refuting PPGL, we tested various algorithms to identify confirmed PPGL patients among all individuals fulfilling eligibility criteria in the North Denmark Region and Central Denmark Region using only their registry data. Algorithms were successively improved through several iterations to maximize PPV and completeness, as described in the Results section. PPV and completeness are defined in the Data analysis section.

Testing PPV of algorithm in external population

To validate the PPV result of the final optimal algorithm, we used the eligible external population of Region Zealand and

Table 2 Expanded eligibility criteria

	Danish National Patient Registry
Registration date	Date of hospital admission or outpatient contact
Type of diagnosis code	Diagnosis code for primary, secondary, or supplementary cause of contact
Possibly PPGL-related diagnosis codes	<p>ICD-8</p> <p>194.0 Malignant neoplasm of endocrine glands—suprarenal gland</p> <p>194.8 Malignant neoplasm of endocrine glands—other</p> <p>194.9 Malignant neoplasm of endocrine glands—unspecified</p> <p>226.0 Benign neoplasm of endocrine glands—suprarenal gland</p> <p>226.8 Benign neoplasm of endocrine glands—other</p> <p>226.9 Benign neoplasm of endocrine glands—unspecified</p> <p>239.1 Neoplasm of uncertain behavior of endocrine glands and nervous system</p> <p>255.9 Other and unspecified diseases of adrenal glands</p> <p>743.4 Neurofibromatosis (von Recklinghausen)</p> <p>ICD-10</p> <p>C741 Malignant neoplasm of medulla of adrenal gland</p> <p>C749 Malignant neoplasm of unspecified part of adrenal gland</p> <p>C754 Malignant neoplasm of carotid body</p> <p>C755 Malignant neoplasm of aortic body and other paraganglia</p> <p>D093B Carcinoma in situ of other endocrine gland</p> <p>D350 Benign neoplasm of adrenal gland</p> <p>D355 Benign neoplasm of carotid body</p> <p>D356 Benign neoplasm of aortic body and other paraganglia</p> <p>D358 Benign neoplasm, pluriglandular involvement</p> <p>D359 Benign neoplasm of endocrine gland, unspecified</p> <p>D361B Benign neoplasm of autonomic nervous system</p> <p>D441 Neoplasm of uncertain behavior of adrenal gland</p> <p>D446 Neoplasm of uncertain behavior of carotid body</p> <p>D447 Neoplasm of uncertain behavior of aortic body and other paraganglia</p> <p>D448A Multiple endocrine adenomatoses</p> <p>D449 Neoplasm of uncertain behavior of unspecified endocrine gland</p> <p>E278 Other specified disorders of adrenal gland</p> <p>E279 Disorder of adrenal gland, unspecified</p> <p>E348 Other specified endocrine disorders</p> <p>Q850 Neurofibromatosis (nonmalignant)</p> <p>Q858D Von Hippel–Lindau syndrome</p> <p>Z031W Observation for suspected malignancy in adrenal gland</p>

Notes: Individuals fulfilled expanded eligibility criteria if registered with a possibly PPGL-related diagnosis code as primary, secondary, or supplementary cause of contact in the Danish National Patient Registry, and the date of their first registered diagnosis code was between January 1, 1990, and February 28, 2015, and while they lived in Denmark. Only individuals living in the North Denmark Region and Central Denmark Region at time of first registration who also were registered with possibly PPGL-related diagnosis code at the Department of Endocrinology and Internal Medicine at Aarhus University Hospital were included in the expanded validation cohort.

Abbreviations: ICD-8, International Classification of Diseases 8th edition; ICD-10, International Classification of Disease 10th edition; PPGL, pheochromocytoma and catecholamine-secreting paraganglioma.

the Capital Region of Denmark (average population in study period 2.39 million). Here, health records were reviewed by a second researcher (SFJ) for a random sample of 110 individuals, identified by the algorithm as PPGL patients, and diagnostic ambiguities were scrutinized by an expert (UFR). This was done in order to verify agreement between the conclusion of the algorithm based on registry data and researcher's conclusion based on health records.

Data analysis

Validity of ICD-8, ICD-10, and SNOMED diagnosis codes was expressed in PPV, defined as the proportion of confirmed

PPGL patients among individuals in the validation cohort registered with the specific diagnosis code.

Accuracy of the algorithms was expressed in terms of PPV and completeness. PPV was defined as the proportion of confirmed PPGL patients among individuals in the validation cohort identified by the algorithm as PPGL patients. Completeness was defined as the proportion of confirmed PPGL patients identified by the algorithm in the validation cohort among all confirmed PPGL patients in the validation area. In order not to overestimate completeness, the denominator also included confirmed PPGL patients identified by expanded validation criteria or reported by adrenal specialist, as they

Figure 1 Identification of PPGL patients in area of validation, the North Denmark Region and Central Denmark Region.

Notes: ^aSeven cases of doubt refuted as non-secreting paragangliomas; twenty-four refuted due to weak clinical evidence despite some inconsistencies; and six refuted due to insufficient information to confirm PPGL. ^bThirty-five cases of doubt confirmed as PPGL based on pathology and clinic despite no lab tests performed (diagnosed at autopsy or by pathologist post-surgery); three confirmed despite no pathological examination (patient abstained from surgery or surgery not technically possible); and fourteen confirmed due to strong clinical evidence despite some missing data or inconsistencies. ^cFive refuted as non-secreting paragangliomas; six refuted as workup were insufficient to confirm PPGL. ^dOne patient with confirmed PPGL who did not fulfill primary or expanded eligibility criteria was reported by endocrine specialist (MGR) at Department of Endocrinology at Aalborg University Hospital.

Abbreviation: PPGL, pheochromocytoma and catecholamine-secreting paraganglioma.

did not fulfill eligibility criteria and therefore could never be identified by the algorithm. PPV and completeness were reported with 95% confidence intervals (95% CIs).

Individuals with no available health records were excluded from all calculations of PPV and completeness. Confirmed PPGL patients were excluded from all calculations if diagnosed before 1977 or while living abroad, as they could not be considered incident PPGL cases.

Data management and calculations were performed in Stata Statistical Software: release 13 (StataCorp LP, College Station, TX, USA) and were based on the final dataset received from the Danish Health Authorities on March 22, 2017.

Ethics

The research project was approved by the Danish Data Protection Agency (reference number 2014-41-3198). Permission to review health records without individually

informed patient consent was granted by the Danish Health Authorities (reference number 3-3013-1021/1) in accordance with Danish law.

Results

Identification of PPGL cases

A total of 2626 individuals with a PPGL diagnosis code were identified in all of Denmark for the period 1977–2016, whereof 787 (30.0%) lived in the validation area of the North Denmark Region and Central Denmark Region at time of first registered PPGL diagnosis code (Table 4): 688 individuals were identified in the Danish National Patient Registry, 21 in the Danish Registry of Causes of Death, and 214 in the Danish National Pathology Registry. A total of 652 individuals had a PPGL diagnosis in a single registry, 134 had a PPGL diagnosis code in two registries, and one in all three registries.

Table 3 PPGL diagnostic criteria for confirming or refuting PPGL**Confirmed**

1. PPGL diagnosed by pathologist and lab tests^a confirming PPGL or with moderate to high suspicion for PPGL
2. PPGL diagnosed by pathologist and lab tests^a performed but report missing and one or more tumors identified by radio imaging in location consistent with PPGL and confirmed in health records by treating clinician
3. Lab tests^a confirming PPGL or with moderate to high suspicion for PPGL and pathological examination performed but report missing and one or more tumors identified by radio imaging in location consistent with PPGL and confirmed in health records by treating clinicians
4. Case of doubt further scrutinized by expert panel, which deemed PPGL the most likely diagnosis.

Examples on cases of doubt confirmed by expert panel:^b

PPGL confirmed in health records by treating clinician but reports on both pathological examination and lab tests^a missing.
 PPGL diagnosed by pathologist but lab tests^a with low suspicion for PPGL
 PPGL diagnosed by pathologist but no lab tests^a performed (eg, an incidental discovery at autopsy or after surgery on other indication)
 Lab tests^a confirming PPGL or with moderate to high suspicion for PPGL and PPGL confirmed in health records by treating clinician but no pathological examination performed (eg patient died before surgery, abstained from treatment or surgery was not technically possible)

Refuted

1. Never suspected of or evaluated for PPGL (eg, incorrect registration of wrong diagnosis code)
2. PPGL refuted by pathologist or other adrenal tumor diagnosed by pathologist (eg, adrenal cortical adenoma, metastasis)
3. Lab tests^a refuting PPGL
4. Lab test^a with low to moderate suspicion for PPGL and refuted by treating clinician in health records
5. Lab test^a with low to moderate suspicion for PPGL and radio imaging performed with no tumors located in location consistent with PPGL
6. Radio imaging performed with no tumors located in location consistent with PPGL and refuted by treating clinician in health records
7. Pathological examination, lab tests,^a or radio imaging performed but report(s) missing and refuted by treating clinician in health records
8. Case of doubt further scrutinized by expert panel, which deemed PPGL refuted, unlikely or with insufficient data to determine if confirmed or refuted.

Examples on cases of doubt refuted by expert panel:^b

PPGL diagnosed by pathologist but lab tests refuting PPGL (eg, hormonally silent paraganglioma)
 Insufficient workup (eg, some clinical suspicion but no relevant workup or lab test with low to high suspicion for PPGL but patient abstained from new test, imaging or any further investigations)
 Inconsistencies in workup (eg, lab tests considered highly suspicious of PPGL but no tumors found by imaging or PPGL pathologically refuted)

Notes: ^aPPGL lab tests include blood and urine measurements of catecholamines, vanillylmandelic acid, and metanephrines. A single lab test elevated fivefold or more above reference range not caused by interfering factors (interacting drugs, trauma, critical disease, etc) was considered as confirming PPGL. Three or more lab tests consistently elevated 2- to 4.9-fold were considered of moderate to high suspicion for PPGL. Varying lab tests with only one or two lab tests elevated 2- to 4.9-fold or lab tests consistently elevated less than twofold were considered of moderate to low suspicion for PPGL. One or more lab tests consistently within reference range was considered as refuting PPGL. ^bList of examples of cases of doubt is not exhaustive.

Abbreviation: PPGL, pheochromocytoma and catecholamine-secreting paraganglioma.

Health records were located and reviewed for 771 (98.0%) of the 787 patients in the validation cohort (Table 4, Figure 1). PPGL was confirmed in 202 patients (26.2%), including 52 confirmed by the expert panel after further scrutinizing 89 cases of doubt. Nine were excluded as they lived abroad at time of diagnosis (N = 2) or were diagnosed before 1977 (N = 7).

In the expanded validation cohort, 913 individuals with a possible PPGL-related diagnosis code had been registered at Department of Endocrinology and Internal Medicine at Aarhus University hospital. Health records were located

and reviewed for 816 (89.4%) and an additional four PPGL patients were identified. Further, one additional PPGL patient was reported by the specialist at Department of Endocrinology at Aalborg University Hospital.

In total, a final PPGL cohort of 198 confirmed incident PPGL patients were identified in the North Denmark Region and Central Denmark Region. The median difference between date of first-registered PPGL diagnosis code and date of clinical diagnosis was 0 days (IQR: clinical diagnosis 32 days before to 4 days after).

Table 4 PPGL registrations and validity of diagnosis codes

Diagnosis code	Individuals in Denmark with diagnosis code	Individuals in validation area with diagnosis code (percentage of total)	Health records available	PPGL confirmed ^e	PPV (95% CI) ^e
Danish National Patient Registry					
255.29 Pheochromocytoma ^a	721	263 (36.5%)	249	49	20.2% (15.4–25.9)
D350A Pheochromocytoma ^b	892	268 (30.0%)	268	82	30.8% (25.3–36.8)
E275x Catecholamine hypersecretion ^{b,d}	877	195 (22.2%)	194	46	23.7% (17.9–30.3)
R825A Elevated urine levels of catecholamines ^b	2	1 (50.0%)	1	0	0.0% (0.0–97.5)
ZM8700x Pheochromocytoma ^{c,d}	24	8 (33.3%)	8	5	71.4% (29.0–96.3)
Total individuals in registry	2323	688 (29.6%)	673	144	21.7% (18.6–25.0)
Danish Registry of Causes of Death					
255.2 Pheochromocytoma ^a	31	9 (29.0%)	8	6	100.0% (54.1–100.0)
D350: Benign neoplasm of adrenal gland ^b	63	11 (17.5%)	11	3	27.3% (6.0–61.0)
E275: Adrenomedullary hyperfunction ^b	1	1 (100.0%)	1	0	0.0% (0.0–97.5)
R825: Elevated urine levels of drugs, medicine or biological substances ^b	0	–	–	–	–
Total individuals in registry	95	21 (22.1%)	20	9	50.0% (26.0–74.0)
The Danish National Pathology Registry					
M8700x: Pheochromocytoma ^{c,d}	630	214 (34.0%)	212	167	79.5% (73.4–84.8)
S29740: Pheochromocytoma syndrome ^c	5	2 (40.0%)	2	2	100.0% (15.8–100.0)
Total individuals in registry	630	214 (34.0%)	212	167	79.5% (73.4–84.8)
Total individuals in all registries	2626	787 (30.0%)	771	193	25.3% (22.3–28.6)

Notes: Each person can be included in the table with more than one diagnosis code and in more than one registry. ^aInternational Classification of Diseases 8th edition. ^bInternational Classification of Disease 10th edition. ^cSystematized nomenclature of medicine. ^dIncluding underlying codes. ^eNine confirmed PPGL patients were excluded as they were diagnosed before 1977 or while living outside Denmark.

Abbreviations: CI, confidence interval; PPGL, pheochromocytoma and catecholamine-secreting paraganglioma; PPV, positive predictive value.

Validity of PPGL diagnosis codes

Overall, PPV of an ICD-8, ICD-10, or SNOMED diagnosis code for PPGL in any registry was 25.3% (95% CI: 22.3–28.6; Table 4) for confirmed incident PPGL. ICD-8 (255.29) and -10 diagnosis codes (D350A, E275, and R825A) had an overall PPV of 21.7% (95% CI: 18.6–25.0) in the Danish National Patient Registry and 50.0% (95% CI: 26.0–74.0) in the Danish Registry of Causes of Death.

SNOMED diagnosis codes for PPGL (M8700 and S29740) in the Danish National Pathology Registry had a higher overall PPV than the two other health registries at 79.5% (95% CI: 73.4–84.8). Forty-three (20.3%) of 212 individuals registered with pathological diagnosis code “M8700 Pheochromocytoma” did not have PPGL. Of these, thirty-one were refuted as incorrect entries (mainly miscoding of T8700 Ovary or M8720 Naevus), three as non-secreting paragangliomas, five due to a suspicion of PPGL later refuted by further examinations, and four by the expert panel as incorrect diagnoses of PPGL.

Algorithms for identifying PPGL patients

To identify true cases of PPGL using registry data only, we tested different algorithms to obtain as high a PPV and

completeness of data as possible by combining data from the three registries.

First, we found that if a person was registered with a PPGL diagnosis code in at least two of the three registries, a PPV of 97.7% (95% CI: 93.4–99.5) was achieved (Table 5). However, the completeness was rather low as this algorithm only identified 127 or 64.1% (95% CI: 57.0–70.8) of the 198 confirmed PPGL patients. Secondly, we found a PPV of 93.6% (95% CI: 88.9–96.8) for PPGL diagnosis codes registered in the Danish National Pathology Registry if the pathological examination had been performed on a relevant tissue or if the patient also had a surgical procedure code for adrenal surgery (086, 088, 090, and KBC) in the Danish National Patient Registry. We defined the examined tissue to be relevant if the pathological examination was registered as an autopsy (material code 31) or with a SNOMED code for either the adrenal glands (T93 and ÆF4330), paraganglioma (T94, T95, M868, and M869), or the body as a whole (T0010).

Combined PPGL diagnosis codes in two registries or PPGL pathologically confirmed in a relevant tissue had a PPV of 93.9% (95% CI: 89.3–96.9) and a completeness of 85.4% (95% CI: 79.6–90.0). However, several patients who

Table 5 Algorithms for identifying confirmed PPGL patients

Algorithms	PPV % (95% CI)	FP, N	Completeness % (95% CI)	FN, N
Registered with any PPGL diagnosis codes in more than one registry ^a	97.7% (93.4–99.5)	3	64.1% (57.0–70.8)	71
Registered in the Danish National Pathology Registry with a PPGL diagnosis ^b code + the examination was performed on a relevant tissue ^c or the patient is registered with a surgical procedure code for adrenal surgery ^d in the Danish National Patient Registry	93.6% (88.9–96.8)	11	81.8% (75.7–86.9)	36
Registered with the ICD-8 diagnosis code 255.2 for pheochromocytoma in the Danish Registry of Causes of Death	100.0% (54.1–100.0)	0	3.0% (1.1–6.5)	192
Registered with a diagnosis code for pheochromocytoma or catecholamine hypersecretion in the Danish National Patient Registry less than 30 days before date of death	83.3% (51.6–97.9)	2	5.1% (2.4–9.1)	188
All algorithms combined	93.1% (88.5–96.3)	13	88.9% (83.7–92.9)	22

Notes: ^aSee Table 1 for included registries and diagnosis codes. ^bM8700 or S29740, including underlying codes. ^cRelevant tissue defined as material code for autopsy “31: deceased body”, or with SNOMED diagnosis codes, including underlying codes: topography codes “T0010: body as a whole”, “T93: adrenal gland” and “T94-95: paraganglioma”, morphology codes “M868-869: paraganglioma” or etiology code “ÆF4330: originated from adrenal gland”. ^dProcedure codes for adrenal surgery, including underlying codes: “086: explorative incision on adrenal gland”, “088: biopsy of adrenal gland”, “090: adrenalectomy”, and “KBC: surgery on adrenal gland”.

Abbreviations: CI, confidence interval; FP, false positive; FN, false negative; ICD-8, International Classification of Diseases 8th edition; PPGL, pheochromocytoma and catecholamine-secreting paraganglioma; PPV, positive predictive value.

had died prior to surgery or prior to definitive diagnosis were not identified.

Thirdly, we found that the ICD-8 diagnosis code 255.2 in the Danish Registry of Causes of Death had a PPV of 100.0% (95% CI: 54.1–100.0). The ICD-10 codes had low PPV in the Danish Registry of Causes of Death and were not included in the algorithm.

Finally, a PPGL diagnosis code in the Danish National Patient Registry less than 30 days before date of death identified five PPGL patients who had not been included by the above-mentioned algorithms.

Other attempts to increase the PPV of registrations in the Danish National Patient Registry included restricting to individuals registered at specialized endocrine departments or with at least two or three separate in- or outpatient contacts with PPGL diagnosis codes. This increased PPV but did not contribute with more confirmed PPGL patients and was not included in the final algorithm (Table S2).

The final algorithm, combining the four algorithms above, had a PPV of 93.1% (95%CI: 88.5–96.3). Of the 569 individuals with a PPGL diagnosis code for whom PPGL was refuted, only 13 (2.3%) were falsely identified by the final algorithm as PPGL patients. It identified 176 of the 198 confirmed PPGL patients in our validation area, resulting in a completeness of 88.9% (95% CI: 83.7–92.9). There were no significant differences in sex, age at diagnosis, or year of diagnosis between PPGL patients who were identified by the algorithm and patients who were missed (data not presented).

Subsequently, we applied the final algorithm to the external population of the remaining three regions. The algorithm identified 394 individuals as PPGL patients, of whom we

sampled 110 from Region Zealand and the Capital Region of Denmark for external validation of the algorithm. Health records were located for 86 (78.2%), and 82 patients were confirmed as PPGL patients, resulting in an external PPV for incident PPGL of 95.3% (95% CI: 88.5–98.7). Thus, with 198 PPGL patients from our validation area and 394 PPGL patients identified by the algorithm in the other regions minus four for whom PPGL were refuted, we identified a national cohort of 588 PPGL patients.

Discussion

In this population-based study, we have validated ICD-8, ICD-10, and SNOMED diagnosis codes for PPGL. We found that overall PPV was low but varied considerably between diagnosis codes and health registries. However, based on data from 198 confirmed PPGL patients, we developed an algorithm, which identified a national cohort of incident PPGL cases in the registries with high PPV as well as high completeness.

We have no previous studies on validity of PPGL diagnosis codes to compare with, but our results on PPV of diagnosis codes in the Danish National Patient Registry are comparable to similar studies on other rare diseases, which found overall PPV ranging from 34% to 55%.^{10–12} Unsurprisingly, we found that records in the Danish National Pathology Registry had the highest PPV when comparing the three health registries, as pathologists are trained in using the SNOMED system and are responsible for registering their own examinations. In addition, the diagnosis code is routinely updated if new tests on or reexaminations of the tissue leads to another diagnosis.¹⁴ In contrast, diagnosis codes in the two other registries

are often registered by MDs with only a limited knowledge of the patient and might be registered as a probable, suspected, or even a refuted diagnosis.^{9,13,16}

It is difficult to assess the completeness of the registries, as we do not know how many PPGL patients we missed in our validation area, whether undiagnosed or diagnosed but not registered. However, we have included three complementary registries, found health records for almost all in the validation cohort, and when we examined other possibly PPGL-related diagnosis codes, we only found a few PPGL patients. Therefore, we believe that we have identified the vast majority of the diagnosed PPGL patients in the validation area. Based on our results, we conclude that while most PPGL patients had a PPGL diagnosis code in the Danish National Pathology Registry or the Danish National Patient Registry, no single registry was sufficient to identify a complete cohort of PPGL patients.

The final algorithm identified PPGL patients with a high PPV, which we also validated in an external sample. This is important for future studies on differences in comorbidity and cause-specific mortality for PPGL patients compared to the background population. A high PPV minimizes the risk of misclassification bias, which could otherwise bias results both toward and away from the null hypothesis. Again, assuming we found most diagnosed incident PPGL patients in the validation area, the algorithm also had a high completeness, meaning it also has the potential for monitoring changes in incidence and prevalence of PPGL over time. However, some limitations of the algorithm must be considered. First, even though accuracy of the algorithm did not change during our study period, future changes in registries or coding procedures could both positively and negatively affect PPV and completeness. Secondly, we did not evaluate the completeness of the algorithm in an external population as we did with the PPV of the algorithm. However, giving the uniform organization of the health care system across all Danish regions, including the health registries, we assume that our results can be generalized to the rest of Denmark. Lastly, even though completeness of the algorithm was high, it may miss PPGL patients with a nonclassical clinical course, for example, patients deemed too old or fragile to undergo surgery who therefore might not have been registered in the Danish National Pathology Registry. While this group is quite small and therefore of little concern in regard to incidence and prevalence, it might be of importance if, for example, studying mortality of PPGL patients who do not undergo surgery.

The algorithm was created using Danish health registries, which, together with health registries in the other Scandinavian countries, are internationally considered to be comprehensive and have a high data quality.⁹ Thus, our

results cannot readily be extrapolated to countries with less comprehensive health registries.

Conclusion

Diagnosis codes for pheochromocytoma and catecholamine hypersecretion had a low PPV in several individual health registries in Denmark. However, with a combination of registries, we could identify a near-complete national cohort of incident PPGL patients in Denmark as a valuable source for future epidemiological research.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary Materials

Table S1 Important changes in health registries

	Danish National Patient Registry	Danish Registry of Causes of Death	Danish National Pathology Registry
Contents	Administrative and clinical information for all hospital contacts, including dates, diagnosis codes, and performed procedures. Diagnoses are registered by the physician discharging the patient. Procedures are registered by the responsible surgeon.	Time and cause(s) of death for every Danish decedent. Cause(s) of death are registered by the physician with most accurate knowledge of patient either hospital physician or practitioner. If autopsy is performed, the pathologist adds his or her findings.	Information on pathological examinations including tests performed, free text description of examination and SNOMED codes on topography and diagnostic conclusions. Data are reported by requisitioning department and pathologist(s) performing examination.
Coverage	Somatic hospital admissions discharged after January 1, 1977, psychiatric admissions discharged after January 1, 1995, and still-active admissions from 2015, and onward. Outpatient contacts ending in or active since 1995. Emergency department contacts since 1995.	Danish residents dying while residing in Denmark since 1970. Danish residents dying in Greenland and the Faroe Islands and Greenlanders and Faroese living in Denmark were included in 1983.	Includes incomplete data from some public pathology departments back to 1970 with national coverage from 1997. Registration became mandatory for private practicing pathologist in 2005.
Important changes in data	Diagnoses registered using Danish adaptations of ICD-8 1977–1993 and ICD-10 1994–now. Changes in registration of surgical procedures in 1981, 1989, and 1996, currently using Danish adaptation of Nordic Classification of Surgical Procedures. Has been basis for reimbursing departments and hospitals since 2000.	Diagnoses registered using Danish adaptations of ICD-8 1977–1993 and ICD-10 1994–now. Data were submitted by paper death certificates in 1970–2006 and electronically since 2007. In the 1970s, 75% of patients dying at hospitals were autopsied compared to less than 20% today. ¹³	Data were submitted by different computer-based systems and with varying data recorded 1970–1996. In 1997 a national standard for which data to register were defined. In 1999 a single national online tool for registering data were introduced.

Note: Data from references 9 and 13 to 16.

Abbreviations: ICD-8, International Classification of Diseases 8th edition; ICD-10, International Classification of Disease 10th edition; SNOMED, Systematized Nomenclature of Medicine.

Table S2 PPV and completeness of diagnosis codes in Danish National Patient Registry by number of in- or outpatient contacts

Diagnosis codes	PPV or completeness	At least one contact	At least two contacts	At least three contacts
255.29, D350A, E275x ^a , R825A, or ZM8700x ^a as primary, secondary, supplementary, or referral diagnosis code	PPV	21.7% (18.6–25.0)	54.5% (47.7–61.3)	72.3% (64.0–79.6)
	Completeness	72.7% (66.0–78.8)	60.6% (53.4–67.5)	50.0% (42.8–57.2)
255.29, D350A, or ZM8700x ^a as primary, secondary, supplementary, or referral diagnosis code	PPV	24.9% (21.1–28.9)	56.4% (48.6–63.9)	75.7% (66.8–83.2)
	Completeness	63.1% (56.0–69.9)	49.0% (41.8–56.2)	43.9% (36.9–51.2)
255.29, D350A, or ZM8700x ^a without referral diagnosis codes	PPV	27.0% (23.0–31.3)	59.3% (51.3–66.9)	76.3% (67.4–83.8)
	Completeness	62.1% (55.0–68.9)	48.5% (41.3–55.7)	43.9% (36.9–51.2)
255.29, D350A, or ZM8700x ^a as primary diagnosis codes	PPV	47.7% (41.3–54.2)	75.9% (67.0–83.3)	85.9% (76.6–92.5)
	Completeness	58.1% (50.9–65.0)	44.4% (37.4–51.7)	36.9% (30.1–44.0)
255.29, D350A, or ZM8700x ^a at any endocrine departments ^b	PPV	42.4% (35.6–49.4)	77.3% (66.2–86.2)	82.1% (66.5–92.5)
	Completeness	44.9% (37.9–52.2)	29.3% (23.1–36.2)	16.2% (11.3–22.0)
255.29, D350A, or ZM8700x ^a at tertiary endocrine departments ^b	PPV	46.3% (39.1–53.7)	77.0% (65.8–86.0)	82.1% (66.5–92.5)
	Completeness	44.4% (37.4–51.7)	28.8% (22.6–35.6)	16.2% (11.3–22.0)

Notes: ^aIncluding underlying codes. ^bNot including referral diagnosis codes to endocrine departments.

Abbreviations: PPV, positive predictive value.

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