Identifying Newly Diagnosed Non-arteritic Anterior Ischemic Optic Neuropathy (NAION) in Insurance Claims Data

Validation Standard Operating Procedure (SOP)

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number 75F40119D10037.

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History of Modifications

Version	Date	Modification
1.0	06/11/2025	Original Version

Objective

We plan to study various insurance claims data coding algorithms to identify newly occurring non-arteritic anterior ischemic optic neuropathy (NAION) in patients with type 2 diabetes based on diagnosis, procedure, provider specialty, service type, and prescription drug information.

Background

Claims data are the preferred data source for studying infrequent health outcomes of medication use because they reflect clinical practice, include a variety of patient groups often under-represented in clinical trials, offer large sample sizes and long-term follow-up, and help identify serious outcomes that prompt patients to seek clinical care. NAION events occur rarely and may therefore be best studied in such claims databases.[1]

However, claims data have limited clinical detail and concerns remain to what extent study endpoints can be identified reliably. Measurement characteristics like sensitivity, specificity, and positive predictive value (PPV) of the outcome are important quality markers for epidemiologic studies.[2] It is well documented that high specificity is desirable in outcome definitions as it will lead to unbiased relative risk (RR) estimates even when sensitivity is imperfect.[3] Once a sufficiently high PPV or specificity is demonstrated in a validation subset study, it may no longer be necessary to adjudicate every single endpoint in a claims data analysis (FDA Guidance for Industry on Real-World Data, Section V.D.3.).[4]

Establishing the measurement characteristics of newly occurring NAION is of great importance for the interpretation of medication safety studies.

Specific Aims

Specific Aim 1: Among patients identified with a claims-based algorithm for NAION, conduct an expert chart review to establish a reference standard and determine the performance of the algorithm in terms of PPV.

Specific Aim 2: Building on the algorithm developed above, explore whether its performance varies meaningfully by age, sex, race, patients with a referral to a neuro-ophthalmologist.

Study Design and Methods

Data Source: the data source is the Mass General Brigham (MGB) Research Patient Data Registry (RPDR) linked with national Medicaid and Medicare claims data from January 2007 through December 2020. The RPDR is a centralized electronic health record (EHR) data registry that gathers clinical information from various MGB facilities, including two academic hospitals, three specialty hospitals, seven community hospitals, home care services, and a robust network of specialty practices, urgent care facilities, and outpatient clinics/surgical centers. The methodology for deterministic linkage between claims and EHR data is established and published (see below).[5,6,7]

Available data include information on patient demographics (age, sex, race, ethnicity, location), hospital admissions, emergency room visits, outpatient visits, and outpatient surgical visits. Diagnoses are coded using the clinical modification of the International Classification of Diseases (ICD)-10 system after September 2015 and surgical procedures using the Current Procedural Terminology (CPT)-4, both of which have been shown to have good accuracy.[8,9,10] The pharmacy file provides a history of drug dispensing, including claims for each filled prescription and refill, including the date of dispensing, the drug dispensed coded by the National Drug Code (NDC), and the strength and quantity dispensed including the days the supply of drug is anticipated to last. All data points are recorded with a date of service so that a longitudinal timeline can be established for all patients.

Linking Longitudinal Claims Data with MGB EHR Data: we have linked all MGB Medicaid and Medicare beneficiaries and their respective longitudinal claims data from the Centers for Medicare & Medicaid Services (CMS) with the MGB RPDR electronic health records (**Figure 1**). The deterministic data linkage is already established using a crosswalk file with Bene_ID (study ID in the CMS research data) and EMPI number (MGB system-wide medical record number) matched by the social security number available in both datasets. The linkage is approved by CMS and a signed data use agreement is in place.

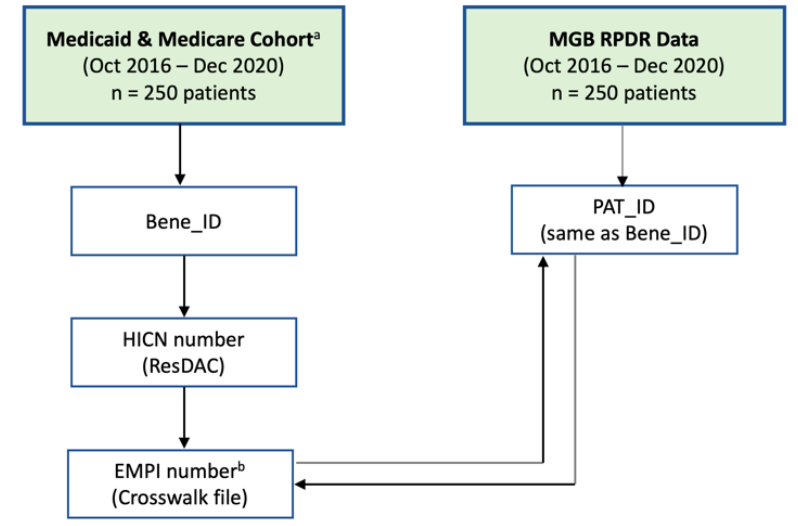

Figure 1. Diagram of the Deterministic Linkage for the Non-arteritic Anterior Ischemic Optic Neuropathy (NAION) Validation Cohort.

NAION Validation Study Cohort: among the patients represented in both the claims data and the MGB EHR data from January 2016 through December 2020, we will identify patients 18 years of age or older with at least one ICD-10-CM diagnosis code

of NAION (H47.01; H47.011; H47.012; H47.013; H47.019, see Algorithm 1 below) generated during a visit to the MGB system.

Each patient's claims-based NAION diagnosis date (index_diag_dt variable) needs to match with an ischemic optic neuropathy (ION) diagnosis within +/- 30 days in the administrative records of the EHRs to ensure that a provider in the MGB system generated the claims code (see **Supplement** for details).

The first occurrence of a qualifying encounter is called the *index event*.

Out of all eligible patients, after applying all exclusion criteria, we will randomly select a sample of 200 patients.

Exclusion Criteria

The following exclusion criteria will be applied in the claims data:

- Younger than 18 years of age for Medicaid beneficiaries and younger than 65 for Medicare beneficiaries
- Not having at least 180 days of insurance enrollment before the index event (with an allowable gap of 31 days)
- Metastatic cancer, benign or malignant tumor of the eye, orbit or brain recorded during 180 days before the index event
- Stem cell transplant recorded during 180 days before the index event

Claims-Based Algorithms to be Validated

We will program several claims data-based algorithms that are nested in each other with increasing specificity (**Table 1a**). We ensure that Algorithm 1 will have 200 patients, however, we cannot control the number of patients in the nested algorithms.

Aim 1: Expert Chart Review and Validation of the Claims-Based Algorithms

For patients identified by the claims-based algorithms, clinicians will review their MGB medical charts (fully available in the EHR data), including medical, pharmacy, hospitalizations, clinical laboratory tests, and free text notes to confirm or refute that a patient has clinically diagnosed NAION. The study team, including a board-certified ophthalmologist and/or neuro-ophthalmologist, has the clinical expertise to establish the diagnosis according to established criteria.

The expert review will use current guidelines on how to diagnose NIAON. The expert assessment will be based on the synthesis of all recorded clinical information, including results from tests that were conducted outside of MGB and reported by other providers (see **Table 1b**). The expert assessment criteria were assembled by board-certified neuro-ophthalmologists at the Mass Eye and Ear based on key articles and guidelines from professional societies.[11,12]

The expert reviewer will provide a five-category assessment:

1. Ruled out NAION

2. Highly likely NAION
3. Likely NAION
4. Unlikely NAION
5. Insufficient data to make a determination

Chart Review Process

The review process follows a structured process:

1. The first 20 records will be reviewed by all 4 neuro-ophthalmologists in the study team. Based on the inter-rate reliability for these 20 records, adjustments will be made to the review process, followed by a review of 10 additional records by all 4 reviewers. Any changes to the protocol will be recorded as such.
2. Assuming we achieve high inter-rater reliability, we will divide the rest of the cases up for a single review with clear instructions to consult with the lead reviewer to resolve any complexities.

Statistical Analyses

As a general strategy, a claims-based algorithm will be created by comparing claims-based identifiers of NAION to the presence or absence of an actual diagnosis of NAION according to the medical record; the medical record is treated as the high-validity diagnosis, serving as the reference standard against which to compare.

The five reviewer categories will be collapsed into two:

1. NAION present = “Highly likely NAION” or “likely NAION”;
2. NAION not present = “Ruled out NAION” or “unlikely NAION”

Patient records that are evaluated as “Insufficient data” will be analyzed in two ways: one analysis will classify those patients as “NAION not present” and another will remove those patients from the analysis.

Descriptive statistics (counts and percentages for categorical variables or mean, median, standard deviation and interquartile range for continuous variables) for patient characteristics measured will be calculated as appropriate for all patients identified by all algorithms (**Table 2**). For Algo 1 we will further stratify by whether the diagnosis of the claims-based algorithm is confirmed by the reference standard or not (**Table 3**). Characteristics will be compared between the 2 groups by computing differences in proportions and means.

The PPV will be computed as the number of those identified as having NAION based on the medical record review divided by the number of those identified as having NAION by the claims-based algorithm. The PPV with 95% confidence interval will be computed for all claims-based algorithms (**Table 4**).

While we do not have control over the number of NAION cases identified by the specific algorithms, **Figure 2** shows how reducing the number of cases influences the estimation precision of the PPV depending on the level of PPV. The estimation

precision of the PPV remains relatively stable with more than 100 cases (for a PPV of 0.8: lower CI= 0.71 at a sample size of 100 and lower CI= 0.74 at a sample size of 200).

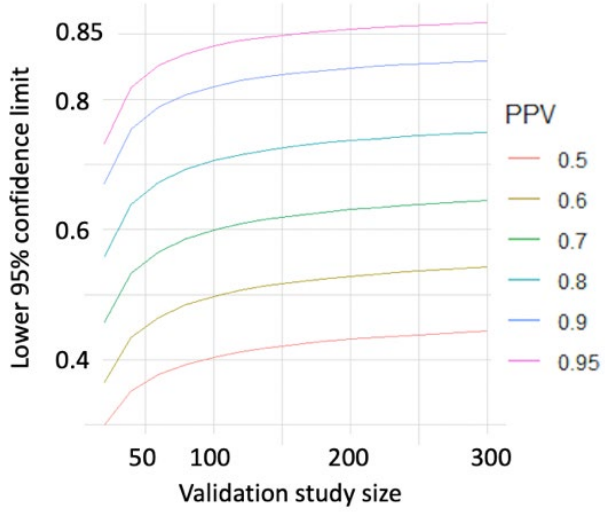

Figure 2. Estimation Precision of Positive Predictive Values (PPVs) Depending on Study Size and PPV Level.

The preferred algorithm will maximize the PPV, since relative risk estimates are unbiased if outcomes are assessed with 100% specificity, even if sensitivity is lower.[3]

We will compare demographics and other patient characteristics between those selected for chart review and those eligible but not selected (**Table 5**).

Aim 2: Variation of Algorithm Performance by Patient Subgroups

We plan to explore whether the claims-based algorithms perform meaningfully differently in key patient subgroups. The sizes of these subgroups are not in our control, and some may be too small for useful interpretations. These analyses are meant to be exploratory. For each patient subgroup, including age, sex, race, and type-2 diabetes, we will compute PPVs for all algorithms (**Table 4**).

We will perform sensitivity analyses by altering the claims-based algorithm in two ways:

1. We will not look for conditions/procedures during the 2 weeks after the index date.
2. We will extend the lookback window to 365 days.

Appendix

Table 1A. Definitions of the Proposed Claims-Based Algorithms, Algorithm 1 through Algorithm 5.

Algorithm	Description	Coding
Algorithm 1	One in- or out-patient code for non-arteritic anterior ischemic optic neuropathy (NAION) (= index event)	ICD-10-CM codes for ischemic optic neuropathy: H47.01; H47.011; H47.012; H47.013; H47.019
Algorithm 1b	Algorithm 1 AND ophthalmologist OR optometrist visit in +/- 30 days	
Algorithm 1c	Algorithm 1 AND ophthalmologist visit in +/- 30 days	
Algorithm 1d	Algorithm 1c AND one in- or out-patient code for NAION within 0 to 30 days after the ophthalmologist visit	
Algorithm 2	Algorithm 2 AND ophthalmologist OR optometrist visit in +/- 30 days	ICD-10-CM codes for the following conditions within 180 days before and 2 weeks after the index event: • Giant cell arteritis: ICD-10-CM diagnosis: M31.5, M31.6 • Granulomatosis with polyangiitis (GPA) / Wegener's granulomatosis: ICD-10-CM diagnosis: M31.3x • Microscopic polyangiitis (MPA): ICD-10-CM diagnosis: M31.7 • Eosinophilic granulomatosis with polyangiitis (EGPA): ICD-10-CM diagnosis: M31.7 • Behçet's disease: ICD-10-CM diagnosis: M35.2 • Urticarial vasculitis: ICD-10-CM diagnosis: L95.x (Vasculitis limited to skin, not elsewhere classified) • Kawasaki disease: ICD-10-CM diagnosis: M30.3 • Central nervous system vasculitis: ICD-10-CM diagnosis: I67.7, I68.2 • Rheumatoid vasculitis: ICD-10-CM diagnosis: M02.2xx • Polyarteritis nodosa: ICD-10-CM diagnosis: M30.0 • Takayasu arteritis: ICD-10-CM diagnosis: M31.4 • IgA vasculitis (Henoch-Schönlein purpura): ICD-10-CM diagnosis: D69.0

Algorithm	Description	Coding
Algorithm 2b	Algorithm 2 AND ophthalmologist visit in +/- 30 days	
Algorithm 2c	Algorithm 2c AND one in- or out-patient code for NAION within 0 to 30 days after the ophthalmologist visit	
Algorithm 2d	Algorithm 2 AND NOT optic atrophy	
Algorithm 3	Algorithm 2 AND NOT optic atrophy	ICD-10-CM code for the following condition within 180 days before and including the index event: • Optic atrophy: ICD-10-CM diagnosis: H47.2x
Algorithm 3b	Algorithm 3 AND ophthalmologist OR optometrist visit in +/- 30 days	
Algorithm 3c	Algorithm 3 AND ophthalmologist visit in +/- 30 days	
Algorithm 3d	Algorithm 3c AND one in- or out-patient code for NAION within 0 to 30 days after the ophthalmologist visit	
Algorithm 4	Algorithm 3 AND NOT conditions associated with potential misdiagnosis of NAION	ICD-10-CM codes for the following conditions within 180 days before and 2 weeks after the index event: • Multiple sclerosis: ICD-10-CM diagnosis: G35 • Neuromyelitis optica / Devic disease: ICD-10-CM diagnosis: G36.0 • Other demyelinating diseases: ICD-10-CM diagnosis: G36.x (except G36.0), G37.x • Optic neuritis: ICD-10-CM diagnosis: H46.x • Papilledema or pseudo papilledema: ICD-10-CM diagnosis: H47.1x, H47.33x • Central (CRVO) or branch retinal vein occlusion: ICD-10-CM diagnosis: H34.81x, H34.83x • Central (CRAO) or branch retinal artery occlusion: ICD-10-CM diagnosis: H34.1x, H34.2x • Systemic shock: ICD-10-CM diagnosis: A48.3, O03.31, O04.81, O07.31, O08.1, O75.1, R57.x, R65.21, T78.2x, T79.4x, T81.1x, T88.2x • Drusen of optic disc: ICD-10-CM diagnosis: H47.32x • Optic neuropathies: ICD-10-CM diagnosis: H46.2, H46.3 • Syphilis: ICD-10-CM diagnosis: A50.x, A51.x, A52.x, A53.x, A65, O98.1x • Uveitis: ICD-10-CM diagnosis: H44.11x, H44.13x

Algorithm	Description	Coding
		• Other disorders of optic disc: ICD-10-CM diagnosis: H47.31x, H47.39x • Optic nerve sheath hemorrhage, hypoplasia, and other disorders: ICD-10-CM diagnosis: H47.02x, H47.03x, H47.09x • Disorders of optic chiasm, visual pathways, visual cortex, or optic nerve injury and disorders: ICD-10-CM diagnosis: H47.31x, H47.4x, H47.5x, H47.6x, H47.9
Algorithm 4b	Algorithm 4 AND ophthalmologist OR optometrist visit in +/- 30 days	
Algorithm 4c	Algorithm 4 AND ophthalmologist visit in +/- 30 days	
Algorithm 4d	Algorithm 4c AND one in- or out-patient code for NAION within 0 to 30 days after the ophthalmologist visit	
Algorithm 5	Algorithm 4 AND NOT Cataract surgery or LASIK	CPT/HCPCS codes for the following procedures within 30 days before and including the index event: • 0671T, 2020F, 3073F, 66830, 66982, 66983, 66984, 66987, 66988, 66989, 66991, G8627, G8628, G9389, G9390, G9391, G9392, S0800
Algorithm 5b	Algorithm 5 AND ophthalmologist OR optometrist visit in +/- 30 days	
Algorithm 5c	Algorithm 5 AND ophthalmologist visit in +/- 30 days	
Algorithm 5d	Algorithm 5c AND one in- or out-patient code for NAION within 0 to 30 days after the ophthalmologist visit	

Table 1B. Rules to Determine a Non-arteritic Ischemic Optic Neuropathy (NAION) Diagnosis in Medical Records.

Decision	Criteria	Items
Ruled out NAION	NAION is ruled out if 1 or more of the following criteria are met:	
	Any intracranial tumor or metastatic tumor	
	Competing / alternative diagnosis is made or suspected in any medical entry during 60 days from an initial diagnosis of ischemic optic neuropathy (ION)	E.g., central retinal vein occlusion (CRVO), branch retinal artery occlusion (BRAO), combined central retinal artery occlusion (CRAO), etc.
	Possible optic neuritis	Select "Possible" if the following 2 criteria are met: • Note from an ophthalmologist or neurologist (MD or DO credential) indicating patient has optic neuritis • Patient reports of pain in the eye with visual loss Supportive of neuritis but not required: • Magnetic resonance imaging (MRI) evidence of enhancement of the involved optic nerve during +/- 60 days from ischemic optic neuropathy (ION) diagnosis • Diagnosis of multiple sclerosis (MS), neuromyelitis optica (NMO) or myelin oligodendrocyte glycoprotein antibody disease (MOGAD)
	Arteritic ION	Select "Arteritic" if ≥1 of the following are present +/- 30 days from ION diagnosis: • Physician note suggesting a diagnosis of arteritis; with or without oral/intravenous steroids • Positive Temporal artery biopsy or ultrasound • Elevated erythrocyte sedimentation rate (ESR) > twice upper limit of age/sex-adjusted normal and/or c-reactive protein (CRP) ≥ 15 mg/L; with or without oral/intravenous (IV) steroids • History of jaw claudication, polymyalgia rheumatica, headache; with or without oral/IV steroids • Visual acuity, i.e., no light perception
	ION secondary to other factors	Select “secondary” if ≥1 of the following:

Decision	Criteria	Items
		• Marked systemic hypotension or significant anemia, including in relation to spine, vascular or cardiac surgery in 30 days prior to vision loss • Medication: for erectile dysfunction (PDE5 inhibitor); amiodarone
	Infections linked to symptoms resembling ION	Syphilis
Highly Likely NAION	Select if <u>all three</u> of the following criteria are met:	
	• Note from an , ophthalmologist or neurologist (MD or DO credential) indicating patient has ION • Automated visual field defect consistent with ION, i.e., altitudinal defect especially inferior • Observation or documentation of optic nerve head edema in one eye if patient evaluated within 30 days of visual loss	
	<u>AND</u> <u>1 or more</u> of the following confirmatory findings:	
	• Finding of a relative afferent pupillary defect with no evidence of pallor in contralateral optic nerve on exam • Optical coherence tomography (OCT) showing thickening of the retinal nerve fiber layer in the acute phase (≤30 days after vision loss) • OCT showing thinning of the retinal ganglion cell layer or complex >30 days after visual loss in the affected eye	
Likely NAION	Select if all of the following criteria are met:	
	Note from an optometrist, ophthalmologist or neurologist (MD or DO credential) indicating patient has ION	
	<u>AND</u> <u>1 or more</u> of the following confirmatory findings:	
	• Observation or documentation of optic nerve head edema in the affected eye if patient is evaluated within 30 days of visual loss • Optic nerve head pallor (possibly with residual edema) in newly	

Decision	Criteria	Items
	involved eye if patient evaluated >30 days after vision loss • OCT thinning of the retinal ganglion cell layer or complex >30 days after vision loss in the affected eye • Automated visual field defect consistent with ION	
Event Date Relative to the Claims Data Index Date	The claims data algorithm provides an index date of the event of interest. Please indicate any discrepancies of more than 1 week between the claims-based index date and the clinical event date.	
Unlikely NAION	Select if all of the following criteria are met:	
	Note from a clinician indicating the patient has ION AND no confirmatory finding on ophthalmologic exam or OCT.	
Insufficient Data to Make a Determination	Select if there is no note indicating ION diagnosis.	

Table 1C. Exclusion Codes.

Exclusion	Criteria
Type 2 Diabetes Mellitus	ICD-10-CM diagnosis: E11.x
Metastatic cancer, benign or malignant tumor of the eye, orbit or brain	Metastatic cancer: ICD-10-CM diagnosis: C77.x, C78.x, C79.x, C7B.x Benign or malignant tumor of the eye, orbit or brain: ICD-10-CM diagnosis: D18.02, D32.x, D31.x, D33.0, D33.1, D33.2, D33.3, D35.2, C69.x, C70.x, C71.x, C72.3x, C72.5x, C75.1 ICD-10-PCS procedure: D000.x, D010.x, D020.x, D0Y0.x, D800.x, D810.x, D820.x, D8Y0.x
Stem cell transplant	ICD-10-CM diagnosis: T86.5, T86.0x, Z94.81 ICD-10-PCS procedure: 30233C0, 30233G0, 30233Y0, 30243C0, 30243G0, 30243Y0

Table 2. Baseline Characteristics of Patients Selected by Each Claims-Based Algorithm.

Characteristics Observed in Claims Data During 180 Days Before the Index Date	Algorithm 1	Algorithm 1B	Algorithm 2	Algorithm 2B	Algorithm 3	Algorithm 3B	Algorithm 4	Algorithm 4B	Algorithm 5	Algorithm 5B
Number of Patients										
Age, years (SD)										
Race										
White (%)										
Black (%)										
Asian (%)										
Hispanic (%)										
Oral Steroid (%)										
…										
# of Visits (mean)										
# of Ophthalmology Visits (0, 1, 2+)										
Hospitalization in Past 30 Days (%)										
Comorbidity Ccore (mean)										
# of Medications (mean)										
…										

Table 3. Positive Predictive Values (PPVs) of Claims-Based Algorithms.

Subgroups	Algorithm 1	Algorithm 1B	Algorithm 2	Algorithm 2B	Algorithm 3	Algorithm 3B	Algorithm 4	Algorithm 4B	Algorithm 5	Algorithm 5B
All subjects										
# of records identified										
# of charts reviewed (%)										
PPV, % (95% CI)										
Subgroup 1: With Type 2 Diabetes Mellitus (T2DM)										
# of records identified										
# of charts reviewed, (%)										
PPV, % (95% CI)										
Subgroup 2: Without T2DM										
# of records identified										
# of charts reviewed, (%)										
PPV, % (95% CI)										
Subgroup 3: Age 18-49 Years										
# of records identified										
# of charts reviewed, (%)										
PPV, % (95% CI)										
Subgroup 4: Age 50+ Years										
# of records identified										
# of charts reviewed, (%)										
PPV, % (95% CI)										
Subgroup 5: Women										

# of records identified	
# of charts reviewed, (%)	
PPV, % (95% CI)	

Table 4. Differences in Characteristics Between Confirmed and Not Confirmed NAION Diagnoses (Algorithm 1).

Characteristics Observed in Claims Data During 180 Days Before the Index Date	**Confirmed by Chart Review**	**Not Confirmed By Chart Review**	**Difference**
Number of Patients			
Age , years (SD)			
Race			
White (%)			
Black (%)			
Asian (%)			
Hispanic (%)			
Oral Steroid (%)			
…			
# of Visits (mean)			
# of Ophthalmology Visits (0, 1, 2+)			
Recent Hospitalization (%)			
Comorbidity Score (mean)			
# of Medications (mean)			
…			

Table 5. Differences in Characteristics Between Those Patients Selected for Chart Review Versus All Eligible Patients.

Characteristics Observed in Claims Data During 180 Days Before the Index Date	Selected for Chart Review	Not Selected for Chart Review	Difference
Number of Patients			
Age , years (SD)			
Race			
White (%)			
Black (%)			
Asian (%)			
Hispanic (%)			
Oral Steroid (%)			
…			
# of Visits (mean)			
# of Ophthalmology Visits (0, 1, 2+)			
Recent Hospitalization (%)			
Comorbidity Score (mean)			
# of Medications (mean)			
…			

Supplement

A Discussion of the System-Use Criterion

The study population is drawn from claims data that were linked with EHR data from MGB. This means that throughout the longitudinal claims data stream, each patient in the linked dataset had at least 1 encounter at MGB generating EHR data.

After applying several exclusions based on information available in claims data the protocol specifies a "*system-use criterion*": 'Each patient's claims-based NAION diagnosis date (index_diag_dt variable) needs to match with an ION diagnosis within +/- 30 days in the administrative records of the EHRs to ensure that a provider in the MGB system generated the claims code' (see page 3). This *system-use criterion* will ensure that the claims code that marked an encounter as a potential ION case in the claims data stream was generated by an encounter in the MGB healthcare system, thereby allowing the respective clinical information in the EHR to be reviewed by our medical experts.

For the patients who were excluded from the study due to the application of the system-use criterion, the ION diagnosis code found in claims could have been generated by another provider that is not operating within the MGB EHR system. For those external encounters, our medical experts would have no data available to review and will not be able to verify or refute the diagnosis of NAION through the review of clinical notes. Of the proposed sample of 200 patients, a meaningful proportion would be classified as not reviewable and would not contribute to the PPV estimation leading to wider confidence intervals. Hence the system exclusion makes the validation study more efficient. To ensure generalizability of our 200 patients sample, we will use information from claims data to compare characteristics with those excluded due to the application of the system-use criterion (see **Table 5**).

The *system-use criterion* is equivalent to Hamedani et al.'s inclusion criteria which states: '… we identified all patients in … health systems who had at least one diagnosis code for NAION (ICD-10-CM H47.01, H47.011, H47.012, H47.013, or H47.019) …'[13]

Note that with the *system-use criterion*, the PPV remains unbiased, because we only limit the population to those patients that are reviewable within MGB. Each claim with a diagnosis of ION that is observed in the claims data must have been generated by a provider who also has coded this diagnosis of ION, which then led to the creation of the claim. There is no claim in the insurance data if there is no claim submitted by the provider.

It is theoretically conceivable, although highly unlikely, that through fraudulent behavior the hospital/clinic billing department comes up with a code for the diagnosis of ION even though the physician did not make any such a diagnosis or mentioning in the notes. However, at MGB we do see the forwarded claims including their diagnoses and these patients would not be excluded by the *system-use criterion*. In these rare circumstances, observations of these patients will be included in the analysis and will reduce the PPV.

Please also note, that in contrast to Hamedani et al. the current validation study can develop and test claims-based algorithms that make use of claims generated outside of the provider institution that generated the index claim. Given the fragmentation of the United States healthcare system this may be important to rule out competing diagnoses.

In conclusion, the system exclusion is not biasing the PPV estimate and makes the PPV estimation more efficient.

References

[1] Schneeweiss S, Huybrechts KF. Pharmacoepidemiology. In: Lash TL, VanderWeele TJ, Haneuse S, Rothman KJ, eds. Modern Epidemiology. 4th ed. Philadelphia, PA: Wolters Kluver; 2021.
[2] Franklin JM, Glynn RJ, Martin D, Schneeweiss S. Evaluating the Use of Nonrandomized Real-World Data Analyses for Regulatory Decision Making. Clin Pharmacol Ther. 2019;105(4):867-877.
[3] Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58(4):323-337.
[4] US Food and Drug Administration. Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products - Guidance for Industry. 2024.
[5] Lin KJ, Singer DE, Glynn RJ, Murphy SN, Lii J, Schneeweiss S. Identifying Patients With High Data Completeness to Improve Validity of Comparative Effectiveness Research in Electronic Health Records Data. Clin Pharmacol Ther. 2018;103(5):899-905.
[6] Lin KJ, Glynn RJ, Singer DE, Murphy SN, Lii J, Schneeweiss S. Out-of-system Care and Recording of Patient Characteristics Critical for Comparative Effectiveness Research. Epidemiology. 2018;29(3):356-363.
[7] Desai RJ, Lin KJ, Patorno E, et al. Development and Preliminary Validation of a Medicare Claims-Based Model to Predict Left Ventricular Ejection Fraction Class in Patients With Heart Failure. Circ Cardiovasc Qual Outcomes. 2018;11(12):e004700.
[8] Fowles JB, Lawthers AG, Weiner JB, Garnick DW, Petrie DS, Palmer RH. Agreement between physicians' office records and Medicare Part B claims data. Health care financing review. 1995;16(4):189-199.
[9] Glynn RJ, Monane M, Gurwitz JH, Choodnovskiy I, Avorn J. Agreement between drug treatment data and a discharge diagnosis of diabetes mellitus in the elderly. Am J Epidemiol. 1999;149(6):541-549.
[10] Romano PS, Mark DH. Bias in the coding of hospital discharge data and its implications for quality assessment. Med Care. 1994;32(1):81-90.
[11] Rizzo JF, 3rd. Unraveling the Enigma of Nonarteritic Anterior Ischemic Optic Neuropathy. J Neuroophthalmol. 2019;39(4):529-544.
[12] Kerr NM, Chew SS, Danesh-Meyer HV. Non-arteritic anterior ischaemic optic neuropathy: a review and update. J Clin Neurosci. 2009;16(8):994-1000.
[13] Hamedani AG, Kim DS, Chaitanuwong P, Gonzalez LA, Moss HE, DeLott LB. Validity of Administrative Coding for Nonarteritic Ischemic Optic Neuropathy. J Neuroophthalmol. 2024;44(3):342-345.