Patient Harm due to Diagnostic Error of Neuro-Ophthalmologic Conditions

Authors: Leanne Stunkel, MD,[1,2] Rahul A. Sharma, MD,[3] Devin D. Mackay, MD,[4] Bradley Wilson, MA,[1] Gregory P. Van Stavern, MD,[1,2] Nancy J. Newman, MD,[5-7] Valérie Biousse, MD.[5-6]

Affiliation Information for All Authors:
1. Department of Ophthalmology and Visual Sciences, Washington University in St. Louis School of Medicine, St. Louis, MO.
2. Department of Neurology, Washington University in St. Louis School of Medicine, St. Louis, MO.
3. University of Toronto, Ontario, Canada.
4. Departments of Neurology, Ophthalmology, and Neurosurgery, Indiana University School of Medicine, Indianapolis, IN.
5. Department of Ophthalmology, Emory University, Atlanta, GA.
6. Department of Neurology, Emory University, Atlanta, GA.
7. Department of Neurological Surgery, Emory University, Atlanta, GA.

Meeting Presentation(s): The material was presented as a virtual poster presentation at the Diagnostic Error in Medicine 13th Annual International Conference, 2020, has been accepted as a platform presentation at the North American Neuro-Ophthalmology Society (NANOS) 47th Annual Meeting, 2021, and is under consideration for presentation at American Academy of Neurology (AAN) Annual Meeting, 2021.

Financial Support: V.B. and N.J.N. are supported in part by NIH/NEI core grant P30-EY06360 (Department of Ophthalmology, Emory University School of Medicine), and by NIH/NINDS (RO1NSO89694). This work was supported in part by an unrestricted grant to the Washington University in St. Louis Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness.

Acknowledgements: The authors would like to acknowledge the contribution of Jennifer Chung, BA, Washington University School of Medicine, for her valuable contributions with inputting and organizing data.

Conflict of Interest: No conflicts of interest relevant to this work. N.J.N. is a consultant for GenSight, Santhera/Chiesi, Neurophoenix, and Stealth. VB is a consultant for GenSight and Neurophoenix.

Running head: Diagnostic Error of Neuro-Ophthalmologic Conditions

Address for Reprints:
Valérie Biousse, MD
Email: vbiouss@emory.edu

Key Words: Neuro-ophthalmology, diagnostic error, medical error

Abstract

Objective: To prospectively examine diagnostic error of neuro-ophthalmic conditions and resultant harm at multiple sites.

Design: Prospective cross-sectional study.

Subjects: 496 consecutive adult new patients seen at three university-based neuro-ophthalmology clinics in the United States in 2019-2020.

Methods: Collected data regarding demographics, prior care, referral diagnosis, final diagnosis, diagnostic testing, treatment, patient disposition, and impact of the neuro-ophthalmologic encounter. For misdiagnosed patients, we identified the cause of error using the Diagnosis Error Evaluation and Research (DEER) taxonomy tool, and whether the patient suffered harm due to the misdiagnosis.

Main Outcome Measures: The primary outcome was whether patients who were misdiagnosed prior to neuro-ophthalmology referral suffered harm as a result of the misdiagnosis. Secondary outcomes included appropriateness of referrals, misdiagnosis rate, interventions undergone prior to referral, and the primary type of diagnostic error.

Results: Referral diagnosis was incorrect in 49% of cases. Misdiagnosed patients suffered harm in 26%, which could have been prevented by earlier referral to neuro-ophthalmology in 97%. Patients experienced inappropriate laboratory testing, diagnostic imaging, or treatment prior to referral in 23%, with higher rates for patients misdiagnosed prior to referral (34% of patients compared to 13% with a correct referral diagnosis, $p<0.0001$). Seventy-six percent of inappropriate referrals were misdiagnosed, compared to 45% of appropriate referrals ($p<0.0001$). The most common reasons for referral were optic neuritis or optic neuropathy (21%), papilledema (18%), diplopia or

cranial nerve palsies (16%), and unspecified vision loss (11%). The most common sources of diagnostic error were the physical examination (36%), generation of a complete differential diagnosis (24%), history taking (24%), and utilization or interpretation of diagnostic testing (13%). In 489/496 (99%) patients, neuro-ophthalmologic consultation impacted patient care. In 2% of cases, neuro-ophthalmology directly saved the patient's life or vision, in an additional 10% harmful treatment was avoided or appropriate urgent referral was provided, and in an additional 48% neuro-ophthalmology provided a diagnosis and direction to the patient's care. **Conclusions:** Misdiagnosis of neuro-ophthalmic conditions, mismanagement prior to referral, and preventable harm are common. Early appropriate referral to neuro-ophthalmology may prevent patient harm.

Diagnostic error is common[1-3] and can lead to serious harm, including death.[4] A large proportion of malpractice claims are related to diagnostic error,[5] and the rate is highest in fields that require complex, analytic diagnostic reasoning.[6]

Neuro-ophthalmologists are trained to approach diagnosis using a systematic, time-intensive, analytic lens,[7,8] and commonly encounter high rates of diagnostic error in the patients referred to their practices.[9-19] When patients are incorrectly diagnosed, providers are likely to order unnecessary or even inappropriate tests and treatments,[9-16,20,21] which may be costly or even harmful.

Prior studies of diagnostic error of neuro-ophthalmic conditions have typically been retrospective.[9,10,12-15,19] Most have focused on a single neuro-ophthalmologic condition, such as third nerve palsies,[10,15] idiopathic intracranial hypertension,[12] optic neuritis,[13] optic nerve sheath meningioma,[14] and papilledema.[16] While some have evaluated the amount of unnecessary or inappropriate diagnostic testing and treatments resulting from these misdiagnoses, such as neuro-imaging studies,[9,11-15,20,21] intravenous steroids,[13,14] lumbar punctures,[12-14] and neurosurgical procedures,[12] they have typically stopped short of measuring direct patient harms. Direct measurement of diagnostic error-related harms,[22] which has been performed in studies of diagnostic error of dizziness due to stroke,[23-31] may sidestep the inherent subjectivity and methodologic limitations that have limited prior research into diagnostic error.[2,32]

Our goal was to prospectively evaluate diagnostic error of neuro-ophthalmologic conditions prior to referral to neuro-ophthalmology at multiple neuro-ophthalmologic services, and to directly evaluate actual patient harms resulting from the diagnostic errors that existed before the time of neuro-ophthalmologic consultation (NOC).

Methods

Institutional Review Board (IRB)/Ethics Committee approval was obtained at Emory University, Washington University in St. Louis, and Indiana University. Informed consent was waived because data were deidentified. The project adhered to the tenets of the Declaration of Helsinki.

We performed a prospective observational study of 496 new patient encounters seen at 3 academic tertiary care neuro-ophthalmology clinics by 5 neuro-ophthalmology attending providers (VB, NJN, LS, GVS, and DDM). Each site individually collected data for consecutive new patient encounters. These collection periods were not simultaneous, but each site's collection period captured all consecutive new adult patients seen within the collection period. Indiana University collected all new adult patients who presented from 9/10/2019 to 10/11/2019; Washington University in St. Louis from 10/7/2019 to 11/8/2019; and Emory University from 1/2/2020 to 3/16/2020. Patients under age 18 were excluded. Referral materials were systematically reviewed by each provider, and further information was obtained from patient histories, as a standard aspect of the NOC in order to determine referral patterns. Each patient underwent a full neuro-ophthalmic assessment as a standard aspect of their clinical care. Final diagnosis was determined by a fellowship-trained neuro-ophthalmologist (VB, NJN, LS, GVS, or DDM) using history, a structured neuro-ophthalmic examination, and any appropriate ancillary diagnostic testing. In some cases, clear diagnosis required following up on results or following the course of the patient over time.

Data collected included: patient demographics (age, gender, body mass index, race/ ethnicity), duration of symptoms, time from referral to NOC, appropriateness of

referral (defined a priori as whether the referral question was a neuro-ophthalmologic question as determined by the consulting neuro-ophthalmologist; examples of inappropriate referrals included monocular diplopia or chronic eye pain from known dry eye syndrome), number and specialties of providers seen before NOC, referral diagnosis (based on detailed review of referral and medical records), tests and treatments preceding NOC, whether those tests and treatments were appropriate, tests and treatments ordered at NOC, final diagnosis, disposition from NOC, and the impact of NOC on patient outcome. Impact on patient outcome was classified into 5 categories: no impact; provided reassurance, avoiding further visits and tests; provided a diagnosis and direction to treatment; avoided harmful treatment or provided urgent referral to an appropriate provider; or directly saved vision or life.

For cases in which the referral diagnosis was incorrect (or absent), the Diagnosis Error Evaluation and Research (DEER) taxonomy tool[33,34] was applied, in keeping with prior studies of diagnostic error of neuro-ophthalmic conditions,[12-15] to identify the type of diagnostic error and to locate the point in the diagnostic process at which the problem occurred. If multiple types of error contributed, the most proximal cause of error was assigned. This convention was chosen based on reasoning that the most proximal error likely had downstream effects that influenced any other errors (for example, if the examination was performed incorrectly and the generation of the differential diagnosis was also incorrect, 2B was assigned rather than 5A, as the incorrect differential diagnosis was highly likely to have been influenced by or directly caused by the incorrect interpretation of the examination).

Data were collected on whether the patient suffered harm as the result of the diagnostic error, and whether quicker access to NOC could have prevented the harm, based on the clinical judgment of the attending neuro-ophthalmologist. Harm was defined by physical injury or adverse effect, including adverse effects of inappropriate medications. We did not capture unnecessary financial expenditures or potential stress or psychological harm.

Data were analyzed using SAS 9.4, SAS Inc., Cary, North Carolina. Proportions were compared using a chi-square test. Means were compared using a t-test.

Data Availability Statement: anonymized data will be shared by request from any qualified investigator.

Results

We included 496 patients (223 from Emory, 162 from Washington University in St. Louis, and 111 from Indiana University). Sixty-six percent were female. Ages ranged from 18 to 97, with median age 50. Races and ethnicities represented were: 72% white, 23% black, 3% Asian, and 2% Hispanic. BMI was collected on 96% of patients, and ranged from 15-69, with mean BMI 32 $\pm$9.

Two hundred forty-two (49%) patients were misdiagnosed, defined as a referral diagnosis that was different than the final diagnosis given at the NOC, or no diagnosis given by the referring doctor. The misdiagnosis rate did not differ based on gender (49% in females, 48% in males). BMI did not significantly differ in the misdiagnosed patients (p=0.79).

Symptom duration was collected for 98% of patients (in some cases, findings were noted incidentally, or symptoms had insidious onset): median estimated time from symptom onset to NOC was 200 days (IQR 71-730 days, range 0-16790 days). Time from referral request to NOC was collected for all patients: median number of days from referral to appointment was 30 days (IQR 10-65, range 0-476 days). Number of providers seen before NOC ranged from 0-22, with median 2 (IQR 2-3). There was no significant difference (p=0.85) in the number of providers seen before NOC for misdiagnosed patients. Patients had most commonly seen either an eye care provider (ophthalmologist or optometrist) or neurologist prior to NOC (Table 1). There was no meaningful difference between rates of misdiagnosis or rates of harm based on the specialty of the providers seen prior to referral.

Referral to neuro-ophthalmology was appropriate in 434 (88%) patients, with appropriateness defined by whether the referral was for a neuro-ophthalmic question. Inappropriate referrals were more likely to be misdiagnosed (76% of inappropriate referrals were misdiagnosed, versus 45% of appropriate referrals, p=<0.0001).

Patients were referred for a wide range of complaints, including papilledema, optic neuropathies, anisocoria, diplopia or abnormal eye movements, headaches or sensory disturbances, sellar masses, unexplained vision loss, or other complaints (Table 2). There were no clinically or statistically significant differences in misdiagnosis rates or appropriate rates between afferent versus efferent disorders (p=0.6). Misdiagnoses were more common in referrals for diplopia (56% misdiagnosed), headache or sensory disturbance (56% misdiagnosed), and vision or visual field loss

(56% misdiagnosed), and relatively less common in referrals for papilledema (39% misdiagnosed) and sellar masses (27% misdiagnosed) (p=0.04).

Disposition from NOC was most frequently to return to the referring provider (59%), but in rare cases the patient required evaluation in the emergency department (ED) or direct admission (6 patients, 1.2%) (Table 3). Four of the 6 patients sent to the ED or directly admitted had been misdiagnosed by the referring provider (representing 2% of the misdiagnosed patients). Twenty percent of patients required referral to an alternative subspecialty, including neurosurgery, neurology (including multiple sclerosis and stroke specialists), otolaryngology (including neuro-otology), ophthalmology (including cornea, retina, uveitis, glaucoma, comprehensive including cataract surgery), optometry and orthoptists for prism, Low Vision services, and psychology (for cognitive behavioral therapy).

In 489 (99%) patients, the NOC had a direct impact on the patient's care (Figure 1). Eight (2%) had their vision or life directly saved—these patients had severe papilledema, angle closure glaucoma, orbital apex syndrome, giant cell arteritis, and choroidal neovascular membrane. Misdiagnosis and inappropriate referrals were both correlated with increased impact of the NOC ($p<0.0001$ for correlation of misdiagnosis and $p<0.0001$ for inappropriate referrals with impact of NOC) (Figure 2). For example, avoiding harmful treatment or providing urgent referral was more common in misdiagnosed patients (17% versus 4% of correctly diagnosed patients). Avoiding unnecessary tests was a more common outcome for inappropriate referrals, occurring in 61% of inappropriate referrals versus 35% of appropriate referrals.

The most common sources of diagnostic error were the physical examination (36%) (inaccurate funduscopic or motility examinations, and underweighing normal examination findings); generation of a differential diagnosis (24%); history taking (24%); and utilization or interpretation of diagnostic testing (13%) (failure to obtain appropriate neuroimaging or poor interpretation of or failure to obtain visual fields) (Table 4).

One hundred sixteen (23%) patients had undergone inappropriate management (laboratory studies, imaging, or treatment) prior to referral. Thirty-four percent of misdiagnosed patients had undergone inappropriate management, versus 13% of correctly diagnosed patients ($p<0.0001$). Sixty-two (26%) patients who were misdiagnosed were directly harmed, with harms including: death due to delay in diagnosis of a diffuse leptomeningeal glioneuronal tumor, stroke that occurred after failure to recognize a TIA with visual symptoms, progression of permanent vision loss due to a treatable cause of optic neuropathy, recurrence of spontaneous CSF leak after failure to recognize underlying IIH, development of irreversible strabismus due to delay in diagnosis of ocular myasthenia gravis, radiation optic neuropathy that was treated with further radiation, and delays in diagnosis and treatment of demyelinating optic neuritis, glaucoma, sellar masses, multiple sclerosis, and glioblastoma multiforme, as well as adverse effects from unnecessary treatments with steroids and acetazolamide. In 60 (97%) patients, earlier access to neuro-ophthalmology could potentially have prevented the harm.

Discussion

238 This is the first prospective, multisite study of diagnostic error to include all
239 neuro-ophthalmic conditions, and the first to directly measure harm due to diagnostic
240 error.

241 In this sample, approximately half (49%) of all new patients referred to neuro-
242 ophthalmology were misdiagnosed. This reaffirms that neuro-ophthalmologists confront
243 high rates of diagnostic error in referrals to our clinics, consistent with prior studies,[9-19]
244 and shows that this high rate of misdiagnosis is not limited to a specific diagnosis[35].
245 Neuro-ophthalmic conditions were more likely to be misdiagnosed-in-excess, while non-
246 neuro-ophthalmic diagnoses were more likely to have been missed. This is expected in
247 the biased sample of patients referred for NOC—these patients were referred due to
248 suspicion for a neuro-ophthalmic condition. The vast majority of referrals were
249 appropriate (asked a neuro-ophthalmic question), and the inappropriate ones were
250 more likely to be misdiagnosed.

251 Similar to our prior retrospective study,[19] access to NOC was limited by wait
252 times, and most patients had seen an eye care provider (ophthalmologist or optometrist)
253 or neurologist prior to neuro-ophthalmology referral. In almost every case (99%), the
254 NOC had a direct impact on care, including saving vision or life in 2%, with misdiagnosis
255 at the time of referral correlating with a higher impact of the NOC. Notably, even for
256 patients who were inappropriately referred for NOC, the NOC had a high impact.

257 Over one-quarter of misdiagnosed patients suffered harm due to the
258 misdiagnosis, and in almost all cases this could potentially have been prevented with
259 earlier access to NOC. Harms ranged from adverse effects of inappropriate medications
260 to death due to delay in diagnosis of a brain tumor. Similar to prior studies[12,13,15]

misdiagnosed patients were more likely to be exposed to inappropriate management (laboratory testing, imaging, or treatment) prior to referral. This study is the first to confirm a statistically-significant relationship between misdiagnosis and exposure to the risk, time, and cost of unnecessary diagnostic testing and treatments.

The most common pitfalls leading to diagnostic errors of neuro-ophthalmic conditions occurred in the physical examination, history, and the generation and consideration of the differential diagnosis. Neuro-ophthalmology subspeciality training and real-world experience provides an expertise in the detailed neuro-ophthalmic history and examination, and the differential diagnosis of conditions that affect the visual pathways. These results emphasize the value of subspecialty-trained neuro-ophthalmologists in diagnosing and managing these potentially devastating conditions.[35-39]

This study was inherently limited by the accuracy of referral records, although this limitation was mitigated by the prospective nature of this study, allowing us to verify information with the patient at the time of NOC. Our evaluation had subjective components (e.g., whether referral was appropriate, whether harm occurred due to diagnostic error, whether harm was preventable). In our study, there were 5 different neuro-ophthalmologists from 3 institutions, and there may have been some differences in how the survey questions were applied; however, it is important to emphasize that all participating neuro-ophthalmologists had experience working together on similar projects, ensuring relative homogeneity of data documentation and collection. There is also subjectivity to the definition of misdiagnosis. We chose to define misdiagnosis as a referral diagnosis that was different than the final neuro-ophthalmic diagnosis or a

referral diagnosis that was missing. Of course, many patients are referred for NOC as a request for help with the diagnosis, but it is not benign for a misdiagnosis or lack of diagnosis to perpetuate while waiting for NOC, especially in light of the known limitations of access to NOC.[8,19,35-40] The DEER taxonomy is inherently subjective. We chose to assign the most proximal error as causative with the reasoning that it influenced or caused more distal errors, but this assumption may not have been true in every case, and may have biased our assessment toward more proximal DEER elements (such as history and physical examination elements). Future directions could include a detailed analysis of the costs incurred in unnecessary diagnostic testing and treatments due to diagnostic errors before NOC. Psychologic harms or stress that patients suffer due to misdiagnosis was not captured by this study, and this also would be interesting to investigate. Finally, we did not capture harms that occurred due to delay in neuro-ophthalmic evaluation for patients who had a correct referral diagnosis, which could also be an avenue for future study.

In this study, misdiagnosis of neuro-ophthalmic conditions and preventable harms due to misdiagnosis were common. In misdiagnosed patients, mismanagement prior to referral was common, and more than one-quarter of misdiagnosed patients were directly harmed due to the misdiagnosis. In almost all cases, these harms could potentially have been avoided with earlier access to NOC. Diagnostic errors could often be traced to history, physical examination, or interpretation of the differential diagnosis, all aspects of the unique skill set honed by neuro-ophthalmology subspeciality training.

Improving access to neuro-ophthalmologists has the potential to prevent patient harm, which is made challenging by the current shortage of neuro-ophthalmologists.

Improving incentives to attract trainees to subspecialize in neuro-ophthalmology will allow expanded access to patients who need care for these complex conditions.

References

1. Berner ES, Graber ML. Overconfidence as a cause of diagnostic error in medicine. *Am J Med.* 2008;121(5 Suppl):S2-23.
2. Newman-Toker DE, Makary MA. Measuring diagnostic errors in primary care: the first step on a path forward. Comment on "Types and origins of diagnostic errors in primary care settings". *JAMA Intern Med.* 2013;173(6):425-426.
3. Singh H, Meyer AN, Thomas EJ. The frequency of diagnostic errors in outpatient care: estimations from three large observational studies involving US adult populations. *BMJ Qual Saf.* 2014;23(9):727-731.
4. Institute of Medicine. *To Err Is Human: Building a Safer Health System.* Washington DC: National Academies Press; 2000.
5. Saber Tehrani AS, Lee H, Mathews SC, et al. 25-Year summary of US malpractice claims for diagnostic errors 1986-2010: an analysis from the National Practitioner Data Bank. *BMJ Qual Saf.* 2013;22(8):672-680.
6. Schaffer AC, Jena AB, Seabury SA, Singh H, Chalasani V, Kachalia A. Rates and Characteristics of Paid Malpractice Claims Among US Physicians by Specialty, 1992-2014. *JAMA Intern Med.* 2017;177(5):710-718.
7. Chung SM, Custer PL. Patient Safety: Its History and Relevance to Neuro-Ophthalmology. *J Neuroophthalmol.* 2017;37(3):225-229.
8. Frohman LP. Neuro-Ophthalmology: Transitioning From Old to New Models of Health Care Delivery. *J Neuroophthalmol.* 2017;37(2):206-209.

9. Dillon EC, Sergott RC, Savino PJ, Bosley TM. Diagnostic management by gatekeepers is not cost effective for neuro-ophthalmology. *Ophthalmology.* 1994;101(9):1627-1630.

10. Elmalem VI, Hudgins PA, Bruce BB, Newman NJ, Biousse V. Underdiagnosis of posterior communicating artery aneurysm in noninvasive brain vascular studies. *J Neuroophthalmol.* 2011;31(2):103-109.

11. McClelland C, Van Stavern GP, Shepherd JB, Gordon M, Huecker J. Neuroimaging in patients referred to a neuro-ophthalmology service: the rates of appropriateness and concordance in interpretation. *Ophthalmology.* 2012;119(8):1701-1704.

12. Fisayo A, Bruce BB, Newman NJ, Biousse V. Overdiagnosis of idiopathic intracranial hypertension. *Neurology.* 2016;86(4):341-350.

13. Stunkel L, Kung NH, Wilson B, McClelland CM, Van Stavern GP. Incidence and Causes of Overdiagnosis of Optic Neuritis. *JAMA Ophthalmol.* 2018;136(1):76-81.

14. Kahraman-Koytak P, Bruce BB, Peragallo JH, Newman NJ, Biousse V. Diagnostic Errors in Initial Misdiagnosis of Optic Nerve Sheath Meningiomas. *JAMA Neurol.* 2019;76(3):326-332.

15. Schroeder RM, Stunkel L, Gowder MTA, et al. Misdiagnosis of Third Nerve Palsy. *J Neuroophthalmol.* Published online September 23, 2020. doi:10.1097/WNO.0000000000001010

16. Blanch RJ, Horsburgh J, Creavin A, Group DS, Burdon MA, Williams C. Detection of Papilloedema Study (DOPS): rates of false positive papilloedema in the community. *Eye (Lond).* 2019;33(7):1073-1080.

17. Stunkel L, Newman NJ, Biousse V. Diagnostic error and neuro-ophthalmology. *Curr Opin Neurol.* 2019;32(1):62-67.

18. Stunkel L, Newman-Toker DE, Newman NJ, Biousse V. Diagnostic Error of Neuro-ophthalmologic Conditions: State of the Science. *J Neuroophthalmol.* August 18, 2020. doi:10.1097/WNO.0000000000001031

19. Stunkel L, Mackay DD, Bruce BB, Newman NJ, Biousse V. Referral Patterns in Neuro-Ophthalmology. *J Neuroophthalmol.* 2019. 2020;40(4):485-493.

20. Sadun AA, Chu ER, Boisvert CJ. Neuro-ophthalmology Safer Than MRI? *Ophthalmology.* 2013;120(4):879.

21. Wolintz RJ, Trobe JD, Cornblath WT, Gebarski SS, Mark AS, Kolsky MP. Common errors in the use of magnetic resonance imaging for neuro-ophthalmic diagnosis. *Surv Ophthalmol.* 2000;45(2):107-114.

22. Newman-Toker DE, Pronovost PJ. Diagnostic errors--the next frontier for patient safety. *JAMA.* 2009;301(10):1060-1062.

23. Kim AS, Fullerton HJ, Johnston SC. Risk of vascular events in emergency department patients discharged home with diagnosis of dizziness or vertigo. *Ann Emerg Med.* 2011;57(1):34-41.

24. Atzema CL, Grewal K, Lu H, Kapral MK, Kulkarni G, Austin PC. Outcomes among patients discharged from the emergency department with a diagnosis of peripheral vertigo. *Ann Neurol.* 2016;79(1):32-41.

25. Newman-Toker DE, Moy E, Valente E, Coffey R, Hines AL. Missed diagnosis of stroke in the emergency department: a cross-sectional analysis of a large population-based sample. *Diagnosis (Berl).* 2014;1(2):155-166.

26. Madsen TE, Khoury J, Cadena R, et al. Potentially Missed Diagnosis of Ischemic Stroke in the Emergency Department in the Greater Cincinnati/Northern Kentucky Stroke Study. *Acad Emerg Med.* 2016;23(10):1128-1135.

27. Bakradze E, Liberman AL. Diagnostic Error in Stroke-Reasons and Proposed Solutions. *Curr Atheroscler Rep.* 2018;20(2):11.

28. Edlow JA, Gurley KL, Newman-Toker DE. A New Diagnostic Approach to the Adult Patient with Acute Dizziness. *J Emerg Med.* 2018;54(4):469-483.

29. Tarnutzer AA, Lee SH, Robinson KA, Wang Z, Edlow JA, Newman-Toker DE. ED misdiagnosis of cerebrovascular events in the era of modern neuroimaging: A meta-analysis. *Neurology.* 2017;88(15):1468-1477.

30. Kerber KA, Meurer WJ, West BT, Fendrick AM. Dizziness presentations in U.S. emergency departments, 1995-2004. *Acad Emerg Med.* 2008;15(8):744-750.

31. Liberman AL, Newman-Toker DE. Symptom-Disease Pair Analysis of Diagnostic Error (SPADE): a conceptual framework and methodological approach for unearthing misdiagnosis-related harms using big data. *BMJ Qual Saf.* 2018;27(7):557-566.

32. Graber ML. The incidence of diagnostic error in medicine. *BMJ Qual Saf.* 2013;22 Suppl 2:ii21-ii27.

33. Schiff GD, Hasan O, Kim S, et al. Diagnostic error in medicine: analysis of 583 physician-reported errors. *Arch Intern Med.* 2009;169(20):1881-1887.

34. Schiff GD, Kim S, Abrams R, et al. Diagnosing Diagnosis Errors: Lessons from a Multi-institutional Collaborative Project. In: Henriksen K, Battles JB, Marks ES, Lewin DI, eds. *Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology).* Rockville, MD: Agency for Healthcare Research and Quality; 2005.

35. Stuart A. Neuro: How to Minimize Diagnostic Errors. In. *EyeNet Magazine.* Vol September 2020. San Francisco, CA: American Academy of Ophthalmology; 2020:44-53.

36. Frohman LP. How can we assure that neuro-ophthalmology will survive? *Ophthalmology.* 2005;112(5):741-743.

37. Frohman LP. The human resource crisis in neuro-ophthalmology. *J Neuroophthalmol.* 2008;28(3):231-234.

38. Frohman L, Digre K. Elimination of consult codes in neuro-ophthalmology: another blow to our subspecialty? *J Neuroophthalmol.* 2010;30(2):210-211.

39. Williams RD. Neuro-Ophthalmology's SOS: Save Our Subspeciality. *EyeNet Magazine.* September 2020. https://www.aao.org/eyenet/. Accessed February 8, 2021.

40. Subramanian PS, Frohman LP, Biousse V, Quality of Neuro-Ophthalmic Care Committee of the North American Neuro-Ophthalmology S. Impact of the

421 Elimination of Consultation Codes on Neuro-Ophthalmology in the United States.
422 *J Neuroophthalmol.* 2018;38(1):4-6.
423

Figure Legends

Figure 1:

Title: Impact of neuro-ophthalmology consultation on the outcome of 496 patients.

Legend: Impact of neuro-ophthalmology consultation was classified into 5 categories: 1) no impact; 2) provided reassurance, avoiding further visits and tests; 3) provided a diagnosis and direction to treatment; 4) avoided harmful treatment or provided urgent referral to appropriate provider; or 5) directly saved vision or life.

Figure 2:

Title: Misdiagnosis rates and inappropriate referral rates stratified by impact of neuro-ophthalmology consultation.

Legend: Impact of neuro-ophthalmology consultation was classified into 5 categories: 1) no impact; 2) provided reassurance, avoiding further visits and tests; 3) provided a diagnosis and direction to treatment; 4) avoided harmful treatment or provided urgent referral to appropriate provider; or 5) directly saved vision or life.

Table 2:

Title: Final neuro-ophthalmologic diagnoses compared with referral diagnoses.

Diagnosis	**Referral Diagnosis**	**Final Diagnosis**	**Δ**
Optic neuropathies			
Optic atrophy, any cause (chronic)	48 (10%)	38 (8%)	↓[a]
Other optic neuropathy, any type (acute)	38 (8%)	23 (5%)	↓
Optic neuritis	16 (3%)	11 (2%)	↓
Glaucoma	4 (<1%)	12 (2%)	↑
Papilledema or Abnormal Optic Disc Appearance			
Suspected due to IIH	89 (18%)	71 (14%)	↓
Suspected due to secondary intracranial hypertension	5 (1%)	6 (1%)	=
Pseudopapilledema or congenital disc abnormality	8 (2%)	23 (5%)	↑
Diplopia and Nystagmus			
Diplopia or acute CN 3, 4 or 6 palsy	79 (16%)	49 (10%)	↓
Nystagmus	17 (3%)	11 (2%)	↓
Childhood strabismus/decompensated phoria	5 (1%)	19 (4%)	↑
Skew deviation	0 (0%)	5 (1%)	↑
Vision Loss			
Vision loss/ Visual field defect	55 (11%)	9 (2%)	↓
Non-organic vision loss	4 (<1%)	19 (4%)	↑
Amblyopia	1 (<1%)	2 (<1%)	↑
Sellar mass	25 (5%)	24 (5%)	↓
Vascular			

Stroke/ Transient ischemic attack	16 (3%)	16 (3%)	=
Transient vision loss, unspecified	10 (2%)	3 (<1%)	↓
Retinal ischemia/infarction (RAO)	2 (<1%)	6 (1%)	↑
Headaches and related symptoms			
Cerebrospinal fluid Leak	10 (2%)	7 (1%)	↓
Primary headache disorder	7 (1%)	23 (5%)	↑
Concussion related visual symptoms	3 (<1%)	1 (<1%)	↓
Pupillary abnormality (Horner, Adie)	12 (2%)	10 (2%)	↓
Other cranial neuropathy, any type	11 (2%)	3 (<1%)	↓
Giant cell arteritis	9 (2%)	3 (<1%)	↓
Myasthenia gravis	9 (2%)	9 (2%)	=
Other orbital process (unspecified)	4 (<1%)	3 (<1%)	↓
Ocular surface disease or cataract	3 (<1%)	24 (5%)	↑
Retinal disease or uveitis	3 (<1%)	24 (5%)	↑
Thyroid eye disease	0 (0%)	2 (<1%)	↑
Uncorrected refractive error	0 (0%)	4 (<1%)	↑
Other	2 (<1%)	33 (7%)	↑
No referral diagnosis	1 (<1%)	N/A N/A	↓
Normal examination	N/A N/A	3 (<1%)	↑
Total	496 (100%)	496 (100%)	=

a. Conditions with lower frequency of final diagnoses than referral diagnoses, meaning that referring providers misdiagnosed-in-excess, are indicated with a downward arrow (↓). Conditions with higher frequency of final diagnoses than referral diagnoses, meaning that referring providers missed the diagnosis, are indicated with an upward arrow (↑). P values were not calculated for comparisons because of small group sizes.

Table 3:

Title: Disposition of patients after neuro-ophthalmology consultation.

Disposition	**# (%) of patients**[a]
Admitted or sent directly to the emergency room	6 (1.2%)
Return to referring provider	291 (59%)
Referral to another provider	100 (20%)
Follow up in neuro-ophthalmology clinic	175 (35%)

a. Total will exceed 496 and total percentages will exceed 100% because patients may have had multiple dispositions (for example, a patient may have both been sent to the emergency department and seen in neuro-ophthalmology follow-up).

Table 4: Diagnosis Error Research and Evaluation (DEER) Taxonomy.

Diagnosis Error Research and Evaluation (DEER) Taxonomy Designation	**# (%) of patients**
1A – Failure/ delay in presentation	1 (0.4%)
2A – Failure/ delay in eliciting critical piece of history	22 (9%)
2B – Inaccurate/ misinterpreted history	21 (9%)
2C – Failure in weighing history	15 (6%)
3A – Failure/ delay in eliciting critical examination findings	36 (15%)
3B – Inaccurate/ misinterpreted examination	38 (15%)
3C – Failure in weighing examination	13 (5%)
4A – Failure/ delay in ordering needed test(s)	12 (5%)
4B – Failure/ delay in performing needed test(s)	1 (0.4%)
4D – Ordering wrong test(s)	2 (1%)
4I – Failure/ delay in reported of result to clinician	1 (0.4%)
4K – Error in clinician interpretation of test	16 (7%)
5A – Failure/ delay in considering the diagnosis	26 (11%)
5B –Too little consideration/ weight given to the diagnosis	7 (3%)
5C – Too much weight on competing or coexisting diagnosis	26 (11%)
5D – Failure to recognize/ weigh urgency	3 (1%)
6D – Failure/ delayed communication/ follow-up of consultation	2 (1%)
Total Misdiagnosed	242 (100%)

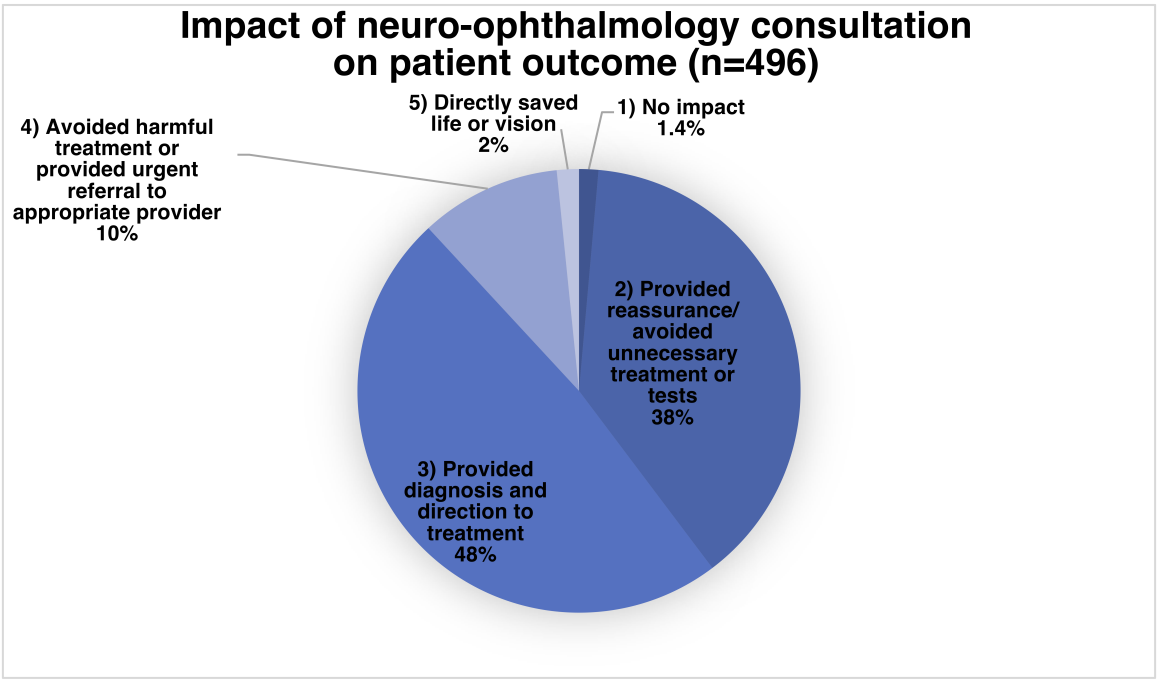
Table 1:

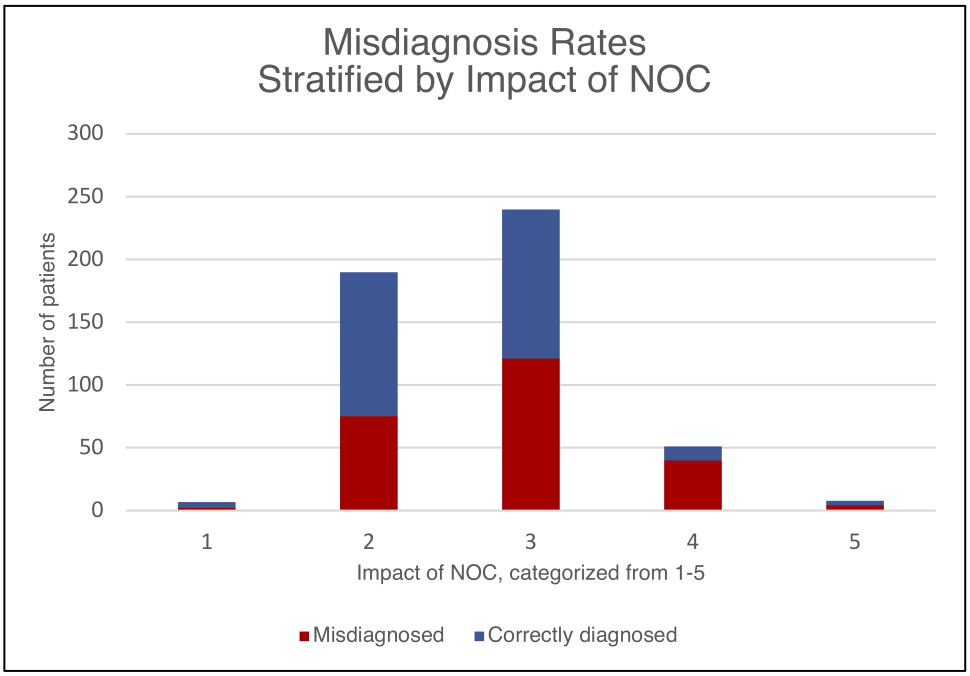
Title: Specialties of all providers seen before neuro-ophthalmology consultation.

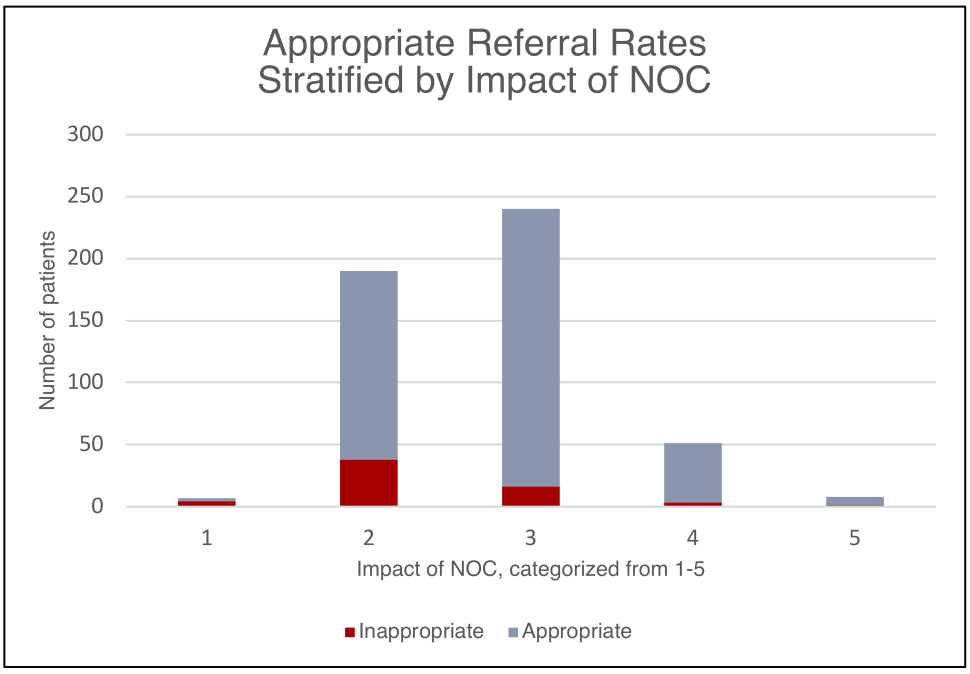
Brief Description: Misdiagnosis and harm rate broken down by specialties patients had contact with prior to neuro-ophthalmology consultation.

Specialty:	**# (%) of patients seen by a provider of this specialty prior to neuro-ophthalmology consultation[a]**	**Misdiagnosis Rate**	**Harm due to Misdiagnosis**
Ophthalmology	296 (60%)	157 (53%)	40 (14%)
Neurology	184 (42%)	97 (53%)	28 (15%)
Optometry	176 (35%)	117 (66%)	24 (14%)
Neurosurgery	80 (16%)	26 (33%)	10 (13%)
Primary Care/ Internal Medicine	105 (21%)	45 (43%)	12 (11%)
Emergency Medicine	95 (19%)	39 (41%)	14 (15%)
Other specialties	76 (15%)	NA	NA

a. Total patients will exceed 496, total misdiagnosed patients will exceed 242, total harmed will exceed 62, and percentages will exceed 100% because patients may have seen providers of multiple specialties prior to neuro-ophthalmology consultation.


Impact of neuro-ophthalmology consultation on patient outcome (n=496)
1) No impact 1.4%
2) Provided reassurance/ avoided unnecessary treatment or tests 38%
3) Provided diagnosis and direction to treatment 48%
4) Avoided harmful treatment or provided urgent referral to appropriate provider 10%
5) Directly saved life or vision 2%


Misdiagnosis Rates
Stratified by Impact of NOC
300
250
200
150
100
50
0
Number of patients
1
2
3
4
5
Impact of NOC, categorized from 1-5
Misdiagnosed
Correctly diagnosed


Appropriate Referral Rates
Stratified by Impact of NOC
300
250
200
150
100
50
0
Number of patients
1
2
3
4
5
Impact of NOC, categorized from 1-5
Inappropriate
Appropriate

Précis

This multisite, prospective, study of neuro-ophthalmic conditions prior to neuro-ophthalmology consultation shows that almost half are misdiagnosed prior to referral, and 26% of those experience harm that could have been prevented by earlier referral.