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AMERICAN ACADEMY OF OPHTHALMOLOGY®

Reports

Accuracy of Referral and Phone-Triage Diagnoses in an Eye Emergency Department

Requests for ophthalmologic evaluation for ocular symptoms are customary in medicine. Whether they are outpatient referrals (from optometrists,[1] ophthalmologists,[1] or other physicians[1–3]), inpatient consultations,[4] or emergency referrals,[1,4] it is convention for the requesting health care professional to specify a suspected diagnosis or to ask a clinical question in the request. However, the literature indicates limited reports examining the diagnostic accuracy of referring healthcare providers.[1–4] Currently, a growing need exists for ophthalmologists to accurately diagnose urgent and emergent ocular referrals remotely, which has been highlighted by the 2019 coronavirus pandemic.

The Wills Eye Hospital Emergency Department (ED) is a high-volume tertiary academic referral center that receives urgent and emergent referrals from outpatient offices, urgent care centers, and outside emergency departments. Referring health care professionals call triaging ophthalmology medical staff via a dedicated transfer line to establish appropriateness of the referral before patient transfer. This study was designed to prospectively evaluate the accuracy of referring health care professionals' working diagnoses and to evaluate the ability of a telephone-triaging ophthalmologist to diagnose these urgent and emergent ocular conditions remotely.

After receiving approval from the Wills Eye Hospital Institutional Review Board, data were collected prospectively from all health care professionals and their patients who were referred to the Wills Eye Hospital ED via the dedicated transfer phone over a 3-month period (June 1, 2018–September 1, 2018). Referral data were collected by a triaging ophthalmology staff member (a second-year ophthalmology resident, supervised by an attending ophthalmologist) on free-text triage sheets and included history of present illness, referring provider specialty, and the working diagnosis. Before patient arrival, the triaging ophthalmologist recorded his or her own suspected diagnosis, based on the collected information, indicating if he or she agreed with the referring diagnosis. The triaging sheets were reviewed after the visit by an ophthalmology resident (J.D.D., D.C.A., D.J.O., L.B., or A.R.M.). Reviewers were masked appropriately to the referring, triaging, and final diagnoses as necessary. Coded diagnosis categories were generated from the free-text entries (Table S1, available at www.aaojournal.org).

After the patients' visits, their charts were reviewed by a reviewer (J.D.D., D.C.A., D.J.O., L.B., or A.R.M.) to collect the final diagnosis and the anatomic location of the diagnosis. Again, reviewers were masked to the referring and triaging diagnoses. The final diagnosis was categorized by primary anatomic location: orbit and ocular adnexa, ocular surface and cornea, anterior segment, glaucoma, retina and vitreous, optic nerve, or central and peripheral nervous system. A final diagnosis was labeled a "can't-miss diagnosis" if it could cause irreversible vision loss or death if not diagnosed and treated emergently. Can't miss diagnoses included giant cell arteritis, cerebrovascular accident, ruptured globe, orbital compartment syndrome, acute angle-closure glaucoma, central nervous system lesion, third-nerve palsy, acute Horner's syndrome, and endophthalmitis (Table S2, available at www.aaojournal.org). The final diagnosis was compared with the prospectively collected data to assess the accuracy of the referring and triaging diagnoses.

Over the study period, 530 patients were referred to the eye ED via the transfer line. Of these patients, 334 (63.0%) were included. The remaining patients were excluded for never appearing at the ED (n = 146 [27.5%]) or incomplete data (n = 50 [9.4%]). Most referring professionals were emergency medicine physicians (52.4% [n = 175]), followed by ophthalmologists (24.9% [n = 83]), optometrists (7.8% [n = 26]), and urgent care physicians (6.3% [n = 21]). Ten referring providers' specialties (3.0%) were not recorded and were categorized as unknown.

Overall, the referring professionals who provided a working diagnosis were correct in 65.1% of cases (n = 203/312). Eye specialists (ophthalmologists, optometrists, and unknown) made the correct referring diagnosis in significantly more cases (77.8% [91/117]) than non-eye specialists (57.4% [112/195]; $X^2_1 = 13.31$; $P < 0.001$). A detailed breakdown of the diagnostic accuracy of referring professionals by specialty can be seen in Figure 1 ($X^2_9 = 16.58$; $P = 0.05$). Non-eye specialists (n = 196) were most accurate at making diagnoses of the orbit and ocular adnexa (81.6% [31/38]), followed by ocular surface and cornea (63.0% [46/73]), glaucoma (61.5% [8/13]), anterior segment (42.9% [12/28]), retina and vitreous (38.2% [13/34]), central and peripheral nervous system (25.0% [2/8]), and optic nerve (0.0% [0/1]; $X^2_6 = 22.433$, $P = 0.001$; Fig S2, available at www.aaojournal.org).

Over the phone, the triaging ophthalmologists were able to interpret the reported histories, physical examination findings, and limited testing capabilities of the referring provider and to make the correct diagnosis in 69.9% of cases (n = 179/256). Prior studies have evaluated the reliability of tele-ophthalmology in the evaluation of diabetic retinopathy, clinically significant macular edema, ocular hypertension, and glaucoma, using a variety of tele-based services ranging from 41.3% to 90.0% accuracy.[5] This study provides data on the ability of a telephone-triaging ophthalmologist to identify urgent and emergent ocular disorders referred by other medical professionals.

Both the referring professionals and the triaging eye ED staff more accurately identified can't-miss diagnoses. Referring professionals correctly identified can't-miss diagnoses in 87.5% of referrals (n = 49/56) compared with all other

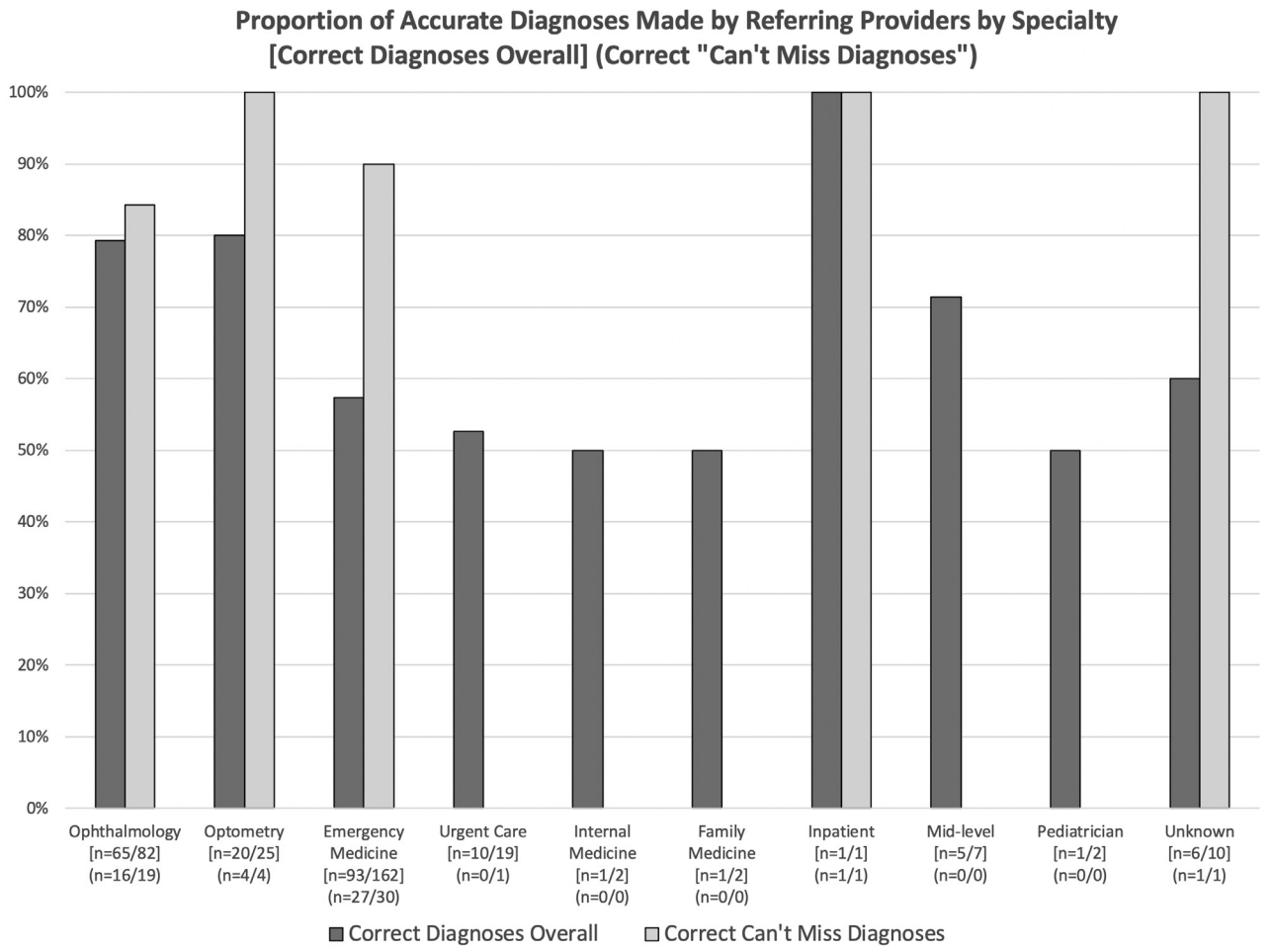

Figure 1. Bar graph showing the proportion of accurate diagnoses made by referring providers by specialty. Data in brackets are correct diagnoses overall and data in parentheses are correct can't-miss diagnoses.

conditions 60.1% (154/256; $X^2_1 = 15.11$; $P < 0.001$). Similarly, the triaging ophthalmology staff correctly identified can't-miss diagnoses in 97.2% of referrals (n = 35/36) compared with all other conditions (65.5%; n = 144/220; $X^2_1 = 14.85$; $P < 0.001$).

The referring professional and the triaging staff agreed on the diagnosis in 160 of the 234 cases (68.4%) in which they both submitted diagnoses ($\kappa = 0.566$; $P < 0.001$). When the referring professional and the triaging ophthalmology staff agreed on the diagnosis, this diagnosis was correct in 85.6% of cases (n = 137/160). When the referring professional and the triaging staff agreed on a can't-miss diagnosis, it was correct in 100.0% of cases (n = 31/31).

This study from the Wills Eye ED found that urgent and emergent ophthalmic problems were misdiagnosed in more than one third of all referred cases. The diagnostic accuracy was significantly worse when non-eye specialists made the referrals. Reassuringly, the rate of misdiagnosis decreased when only sight- and life-threatening eye disease were analyzed; most of these cases were referred appropriately. This study underscores the limitations of ocular diagnostic accuracy in the healthcare community and highlights the usefulness of a telephone-triaging ophthalmologist in the diagnosis of urgent and emergent ocular conditions.

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Evaluation of Metagenomic Deep Sequencing as a Diagnostic Test for Infectious Keratitis

Conventional corneal cultures for infectious keratitis have long been plagued by low sensitivity.[1] With patients presenting on microbiologic therapy and fastidious organisms difficult to grow in microbiology laboratories, atypical and unexpected organisms can be missed.[2]

Metagenomic deep sequencing (MDS), both RNA sequencing and DNA sequencing, carries potential for improved diagnostic sensitivity and accuracy.[3,4] The unbiased nature of total RNA and DNA sequencing allows for identification of almost any pathogen and includes the potential for pathogen discovery. However, these deep sequencing techniques have challenges with nucleic acid recovery, contamination from the environment, normal microbiota, and variable bioinformatic interpretive strategies.[5]

In the absence of a directly observed gold standard for the diagnosis of infectious keratitis, we used latent class analysis (LCA) to evaluate the sensitivity and specificity of conventional diagnostics tests, RNA sequencing, and DNA sequencing. Institutional Review Board approval was obtained. This study adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from all patients.

Corneal scrapings were obtained for potassium hydroxide (KOH) wet mount, Gram stain, and traditional cultures. For MDS, the affected cornea was swabbed with a sterile polyester tipped applicator (Puritan). A second swab of the inferior fornix of the unaffected, contralateral eye was obtained. Swabs were placed in DNA/RNA-Shield (Zymo Research) and shipped to the Proctor Foundation/University of California San Francisco on dry ice and stored at −80°C.

Conventional microbiologic testing and MDS were performed as previously reported.[4,6] Because the ocular surface is normally colonized, the taxa (at the species level) identified from the control contralateral conjunctiva were bioinformatically subtracted before final analysis. In cases in which the suspected pathogen was common microbiota (e.g., *Staphylococcus* spp., *Streptococcus* spp.), a water control from the same sequencing run was used as background subtraction. The organism was identified as positive by MDS if it was known to cause ocular infection and if it represented the most abundant reads after background subtraction. All laboratory personnel were masked.

Sensitivity and specificity of different microbiologic diagnostic tests and latent gold standard prevalence were estimated using LCA. Uncertainty was estimated using bootstrap percentile 95% confidence intervals (CIs) (1000 simulations).

Baseline information from all participants and comparative diagnostic results are presented in Table S1 (available at www.aaojournal.org). KOH or Gram stain was positive in 32 samples (70%). Of these, 23 were positive for fungus and 9 were positive for bacteria; 18 (56%) were taking antibacterial or antifungal drops. Traditional culture was positive in 24 patients (52%).

Metagenomic deep sequencing (combining RNA and DNA sequencing) was positive in 34 cases (74%). Twenty ulcers were identified by MDS as fungal and 14 as bacterial. Nineteen of the 34 cases (56%) were on topical therapy. Of the 12 MDS negative cases, 6 (50%) were using antibacterial or antifungal drops. There were 5 cases (patient numbers 14, 36, 43, 44, and 45) (Table S1, available at www.aaojournal.org) in which conventional microbial diagnostics were negative and MDS was positive. There was 1 case in which MDS was negative (patient number 24) (Table S1, available at www.aaojournal.org) and culture and Gram stain were positive for viridans streptococci. There was 1 case (patient number 38) (Table S1, available at www.aaojournal.org) in which the culture results (fungus) were discrepant from the sequencing results (bacteria by RNA and DNA sequencing). Gram stain and KOH prep were negative in this case. Six (13%) of the 46 ulcers were diagnostically negative by all tests.

An LCA comparing the performance of 3 diagnostic tests (combined KOH prep/Gram stain/culture, RNA and DNA sequencing) is presented in Table 1. For this population of bacterial ulcers, the LCA estimated the highest performance from RNA sequencing with an estimated sensitivity of 100% (95% CI, 79–100) and estimated specificity of 97% (95% CI, 84–100). Likewise, for fungal ulcers, RNA sequencing outperformed DNA sequencing and conventional diagnostics with a sensitivity of 100% (95% CI, 86–100) and specificity of 100% (95% CI, 89–100).

An LCA comparing stains, culture, RNA sequencing, and DNA sequencing separately is presented in Table S2 (available at www.aaojournal.org). LCA considers each test as conditionally independent. In this study, the microbiology laboratory was not formally masked to the KOH and Gram stain results, raising the