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Research Article

Robotic Ocular Surgery, Navigating the AI Terrain from Machine and Deep Learning to Autonomous and Embodied Artificial Intelligence

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Abstract

In the realm of leaps in understanding of eye disease, like the introduction of the slit lamp illumination of the globe by Allvar Gullstrand in 1911, Gulshan et al. (2016 Dec 13;316(22):2402-2410) demonstrated that deep learning could match ophthalmologist performance for referrable diabetic retinopathy detection on fundus photography retrospective datasets. In 2018 Abramoff et al (NPJ Digit Med,2018 Aug 28;1:39) reported the first FDA approved autonomous AI diagnostic system to detect diabetic retinopathy from fundus photos. Camino et al. in 2018 (Biomedical Optics Express, 9:7, 3092-3105)** implemented a convolutional neural network, CNN, to segment regions of preserved retinal photoreceptors, (90%accuracy), in retinitis pigmentosa and choroideremia patients from OCT images.

Camino et al. explained that the extent of ellipsoid zone pattern integrity (from ocular trauma to macular telangiectasia to diabetic retinopathy to several inherited retinal diseases) using a CNN trained OCT B-scan provided a morphological photoreceptor mapping, comparable to an expert OCT image grader.** T Pham et al. in 2019 (Br J Ophthalmol, 2021 Sep;105(9):1231-1237) used an ensemble of deep CNNs to segment the anterior ocular segment structures, iris, corneoscleral, and anterior chamber to detect scleral spur on segmented OCT images as accurately as an experienced ophthalmologist on the same dataset as well as isolate anterior segment angle structures.

From surgical video recordings of adult patients undergoing cataract surgery at Moorfields Eye Hospital, Shah et al. used an AI system to first segment surgery into phases based on the International Council of Ophthalmology-Ophthalmology Surgical Competency Assessment Rubric tool in phase I. In phase 2 efficiency metrics for phacoemulsification were compared: junior trainees vs advanced trainees vs consultants. Consultants had an average case duration of 11.8 minutes, advanced trainees had an average of 17.54 minutes and junior trainees had an average of 21.36 minutes. This was the first use of a fully independent AI Platform to analyze efficiency metrics in cataract surgery.

Similar to the above types of AI studies supporting leaps of understanding in ophthalmology, additional studies are presented in the sub sections of this paper. Starting with early robots in medicine, surgery, and ophthalmology, and moving to cataract surgery, abetting retinal fundus photo and OCT image diagnostics, corneal and glaucoma surgery, and subretinal injections and retinal membrane surgery, Machine Learning and Deep Learning have provided a noteworthy educational platform. Embodiment AI in ophthalmic surgery, and Autonomous AI in retinopathy of prematurity, ROP, have added dimension to this platform and are discussed in later sections of this paper.

AI techniques presented in this paper span from 1. early data driven **algorithms** (e.g. retrospective dataset analysis: e.g.: doctor explains history, physical and lab data to patient); 2. algorithm aggregation with multimodal data fusion (or e.g. **machine language**: checks exam, fundus photos, OCT photos and compares aggregate data points outputs to established standards for diagnosis and explanation). 3. **deep learning** takes images, e.g. OCT of the anterior segment angle or retinal layers and uses convoluted neural networks, CNNs to, with computer coded precision, take sections, edges, or shapes or pooled areas of digital pixels and interrogate the specific section selected for apparent and occult possible disease patterns. These patterns can then inform on early diagnostic clues to simple vs complex elements of the images, e.g. appositional vs synechial angle closure in glaucoma or low or nil Ellipsoid Zone layer in retinal degeneration. 4. **Autonomous AI** can could reliably navigate a needle surgical tool to different desired retinal locations within 137um accuracy; or take telemedicine images of ROP from distant rural parts of the globe, label and compare them to reference images, grade them and advise quick referral for expert care or just follow with close clinical observation. 5. **Embedded AI** can actively take multimodal fundus images, OCT images, interact with surgeon for eye tracking and biomechanics, illustrate previous surgical learning and new surgeon/surgical maneuver feasibility, re-enforcement learning, millisecond real time feedback, aid and enhance surgical decisions and invoke additional computer resources including 1-4 above.

Methods

Pub med, google scholar, Dox gpt, Google Gemini AI, and Microsoft Copilot were searched for references with titles containing words of: AI, Machine Learning, Deep Learning, CNNs, Autonomous AI Learning and Embedded AI Learning in ophthalmology, glaucoma, cornea, cataracts and retina from the last 10 years; This resulted in ophthalmic diagnostic categories with AI of different types; The promontory papers of each diagnostic category were reviewed for references of early, middle and late AI applications and categorized accordingly. Papers illustrating in depth AI tactical descriptions, e.g. UNet CNN OCT image architectural application, large training data sets and compelling testing data sets with large number of cross validation data sets, and/or cited by several other authorities in the field, were given priority for presentation and discussion. First in class papers using AI in major ophthalmological diagnostics were also given priority.

Introduction

Early Robots

The International Organization for Standardization defines a robot as "an automatic, position-controlled, programmable multi-functional manipulator with several axes. It can process various materials, parts, tools and special devices through programmable automation to perform intended tasks"[1,2,3]. Typically, a robot consists of four parts: the actuation system, the drive transmission system, the control system, and the intelligent system [2]. The robot part that performs the work, similar to the human hand is the actuation system. A power source through a drive transmission system transmits a force and motion to the actuator system. The control system made of a computer, software, and servo controllers in conjunction with an analytical decision making system allow for perception and intelligent decisions [2].

Although the history of robots can be traced to over 3,000 years ago, Joseph Engelberger who founded the Unimation Corporation with George Devol, the world's first robot manufacturing factory, in 1962 in Danbury, Connecticut (Wikipedia), is credited as the Father of Robotics. Devol had applied for the patent of an industrial robotic arm in 1954. In 1978 Unimation Corporation developed PUMA, Programmable Universal Machine for Assembly, which is the basis for the development of international industrial robotics [2]. With time, the International Federation of Robotics classified robots into industrial or service groups. Industrial robots have programmability, fixed autonomous control and are used in industrial production. Service robots have driving mechanisms with diverse requirements and meet different needs, classified by either different types of movement or different applications: domestic, social, educational, homecare, professional, agriculture, hospitality, cleaning, inspection, maintenance, search and rescue, construction, demolition, transportation, medical care, surgical care, rehabilitation, diagnostics, laboratory automation, and "other" medical robots [2].

Early Medical and Surgical Robots

The Puma 200 robot (Westinghouse Electric, Pittsburgh PA), in 1985, used for needle placement in computer tomography guided brain biopsy at Los Angeles Hospital, USA, is the first of a 40 year era of medical robotic applications [2,4,5]. The first instance of a robot actively removing tissue from a human patient was transurethral resection of the prostate in 1991 [6]. In the early 2000s, the da Vinci Surgical System received FDA clearance (2000–2001) and became the dominant platform for urologic and gynecologic procedures [7]. Although Kwoh et al [5] was first in using computational intelligence for robotic improved positioning accuracy for CT-guided stereotactic brain surgery, Hashimoto et al in 2018 gained formal recognition of AI as a field in surgery, with robotics employing computer vision and decision support [8].

Results

Early Ophthalmologic Robotics

Several robotic vitreoretinal eye surgery devices were tried since 1989 [9,10,11,12]. After animal model testing, a teleoperated robotic micromanipulator for intravascular drug delivery, with a dedicated remote center of motion for intraocular surgery with 7 degrees of freedom was developed by Yu at al. [13]. Grace et al. [14] designed an intraocular micromanipulator with 6 degrees of separation with remote center of motion using software control of intraocular motion, instead of mechanical motion control. In 2007, using the da Vinci system, (where the surgeon was seated at the console controlling the slave arms and the camera), the first instance of robotic ocular microsurgery was reported for corneal laceration repair with 10-0 nylon sutures in porcine models [10].

Using the IRISS system in 2013, the first robotic completely automated cataract surgery was performed on post-mortem porcine eyes [10, 15, 16, 17]. With IRISSs, the surgeon teleoperates the robotic system using a pair of joysticks and the robotic system contains motion scaling and tremor reduction elements. Capable of being mounted on any commercially available surgical instrument and ideally developed to perform anterior and posterior ocular surgeries, two manipulators are mounted and travel on semicircular tracks. Visual feedback is derived through a 3-D stereo camera displayed to the surgeon by a head-up monitor [18,19].

In 2016, Preceyes Surgical System and KU Leuven were the two intraocular magnetic robotic systems in clinical use. Preceyes was the first in human robotic system in 2018 for patients requiring epiretinal or inner limiting membrane dissection over the macula [20]. Preceyes has been integrated with an external OCT imaging to serve intraoperatively to establish tool tip boundaries and positioning [21]. Preceyes was used in a human randomized controlled study for epiretinal or inner limiting membrane peeling. Surgical outcomes were equally successful and safe with the system as with conventional manual technique [24]. Subsequently, Preceyes in the first in human randomized control trial for subretinal drug delivery of tissue plasminogen activator, TPA, with intra-operative OCT, was safe and well tolerated obtaining similar surgical time and retinal microtrauma when compared to manual technique [25].

In 2016, Preceyes was used in an in-vivo porcine model for retinal vein cannulation. After inducing a retinal vein occlusion with laser (and obtaining fluorescein confirmation) Preceyes robotic introduced a glass catheter tip, with a terminal 30 um outer diameter, either tethering the vessel to underlying structures or adjacent to the occlusion. In 9 out of 9 eyes, using this approach, a balanced salt solution was injected [26,27]. Another pre-clinical study was performed in porcine eyes with retinal vein cannulation and direct intraluminal injection of ocriplasmin. [27] The thrombus was successfully released in all eyes that had vein cannulation beyond the last venous branch point prior to the site of the occlusion [27]. The studies discussed in this paragraph illustrated the technical feasibility of robotic retinal membrane peeling and that of protracted retinal vein cannulation [10].

In 2018, Preceyes robotic performed successful epiretinal membrane dissection over the macula of patients [28]. In a double-armed randomized clinical investigation comparing Preceyes robot-assisted vs traditional manual surgery in patients undergoing removal of retinal membranes under general anesthesia, (although flap initiation time was longer in the robot assisted group), the final anatomical outcomes were equally successful in robot-assisted vs manual controlled eyes involving closure of macular holes and removal of epiretinal membranes in all patients. This was confirmed by SD OCT, Spectralis Heidelberg. Of interest is that the robot group had statistically insignificantly less iatrogenic microtrauma and micro-hemorrhages [10,28]. In 2019 Preceyes Surgical System obtained the CE mark for clinical use [10].

The KU Leuven system, designed to stabilize the eye with a pre-operative alignment system and a surgeon precision motion control was tested in a porcine retinal vein model. Prolonged retinal vein cannulation with local intravenous medication infusion up to 10 minutes was possible. In 2017, the KU Leuven system was used for retinal vein occlusion cannulation in 4 patients with ocriplasmin injected into the targeted retinal veins. Report details are awaiting publication [10]. Retinal vein cannulation remains an experimental procedure exceeding manual surgical capabilities. The 2025 American Academy of Ophthalmology Preferred Practice Pattern [29] for retinal vein occlusions does not include robotic-assisted endovascular surgery among recommended treatments, noting that current standard of care focuses on anti-VEGF therapy and laser photocoagulation. No robotic system for retinal vein cannulation has received FDA approval or widespread clinical adoption.

AI in Ophthalmic Surgery

Combining different surgical tech abilities into one operating theater has been termed “the smart operating theater” [30]. Although AI has been successfully applied in diabetic retinopathy, macular degeneration, and glaucoma, the relatively small number of intraoperative applications is in part because of the absence of large, categorized and available data sets [30]. However, with the operating theater functioning as a hub, different building blocks are interacting with each other to assist the surgeon and the surgical team in real-time with data driven decision making capabilities. In essence, electronic patient records, surgical data, intraoperative audio-visual recording, telemedicine, surgical robotics, virtual and surgical reality and remote communicating methods can coalesce to facilitate “smart” functionality [30].

Thus, combined with computational data science, engineering, statistics, and mathematics the pillars for growth of the “smart operating theater” are there for AI to rest on and develop in the future [30]. For example, in the realm of preparation for cataract surgery: cataract detection, cataract grading, recognizing lens dislocation, coexisting pathology: corneal haze or keratoconus, pre-, intra-, and postoperative refraction, intra-ocular lens, IOL, power calculation, AI and linked mathematical modeling have provided accurate decision metrics and risk stratification for surgical planning [31-38]. Machine learning can be used to improve the IOL inventory of a cataract service in lesser resource locations [39]. X Zhang, et al. used neural network to predict myopic shift in pediatric pseudophakia [35].

Intraoperative AI has seen progress in computer aided vision algorithms, automated recognition of different phases of cataract surgery, in surgical videos and instrument detection and tracking [40,41,42]. The main role of intraoperative tracking devices is surgical monitoring, surgical phase detection, context awareness, surgical duration, intraoperative risk stratification regarding safety, efficiency, team communication and quality of care [43]. AI has enabled voice driven interactive systems that provide information about the patient surgery and medical information in addition to tracking controls on surgical devices and resources and materials [44].

The widespread adoption of simulation in surgical training has been able to increase skill transfer and patient safety. Automated numerical data that stratifies performance and offers feedback to surgeons aid in further skill development [45-49]. Machine learning in examining cataract surgery procedural steps reliably discriminated junior from senior surgeons based on instrument path length, number of movements, and surgical time [42]. In phacoemulsification, AI achieved automated recognition of instrumentation and operative phases from raw video data alone [40,41]. J Chapman compared the time efficiencies between traditional femtosecond laser with robotic laser in a single room model in 23 patients undergoing cataract surgery [49]. Robotic ALLY, laser completion to phacoemulsification time: 57 sec vs LenSx: 4.39; total laser time for surgeon: ALLY, 3:17, LenSx, 4:53; laser set up start to docking start: ALLY 10:05, LenSx, 19:31; total case time for surgeon: ALLY, 14.27, LenSx, 19:40; total patient time patient in OR: ALLY, 25:25, LenSx, 33:22; no significant differences in total phaco procedure time [49].

Ngenuity 3-D Visualization System (Alcon, Inc) and Trenion 3-D HD (Carl Zeiss Meditec) offer 3 -dimensional head-up viewing platforms with real-time digital video capture of surgery with video screen projection. As two different cameras capture slightly different views, this can be similar to the stereoscopic view seen by the surgeon. AI platforms can then undertake further depth analysis and image understanding [50, 51, 52]. AI which has been used for image analysis of OCT data in anterior and posterior segment diagnostics can provide the surgeon with intra-operative information on epiretinal membranes, subretinal injections, anterior chamber depth, angle analysis and anatomic and pathologic features in cataract surgery [30,53,54]. Intraoperative OCT devices use a broadband laser combined with a surgical microscope to capture anterior and posterior segment images, which can be queried through AI applications [55].

Pujari A et al. reviewed intraoperative OCT, iOCT, with broadband laser mounted on the surgical microscope, noting findings from PIONEER and DISCOVER STUDIES, that iOCT altered surgical decisions in 48% of lamellar corneal procedures and 43% of membrane peeling procedures. This review also covered corneal surgery, DSAEK and DMEK, cataract/refractive procedures, glaucoma and vitreoretinal surgery. Cost and availability were also mentioned in this review [55]. “Higher cost and sparse availability make it a lesser essential tool for a great proportion of ophthalmic surgeons during their routine clinical practice”. Nonetheless, iOCT has helped early ophthalmologic understanding of a diverse group of conditions and iOCT provides detailed intraoperative anatomical and morphological data and detailed depth of events in real time [55]. Ehlers J et al. with three year DISCOVER results, having enrolled 244 anterior segment cases and 593 posterior segment cases, using microscope integrated intraoperative OCT during surgery (Zeiss Rescan 700, Leica EnFocus, or Cole Eye iOCT systems), demonstrated 98% image acquisition. Surgeons reported that iOCT information altered surgical decisions in 43.4% of anterior segment procedures and 29.2% posterior segment procedures [56].

AI: in anterior segment robotic surgery, glaucoma surgery and early glaucoma diagnosis and progression

Robot assisted surgery has been shown to be feasible in cataract surgery, [56, 57, 58], penetrating keratoplasty, [59], corneal laceration, [60], pterygium surgery, [61] and amniotic membrane transplantation, [62]. The first demonstration of the feasibility of robot assisted glaucoma surgery was Kamthan G. et al. in 2024, using a Preceyes Surgical System. Synthetic eye models in stage 1 had robot-assisted 3 clock hours goniotomy by 2 surgeons with and without robotic assistance using a flexible goniotomy instrument. Stage 2 had with and without robot assisted stent implantation by 2 surgeons, using a trabecular bypass stent. Stent deployment was achieved successfully in 100% of the 10 trials of ab-interno sectoral goniotomy and stent implantation. By the last 5 synthetic eye cases, the average robotic assisted time was 12.5 seconds and the manual surgery took 8.37 seconds. Peri-implantation site trauma or tissue disruption was nil in the robotic group but 8/20 in the manual istent implantation group [63].

Although actual AI robotic models for glaucoma surgery have not as yet been reported, AI has emerged as a valuable tool in predicting glaucoma surgical outcomes in efforts to develop individual treatment plans [64,65,66]. When systemic features such as cardiovascular history and medication records were incorporated into machine learning models of trabeculectomy (230 cases), (thus containing multidimensional data integration), including random forest, support vector machines and artificial neural networks, the trabeculectomy model predictive accuracy was increased to 0.68 and the AUC was increased to 0.74 [66]. When Barry et al. (2024) examined 2398 trabeculectomies and minimally invasive glaucoma surgeries, MIGS, utilizing random forest, gradient boosting, multilayer perceptron and deep neural network, of all the AI models, gradient boosting achieved an area under the curve of 0.85, the highest in predicting failure in intraocular pressure control. The study also found the value of integrating electronic health records, (EHR), clinical variables and medical imaging to enhance predictive performance in complex surgical cases [67].

Lin et al. developed a multimodal deep learning model integrating free text operative notes with structured EHR. With free text operative notes added to EHR, the prior data only models were surpassed in area under the curve to 0.75, vs 0.712, without the free text data. Although at first look, that may not seem like much, the multimodal model had a higher precision, 0.884, for predicting hypotony-related surgical failures at one year after surgery [68]. Agnifili et al. using a classification tree algorithm to predict filtration surgery in 102 glaucoma patients, added additional parameters to the model [68]. Ocular surface clinical tests, surgical site biometrics, conjunctival vascularization, conjunctival thickness, and age were influential predictors of filtration surgery failure. Conjunctival stromal thickness was the most critical factor. Thicker, hyper-reflective conjunctival stroma and younger age (learned from multimodal data integration) were associated with the highest risk for filtration surgery failure [69].

Mastropasqua et al. trained and validated a deep learning model to classify post trabeculectomy filtering bleb functionality using slit lamp images of 119 filtering blebs [69] The model achieved an accuracy of 74%, sensitivity of 74% and a specificity of 87%. The model’s ability to distinguish functioning from failure may be particularly useful when adjunctive or precursor clinical material is unavailable [70]. That said, AI has been developing in the non-invasive data driven strategies for predictive glaucoma diagnosis and monitoring. Dai et al. employed logistic regression, random forest, least absolute shrinkage and selection operator algorithms to publicly available RNA datasets (GSE9944 and GSE2378) to construct diagnostic models for three candidate glaucoma genes, ENO2, NAMPT, and ADH1C [70]. ENO2 was significantly downregulated in glaucoma tissues and negatively correlated with expression of NAMPT and ADH1C. In molecular docking analysis, EN02 was found to be a therapeutic target in the AI enabled gene discovery pipeline [71].

Han et al. [74] used *transfer learning to train three CNN models for image gradeability of vertical cup to disc ratio, VCDR, and vertical disc diameter, VDD, from ~70,000 UK Biobank fundus images [71]. *(In an earlier study the VCDR and VDD were graded by two clinicians in ~70,000 photos with a custom Java program. This data was then transferred.) The AI labeled models were also applied to the Canadian Longitudinal Study on Aging for several ancestries and multiple UK ancestries. This enabled AI based Genome Wide Association Studies, GWAS, for VCDR and VDD [72,73]. Because of variation of optic disc size, a 0.5 cup-to-disc in a small disc could be pathologic; on the other hand, a 0.8 cup-disc in a large disc might be physiologic cupping. So, family studies that illustrate heritable optic disc morphology and VCDR and VDD could lead to more precise diagnosis of glaucoma [74,75].

Briefly, in examining individuals of varying ancestry, African ancestry glaucoma incidence is driven by elevated intraocular pressure, IOP, and VCDR. East Asian ancestry glaucoma is driven by VCDR but helped with lower pressure. South Asian ancestry glaucoma is driven by VCDR, but not by changes in IOP, relative to Europeans, affected by both IOP and VCDR; After adjusting for age and sex, VDD and VCDR was markedly higher in Asians and Africans than it was in Europeans. Relative to Europeans, South Asians had similar IOP, East Asians had lower IOP, but Africans had higher IOP [73-76]. (The increasing role of AI in predicting significant phenotypic and genotypic proclivities in early glaucoma is presented in the above section as a prelude to the next section, where Embodied AI, EAI, in robotics is discussed. EAI involves far more extensive pre- and intra-surgical data analytics in carrying out its coordinating functions and surgical information relay to the surgeon for e.g. glaucoma intra-operative robotics.)

AI In posterior segment robotics and Embodied AI, EAI

Combining intraoperative OCT and 3D digital visualization for vitreoretinal surgery in the DISCOVER study, Ehlers et al. improved the visualization of the OCT data stream compared with the semitransparent ocular view. Using the 4K screen they were able to identify epiretinal membranes, macula hole, proliferative vitreopathy, symptomatic vitreous opacity without reverting to the external display system of the microscope. The system provided a uniform surgical visualization for the surgeon and assistant. All eyes (n=7) underwent uneventful vitrectomy without adverse events [77].

Although traditional AI systems in ophthalmology, such as algorithms in fixed computational environments, microscopic robotics (with Machine Language), Deep Learning with CNN, (convolving neural networks with hidden, activation, pooling and special -Net architectural system layers for advanced OCT image recognition,) are all, in themselves, noteworthy AI achievements, Embodied AI, EAI, represents a new dynamic, in human achievement. It is not only the impressive features listed above, but also the live, autonomous activity of a robot co-pilot. [78,79]. Based on the paradigm of integrating AI into physical entities such as robots, enabling perception, learning, and dynamic interaction with the environment, Embodied AI is based on the Embodiment Hypothesis: physical interaction plays a central role in cognition [80].

Whereas conventional AI models rely on preselected data sets, EAI uses real-time multimodal inputs for contextual awareness adaptations. Thus, EAI can work well in changing environments and solve in the moment and evolving surgical problems [78,81]. LLM, large language models, VLM, vison-language models, and RL, reinforcement learning, recent advances, have moved EAI to next generation systems so that they can work as an “intelligent brain”, assisting decisions in clinical applications, personal queries and sensitive responses to patients [78,82,83]. EAI is a dynamic amalgam of sensory perception (audio/visual), robotic control, iterative algorithms, and ongoing decision making [84]. It draws from psychology, neuroscience, robotics, machine learning, and LLM technology. EAI systems keep learning and adapting to perceptions, language, understanding, reasoning, memory, planning, navigation, and motor execution [78,84]. So the EAI model takes the concept of learning and intelligence in computers, robots, and especially in humans to an autonomous level [78,84].

Just as convolutional neural networks, CNNs, were helpful in detecting subtle OCT retinal image elements such as outer and inner segment defects, retinal pigment epithelium and external limiting membrane degenerative changes, [85,86,87,88], EAI with large scale analysis has the potential to move ophthalmology forward in traditional research, patient monitoring, automating tasks, delivering precise outcomes, dosimetry, protein engineering, manual data collection, high throughput screening, simultaneously testing multiple variables, and even educating patients, medical students, physicians, nurses, and skillful AI operators [78,89, 90,91,92,93]. EAI can also generate automated referral recommendations for primary care physicians and non-ophthalmologic physician specialty care. For example, RobOCTNet system can detect referable posterior segment pathologies in emergency departments with 95% sensitivity and 76% specificity [78, 94,95]. Potentially for at home and broader community screening, IOMIDS, Intelligent ophthalmologic multimodal interactive diagnosis system, combines AI chatbot with multimodal learning to support self-diagnosis and triage based user history and imaging data [96]. Additional automated chatbot systems for ophthalmic disease diagnosis, fundus fluorescein angiography interpretation (ChatFFA), patient inquiries and medical education from LLMs (EyeGPT), indocyanine green angiography (ICGA-GPT) analysis generation and question answering have been reported and show promise in the EAI field [97- 103].

Although current robotic assistance can improve surgical assistance with reducing the effects of physiological hand tremor [104], current surgical robots are unable to make autonomous decisions or operate without operator surgeon or supervised controls [105]. Nespolo et al. investigated YOLACT++platform (a one stage, instance type, segmentation Deep Neural Networks, rather than the traditional fully convoluted neural network). YOLACT++ in addition to a speed >30 FPS, can detect and help track anatomic location. It can also track multiple instruments; vitrector, forceps, and endolaser. Because of CNN instance segmentation, specific instrument-tissue contact points can be tracked rather than generic “instrument/tissue” perception [106]. The vitrector tooltip can detect and classify correctly with a mean AUPR of 0.972. The segmentation of optic disc and fovea had a AUPR of 0.928 and macular hole AUPR of 0.916. Potential applications from the study also included: collision avoidance to prevent instrument-tissue damage and fine spatial localization and movement of surgical instruments for data science research [106].

In another study, evaluating de-identified surgical videos of phacoemulsification cataract operations performed by faculty and trainee surgeons in a university-based ophthalmology department between 2020 and 2021, Nespolo et al. using a region based neural convolutional network was able to identify the stage of the operation with a mean under the receiver curve greater than 95% [107]. The latter two Nespolo et al investigations provide an important platform for understanding and developing EAI by leveraging DNN and CNN structures to gain deep knowledge of real-time CNN segmentation image data in surgical decisions [78,106,107]. Along these lines of precise surgical instrument localization and intra-operative OCT image segmentation, robotic assistance with deep learning has been reported for: subretinal injection, [108], labelling for intra-operative OCT image segmentation, [109], simulated

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subretinal injections for gene therapy, [110], and vitreoretinal surgical instrument tracking in three dimensions, [111].

Wu, et al. [112] developed an autonomous robotic system for subretinal injection with OCT and deep learning based motion prediction to enable precise needle control even under dynamic retinal conditions. A Long Short-Term Memory, LSTM, neural network is used to predict internal limiting membrane motion, (which outperforms the Fast Fourier Transform based model). At the same time a real-time registration aligns the needle tip with the robot's coordinate frame. A dynamic proportional speed control strategy then directs a smooth and adaptive needle insertion. Experimental validation in porcine eyes demonstrated precise motion synchronization and successful needle control for subretinal injections [112]. To alleviate uncertainty of surgeon depth navigation, Kim, et al, [113] developed an automated tool navigation task where a deep neural network is trained to imitate expert trajectories toward various surgical locations on the retina based on recorded visual servo mechanism goal specification. The experimental setup consisted of a Steady Eye Hand Robot (a surgical robot specifically built for eye surgery) [114], a surgical needle, which is attached at the end-effector with thickness 500µm in diameter and its small tip measuring 300µm in diameter, an artificial rubber eye model, 25.4mm diameter, and a microscope on robot joints with images derived from robot motor encoders, that records top-down view of the surgery. For real-life experiments, 2000 trajectories under a range of brightness conditions were collected. For simulation, 2500 trajectories under variable brightness and backgrounds were collected [113].

The autonomous navigation system was evaluated in simulation and physical experiments using a silicone phantom eye. Kim et al. found that their autonomous navigation system network could reliably navigate a needle surgical tool to different desired retinal locations within 137um accuracy in physical experiments and 94 um in simulation experiments, on average. These "safe" depth surgical tool depth proximities generalized well even with auxiliary surgical tools, variable eye backgrounds and different brightness conditions [113, 114]. Gomaa et al. [115] by incorporating the surgeon's actions and preferences into the training process, engineered the robot's adaption to individual surgical techniques, to all or portions of the procedure. "Our approach trains reinforcement and imitation learning agents simultaneously using curriculum learning approaches guided by image data to perform all tasks of the incision phase of cataract surgery. By integrating the surgeon's actions and preferences into the training process, our approach enables the robot to implicitly learn and adapt to the individual surgeon's unique techniques through surgeon-in-the-loop demonstrations" [115].

AI in Retinopathy of Prematurity, ROP

While "Embodied AI" usually consists of artificial intelligence systems that interact with the real world through robotic or sensor-equipped platforms, ROP management approximates this standard by autonomous AI screening systems. The latter capture and analyze retinal images at the point of care. Smartphone-based image acquisition platforms provide images for the non-specialist to screen from diverse and sometimes lesser advantaged clinical environments. The **i-ROP** DL system developed by ROP Consortium is the most extensively validated clinical application for this approach. Deep learning algorithms generate vascular severity scores from fundus photographs. This system has been shown to be comparable to or better than human experts in several external validation studies [127].

A deep convolutional neural network with U-Net architecture, (using a vessel segmentation network trained to output a new image with pixel intensities from 0 to 1 to then gauge pixel values that are close to that of a retinal vessel) was trained with 5511 retinal photographs; each image was previously assigned a reference standard diagnosis, RSD, based on a consensus grading by three experts, (normal, pre-plus disease, or plus-disease). The algorithm was evaluated by 5-fold cross-validation and tested on an independent set of 100 images. The images were collected from 8 academic institutions participating in the study. The deep learning algorithm was tested against 8 ROP experts, each of whom had more than 10 years of clinical experience and more than 5 peer-reviewed publications in ROP [127].

Based on the RSD of the 5511 retinal photographs, 83.3% were graded as normal, 14.6% were pre-plus disease, and 3.1% or 172 as plus-disease. Mean (SD) area under the receiver operating curve were: 0.94 for normal, 0.98 for pre-plus disease, and for a diagnosis of plus-disease in an independent set of 100 retinal images, the algorithm achieved a sensitivity of 93% and specificity of 94% [127]. The presence of plus-disease, defined during the 1980s by an international consensus panel as "arterial tortuosity and venous dilation of the posterior retinal vessels that is greater than or equal to that found in a standard published retinal photograph" [127,128,129]. To capture intermediate ROP disease severity, a three tier grading system was created, normal, pre-plus, and plus. However, severe ROP is characterized by plus-disease. [127,130, 131,132,133].

Between January 2012 to July 2021 an imaging processing line was created [134] using deep learning to autonomously identify **more than mild ROP** and type 1 ROP via telemedicine in US and India. The prevalence of more than mild ROP, mtmROP, was 5.9% and type 1 ROP was 1.2% in the Stanford telemedicine data set and 6.2% for more than mild and 2.5% for type 1 ROP in the Aravind telemedicine data set from India. Examination-level AUROC for more than mild ROP was 0.896 and for type 1 ROP was 0.985 in the Stanford data set, and 0.920 for more than mild ROP and 0.982 for type 1 ROP in the Aravind data set. Thus, autonomous AI ROP telemedicine screening programs had the high accuracy for detecting ROP, a leading cause of childhood blindness, with significant healthcare disparities in outcome between high and low income countries [134].

Images in the above i-ROP study were from infants who underwent routine ROP screenings using a RetCam, Natus. Five standard images, posterior, nasal, temporal, inferior, and superior were obtained. Bedside exams were conducted with retinal fundus images by four expert readers who assessed image quality. Images not acceptable for diagnosis by a consensus of three readers or those having stage 4 or 5 ROP were excluded. Using a special, detailed segmentation CNN network, retinal blood vessels were segmented into black and white vessel maps and then used to train and validate EfficientNet-BO models for detection of normal, pre-plus and plus disease.*** Every image was passed through five models five times resulting in 25: normal, pre-plus and plus disease probabilities per image. These probabilities were averaged for each group and converted into an image for a single eye exam. These were then used for screening in each category of disease and evaluated for incremental changes for detecting more than mild ROP. Images were then stratified into training and testing and validating data set, 75%, 25% and 25% respectively [134].

*****(Why EfficientNet-B0 is Effective for ROP Screening**

1. **Fine Vascular Feature Detection:** Plus and Pre-plus diseases depend on subtle vascular changes around the optic disc. The SE attention modules ("S" is for Squeeze to achieve global average pooling to produce a CNN network channel descriptor; and "E" is for excitation, a learnable gating mechanism that outputs learned channel-wise multiplication of original features by using scaled learned weights. Channel patterns related to specific sought after fine vessel features are enhanced for weighted outputs with irrelevant material suppressed. SE modules are then embedded within Inverted Bottleneck blocks which scale and adjust the depth, width and vessel resolution preserving the channel's attention.

2. **Edge & Point-of-Care Deployment:** ROP screening frequently takes place in neonatal intensive care units (NICUs) or remote clinics using portable/handheld fundus cameras. EfficientNet-B0's small footprint (~5.3 million parameters) allows it to run real-time inference on edge devices or modest local clinic hardware.) Five models were trained to create cross validation ensemble, including the Monte Carlo dropout, MCD, convoluted neural network architecture for the images (see Coyner et al. [134,144] three paragraphs down in this paper. MCD enriches model training by enhanced image convolving diversity) [144,145]. In autonomous AI, the major purpose is screening for the disease. (e.g. In diabetic retinopathy, DR, an output of more than mild DR that compliments the Early Treatment of Diabetic Retinopathy Study, ETDRS, was developed [134,135]).

In ROP, ICROP, International Classification of ROP, and ETROP, Early Treatment for ROP, are the diagnostic frameworks. From the latter, there are 4 categories: no ROP, mild ROP, type 2 ROP and type 1 ROP [134,136,137]. Ultimately, however, the major finding for the need for treatment is the presence of plus disease. [134, 138] So, to integrate these two diagnostic categorizations, a binary heuristic with "refer the patient" or "not to refer the patient" for more than mild ROP, (which is defined as type 1 or 2 disease, or any eye with pre- plus disease) was devised. [134,138].

(For the sake of simplicity:** plus disease in ROP has retinal venous dilatation and arteriolar tortuosity, within 2 disc diameters of the optic nerve, with equal to or greater than 2 quadrants extent, meets or exceeds standard reference photographs, and may have iris vascular engorgement, poor pupillary dilation, and vitreous haze [134,138,139].

The i-ROP deep learning, DL, algorithm, developed as a plus disease classifier, has since been adapted to a **vascular severity score**, VSS, to reflect the spectrum of plus disease, which has been endorsed as a software device for ROP [134, 140,141,142]. Although previous work validated the VSS as a meaningful marker of ROP severity, early AI algorithms failed to demonstrate efficacy in clinical practice [134]. Thus, Coyner at al. [134] optimized the i-ROP DL algorithm using a Monte Carlo dropout model, MCD. With the MCD model, unlike the traditional dropout model, which is used only during the data training phase, MCD activates dropout during CNN convolving inference, so that each forward pass of an image through the neural network traverses a slightly different version of the trained model. Thus, every image was passed through each of the five models five times, resulting in 25: normal, pre-plus disease and plus-disease probabilities and this results in an image-level VSS. So a more diverse, comprehensive vascular severity score emerges and a more efficient model was obtained. Coyner et al also developed an image processing pipeline for different fields of view and image quality [134]. The performance of the fields of view and image quality were shown to be effective on the Standford and Indian cohorts to identify more than mild ROP and type 1 ROP.

(For clarity, Type 1 ROP, which requires treatment at any stage **with plus disease**, is ROP** Zone 1, in a circle with an optic nerve center to the fovea, 22-23 degrees disc foveal angle; Type 2 ROP Zone 1, disc to fovea, mild ROP w/o plus disease; needs close monitoring [134, 143]. To use the VSS output for screening, Coyner et al. evaluated each 0.1-VSS increment for detection of more than minimal ROP, looking for at least 80% sensitivity and specificity. After training and calibration of the images, (including quality, vessel segmentation, VSS inference and checking for "more than mild ROP"), the images were sent for external validation by a clinician for ROP diagnosis (zone, stage and plus disease).

In the autonomous ROP screening, the VSS was 2.4 points higher for eyes with more than mild ROP than those without, in the Stanford dataset, and 3.1 points higher in the Indian dataset. Compared with eyes with no or mild ROP, eyes with type 1 ROP had a VSS 4.3 points higher in the Stanford dataset and 5.0 points higher in the Indian dataset [134]. Thus, a real world telemedicine diverse dataset collection from different parts of the world using an autonomous deep learning AI system which trained and calibrated 2530 examinations from 843 infants in the i-ROP study had an 80% sensitivity and specificity for more than mild ROP and 100% sensitivity for type 1 ROP [134].

Fleifel et al [143] in a recent review of ROP have indicated that Telemedicine screening programs for ROP using fundus photos have been successful in clinical trials and real world settings with contact devices: Retcam,(Natus Medical Inc), ICON, (NeoLight) and Panocam (Visunex Medical Systems) and non-contact devices: Optos system and a handheld smartphone-based imaging technology. P-Score which uses reference ROP images to enhance inter-grader consistency in identifying ROP plus disease offers potential for remote areas to be aided by imaged based diagnosis [143,146]. AI technology and Telemedicine are emerging as valuable diagnostic and management tools in grading severity and progression of ROP [143]. Although laser photocoagulation has remained as a significant treatment modality, particularly for type 1 ROP in anterior zones, anti-VEGF agents offer distinct advantages especially in Zone 1 disease or aggressive ROP. Ongoing research for optimal initial treatment, recurrent disease and dosage of treatments is necessary. However, telemedicine with AI studies holds promise for urban and disadvantaged rural access to gain ROP diagnosis and treatment and follow up care [143,146].

Conclusion

EAI, Autonomous Machine Learning, ML, and Deep Learning, DL, AI Challenges in Ophthalmology

Acquiring, maintaining and validating large scale evolving datasets and their factual representative nature in the ophthalmic medical and surgical environments, as in Autonomous and EAI, can be daunting both from the up to date reference resource magnitude as well as a ponderous cost basis. These datasets need to reliably capture the complexity and variability of real world clinical, research and teaching scenarios for accurate training, testing and validating of new AI data sets and hypothesis and even putatively established theories [78-80].

Then, training and re-training Autonomous, EAI, ML and DL algorithms generic to epidemiology, statistics, biometry, medicine, surgery and ophthalmology requires large amounts of complex data interaction. Especially for LLM /VLM adaptation for real world problems and their iterative complexity and variability from single entity disease diagnosis and management to mutational evolution of infectious and genetic diseases [78, 116, 117]. All of the above for EAI especially need to be synthesized into a multimodal, agentic, and unbiased dynamic linguistic and decision framework [118-122].

Compared to traditional AI systems, EAI will require sharper and higher guardrails. Ongoing FDA or CE certification and standards for "levels of autonomous surgical robots" are essential. They will have to be re-evaluated at fairly short intervals and re-tailored to evolving levels of AI autonomy and its operational nuances and malfunctions. e.g. for possible malfunctions, possible corrective strategies will need to be available [123,124,125,126]. Similarly, levels of responsibility, ethical, legal, and privacy issues arising from developers through marketers, healthcare institutions and healthcare providers in all AI applications in medicine and ophthalmology will need careful initiation, delineation and ongoing updates with appropriate guardrail protections for the public [124,125].

Conflicts of interest

None.

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