Artificial Intelligence-based Strategies to Identify Patient Populations and Advance Analysis in Age-Related Macular Degeneration Clinical Trials

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Word count: 4357

In the fast-paced, data-driven world we are living in, there is an ever-growing need among ophthalmologists and researchers alike to integrate new technologies in both the clinical and research settings to optimize patient care and increase drug development efficiency. The advent of big data in ophthalmology in the form of large clinical registries("IRIS Registry Data Analysis: Overview - American Academy of Ophthalmology," n.d., "Moorfields AMD Dataset 002," n.d.; Khan et al., 2021) and image databases and parallel advances in artificial intelligence (AI) created a unique opportunity to mine this data for patterns that carry the potential to be valuable in clinical practice.

Artificial intelligence is a branch of computer science that specializes in building computer systems able to perform tasks that normally require human intelligence. Machine learning (ML) is a branch of AI that uses an algorithm to find patterns in a training data set and is able to generalize and perform accurately on future data sets without further programming. In short, ML models can learn from data that they have been fed during a training process. Training can either be supervised, where the algorithm is trained on labeled data or unsupervised, where the algorithm is trained on unlabeled data and will come up with patterns itself through a process of layered data extraction. Deep learning (DL) is a subset of ML that consists of multiple layers of algorithms forming a neural network able to self-iterate and increase in performance and accuracy the more data it is fed.

In ophthalmology, AI and ML models are being used for basic tasks such as image segmentation (Cunefare et al., 2019; Loo et al., 2018; Pekala et al., 2019) and more complicated task of disease detection, specifically diabetic retinopathy,(Abràmoff et al., 2016; Adhi et al., 2016; Bhardwaj et al., 2021; Gargeya and Leng, 2017; Gulshan et al., 2016; Nazir et al., 2021; Ting et al., 2017; Wang et al., 2021) age-related macular degeneration (AMD), (Burlina et al., 2019a, 2017; Grassmann et al., 2018; Peng et al., 2019) glaucomatous optic neuropathy, (Liu et al., 2019) and retinopathy of prematurity.(Brown et al., 2018) One particular use case with limited exploration to date is AMD clinical trials, specifically how AI/ML can be applied to enhance trial efficiency, from the patient enrollment phase up to the outcome assessment phase.

1. Problems facing clinical trials

Clinical trials in the United States are expensive, with costs exceeding $1 billion to bring a new drug to the market.(Adams and Brantner, 2017; DiMasi et al., 2003; Morgan et al., 2011) Part of the high cost derives from the long duration of clinical trials, which typically last years before FDA approval of the investigated drug.("Step 3: Clinical Research | FDA," n.d.) Another part is derived from unsuccessful patient accrual which often leads to premature trial termination and waste of time, effort, and money.(Carlisle et al., 2015) Worldwide, there are 1932 clinical trials registered under the category 'age-related macular degeneration', of which 76 are

active and ongoing.("Search of: Active, not recruiting Studies | Age-Related Macular Degeneration - List Results - ClinicalTrials.gov," n.d., "Search of: Age-Related Macular Degeneration - List Results - ClinicalTrials.gov," n.d.) The vast majority of these active trials are located in the United States and Europe (Figures 1). The relatively large number of active AMD clinical trials and the relatively static methodology of enrolling patients creates an opportunity for the application of novel technologies to ensure the sustainability of ongoing clinical trials and the creation of new ones.

Lengthy clinical trials pose a significant challenge to drug development. Phase I clinical trials last several months, phase II several months to 2 years, phase III one to four years, and phase IV several years.("Step 3: Clinical Research | FDA," n.d.; Suvarna, 2010) Recruiting participants is an arduous and time-consuming process.(Thoma et al., 2010) Commonly, at trial initiation, recruiters often enthusiastically overestimate the number of patients meeting the inclusion criteria. With the brutal emergent reality of recruitment challenges, the initial enthusiasm fades, a phenomenon known as Lasagna's law and Muench's Third Law.(Bearman et al., 1974; Lasagna, 1979) Inefficient recruitment, which may often include pre-entry review by reading centers, lengthens the already interminable clinical trial length, thereby delaying the development and availability of a promising therapeutic to the waiting public.(Watson and Torgerson, 2006) Integrating new technologies that optimize the recruitment and stratification of clinical trial participants would help not only during the recruitment phase but also throughout the clinical trial duration by increasing the incidence of and decreasing the time to endpoints.

There are several instances in which ML can be applied to enhance AMD clinical trials efficiency. ML models can be built to adjust for covariates, including demographic and disease characteristics, prior to randomization in an attempt to decrease sample size, shorten trial duration, and/or increase statistical power.(Cder and Cber, n.d.; Williams et al., 2021) Other models can be built based on a predetermined set of inclusion and exclusion criteria and be used to facilitate overall patient *recruitment* by screening eligible patients from large imaging databases. Models can also be built to identify markers of disease progression and be used to enrich clinical trials with patients that are more likely to demonstrate disease progression within a given time interval (i.e. the duration of the trial), therefore reducing the number of enrolled patients needed to demonstrate the effect of a progression-slowing drug. Additionally, models trained to correlate function with anatomical structure may be used for the development and validation of clinical trial surrogate endpoints, the determination of disease activity based on imaging criteria (e.g. amount of retinal fluid in patients with exudative AMD), or even the prediction of clinical outcomes, all of which may help shorten the duration of clinical trials.

Herein, we explore the possible application of ML to optimize clinical trial efficiency in AMD by enriching trials with an ideal patient population, potentially shortening trial duration, reducing costs, and improving outcomes. We also explore the use of ML in measuring imaging outcomes in AMD clinical trial participants as well as predicting visual function from structure.

2. Using ML models to optimize patient recruitment and enrollment

The ultimate goal of every clinical trial is for the investigator to demonstrate the safety and efficacy of the investigated drug, procedure, or device. To achieve this goal, both an optimal quantity and quality of participants and data are needed.

2.1. Quantity of participants: using ML models to screen for eligibility

Phase I clinical trials require the recruitment of volunteers who are either healthy or with the disease/condition and aim to assess drug safety and optimal dosage. Phase II trials may enroll several hundred participants with the disease to assess drug efficacy and side effects. Phase III trials tend to be larger with several hundred to even thousands of disease subjects to assess drug efficacy and adverse events. Phase IV or post-marketing trials may have several thousand participants with the disease to assess drug safety and efficacy.("Step 3: Clinical Research | FDA," n.d.) More participants translate into higher statistical power when interpreting results and therefore more robust conclusions about the drug's safety and efficacy.

Nowadays, patient eligibility assessment can be done by computerized recruitment support systems using electronic medical records (EMR) to aid in the manual screening process.(Köpcke et al., 2013) These computerized systems depend on data points that have been previously entered into an EMR, such as demographic and clinical features, but do not typically include imaging features. Recruiting patients that meet certain imaging criteria nowadays takes time as it is dependent on manual grading by trained human graders at a reading center. The ability of ML models to handle complex tasks can be leveraged by training models on large datasets of images to identify candidate patients that meet certain *imaging* eligibility criteria based on identifiable and/or measurable imaging features. This helps streamline patient identification and allows subsequent additional screening assessment and careful review of inclusion and exclusion criteria by the investigator. ML models to classify AMD (e.g. atrophic vs. neovascular AMD) and to specifically grade imaging features (e.g. geographic atrophy area) have already been described in the literature but have not yet been applied in the context of clinical trials.(Arslan et al., 2020; De Fauw et al., 2018; Hwang et al., 2019; Tak et al., 2021) Such models can be deployed to routinely

scan clinical imaging databases and pre-identify and flag candidate patients for trial participation. Additionally, models can be used to integrate demographic, clinical, and imaging data and inform both clinician and patient during the clinic visit about the patient's eligibility for a certain trial.

2.2. Quality of participants: using ML models for patient enrichment

High-quality recruitment of participants for a certain clinical trial is both *participant*-dependent where ideally recruited patients remain in the trial as long as intended and *disease*-dependent with participants whose disease/condition perfectly suits the purpose of the investigational therapy are recruited.

2.2.1. Participant-dependent factors

Previous reports have examined predictors of dropout from clinical trials, which are versatile, disease-specific, and often dependent on the patient population recruited.(Jensen et al., 2012; Karyotaki et al., 2015; Keefe et al., 2020; McHugh et al., 2013; Oberoi et al., 2020; Westhoff et al., 2012) This is where the predictive nature of ML algorithms can come into play. Models that incorporate large amounts of clinical and sociodemographic data can determine patterns in the data that predict the subset of patients that will probably develop adverse events or drop out from the trial for other reasons. If used with caution, such predictive models carry the potential of ensuring patient safety and successful trial completion.

2.2.2. Disease-dependent factors

The randomized and often double-masked nature of clinical trials allows the recruitment of patients with a specific disease/condition and the inference of a drug's safety and efficacy with minimal selection bias. Ideally, investigators would like to recruit 1- patients whose disease status is ideal for optimal testing of a drug's efficacy and 2- patients who are most likely to respond to a particular drug. Recruiting patients based on an optimal risk of progression of disease may be of great value for clinical trials as it improves the chances of identifying a true drug effect within the duration of the trial. On a four-point scale of risk of disease progression (extremely low, medium, high, and extremely high risk), recruiting patients with an extremely low risk of disease progression would lead to an underpowered trial that requires the recruitment of a large number of patients and the lengthening of the trial to increase the study's power. Likewise, recruiting patients with an extremely high risk of disease progression is not favorable as the disease might have crossed the point of no return in regard to response to treatment, hence masking the effectiveness of the tested intervention. Recruiting patients with a medium to high risk of disease progression would therefore be optimal as long as the cohort remains representative of the population in question and the results generalizable. On a four-point scale of response to treatment (non-

responders, sub-responders, moderate responders, and super responders), recruiting super responders would showcase the maximum effect of the drug. However, recruiting patients that are less likely to respond or even not respond at all is as valuable as it gives insight as to why the response in these patients was suboptimal and search for solutions to maximize it. Thus, ML models that 1- can identify patients with medium to high risk of disease progression based on demographic, clinical, and imaging features and 2- can predict the response to a certain drug based previous trials can be of great use when recruiting patients for a clinical trial as they can help reduce the sample size needed, increase the power of the trial, and reduce both the duration and overall costs of the trial.

ML models have been used to predict progression of disease in different stages of AMD.

2.2.2.1. Intermediate AMD

Given the fact that advanced stages of AMD [i.e. GA and macular neovascularization (MNV)] are associated with high rates of decreased vision and sequelae,(Csaky et al., 2019; Pfau et al., 2020; Starr et al., 2020) the focus of drug development has increasingly shifted to earlier stages of disease to aid in the management of intermediate AMD cases by either administering prophylactic intravitreal therapies and gene therapies("World's first gene therapy operation for common cause of sight loss carried out - NIHR Oxford Biomedical Research Centre," n.d.) or longer-acting intravitreal therapies. (Dugel et al., 2020; Sahni et al., 2019) Several groups have developed ML models to identify predictors of progression of disease in intermediate AMD. In 2014, de Sisternes *et al*. developed a model that estimates the likelihood of conversion of early and intermediate stages of AMD to MNV based on drusen image features such as drusen area, volume, and internal reflectivity.(de Sisternes et al., 2014) In 2017, Schmidt-Erfurth *et al.* developed a model that predicts the risk of progression to late AMD and were able to identify imaging features that differentiate between the atrophic and neovascular pathways of AMD such as drusen and hyperreflective foci.(Schmidt-Erfurth et al., 2018) Since then, several groups developed a variety of increasingly accurate models to predict the progression of intermediate AMD based on either color fundus photos(Babenko et al., 2019; Bhuiyan et al., 2020; Burlina et al., 2018), OCT images, (Banerjee et al., 2019; Russakoff et al., 2019; Saha et al., 2019; Yim et al., 2020) or fundus autofluorescence.(Bui et al., 2021) These models can be used to enrich clinical trials with AMD patients whose disease course will be optimal to showcase a drug's efficacy.

2.2.2.2. Geographic Atrophy

Other groups have developed ML models to assess imaging features specific for the atrophic late stage of AMD (GA).(Keenan et al., 2018; Liefers et al., 2020; Niu et al., 2016; Schmidt-Erfurth et al., 2020a; Waldstein

et al., 2020) These models specifically predict growth of GA based on imaging features seen on color fundus photos,(Liefers et al., 2020) fundus autofluorescence, or OCT images.(Niu et al., 2016; Schmidt-Erfurth et al., 2020a; Waldstein et al., 2020) Interestingly, these groups used automation not only in segmenting GA area on color fundus photos (Liefers et al., 2020) but also in extracting quantitative imaging features that are predictive of GA enlargement from OCT B-scans.(Niu et al., 2016; Schmidt-Erfurth et al., 2020a; Waldstein et al., 2020) These automated methods in imaging analysis combined with the accuracy of ML models in predicting GA enlargement can be of great use in all stages of clinical trials testing treatments that prevent further retinal atrophy and vision loss.(Liao et al., 2020) For instance, at clinical trial recruitment phase, such models can help identify eligible participants by detecting GA from large image data sets as well as assess baseline quantitative (area) and qualitative (centrality, focality, and laterality) GA features.(Fleckenstein et al., 2018; Keenan et al., 2018) At the enrollment phase, models that predict GA enlargement rates can help enroll patients belonging to a spectrum of GA growth rates dependent on the study's inclusion criteria. At the outcome measure phase, models can be used to detect and measure changes in GA area. At trial completion, models that initially adjusted for covariates will enable drug treatment effect estimates to be more precise as well as determine the effectiveness of a drug (e.g. complement inhibitor) by comparing actual vs. predicted GA enlargement.(Keenan and BCh, 2021)

2.2.2.3. Macular Neovascularization

Likewise, several groups have developed ML models to assess imaging features specific for the neovascular late stage of AMD (MNV).(Chakravarthy et al., 2016; de Sisternes et al., 2014; Feng et al., 2020; Keenan et al., 2021a; Schlegl et al., 2018; Schmidt-Erfurth et al., 2020c) One group developed a model that automatically segments intraretinal, subretinal, and sub-RPE fluid, allowing better therapeutic assessment of neovascular AMD by assessing response to anti-vascular epithelial growth factor (anti-VEGF) injections, or act as a "VEGF meter" as described by the authors.(Schmidt-Erfurth et al., 2020b) Another group recently developed a predictive model that can estimate the effectiveness of anti-VEGF treatment in AMD patients with MNV or cystoid macular edema.(Feng et al., 2020) These models might be useful at all stages of clinical trials assessing treatments for neovascular AMD as they likely have advantages over existing metrics such as central subfield foveal thickness, presence/absence of fluid, or maximum height of fluid.(Keenan et al., 2021a) At clinical trial recruitment, such models can help identify eligible participants that meet certain inclusion criteria, such as eyes with intraretinal or subretinal fluid only. During study visits, these models can be used to better estimate the dosage and frequency of the different anti-VEGF injections being administered to the control/treatment arms. At trial completion, they can be used to identify non-responders for possible recruitment in future trials.

3. Using ML models to measure imaging outcomes

The response of AMD patients to a tested intravitreal drug, or lack thereof, is often assessed by measuring imaging outcomes, creating an additional challenge that faces clinical trials: the subjectivity that is associated with human grading. Even the most experienced graders often do not achieve perfect agreement with each other when assessing the same set of images, and this variability may have an impact on the results of a clinical trial. This challenge can be overcome by using ML models trained on large data sets of images. For instance, ML models have been extensively applied for the segmentation of retinal fluid in patients with neovascular AMD.(Guo et al., 2020; Keenan et al., 2021a; Lee et al., 2017; Schlegl et al., 2018; Schmidt-Erfurth et al., 2020c) In 2017, Lee *et al.* developed a model to automatically segment macular edema and found very similar mean Dice coefficients for human inter-rater reliability as compared to the model (0.750 vs. 0.729).(Lee et al., 2017) Later in 2018, Schlegl *et al.* developed a model that automatically detects and quantifies intraretinal and subretinal fluid.(Schlegl et al., 2018) The model was trained on data from patients with AMD, diabetic retinopathy, and retinal vein occlusion and was found to have a high correlation compared to manual human graders (average Pearson's correlation coefficient of 0.9 for intraretinal fluid and 0.96 for subretinal fluid).(Schlegl et al., 2018) In 2020, Guo *et al.* used both optical coherence tomography angiography (OCTA) and OCT volumes to enhance fluid segmentation and achieved a higher F1 score than other models trained on OCT volumes alone.(Guo et al., 2020) This only shows the potential of ML models to grade images of clinical trial participants with an increasing accuracy that mirrors the sophistication of future models.(Keenan et al., 2021b) The accuracy of such models can be capitalized on in neovascular AMD trials for instance by combining models that quantitate retinal fluid with home or local OCTs.(Keenan et al., 2021c) Combining the ease-of-use of home OCTs with the instantaneous decision-making of ML models allows the amassing of huge amounts of data about the temporal changes in retinal fluid and its response to treatment. This allows a deeper understanding of retinal fluid dynamics that might translate into a modification of the timing and frequency of anti-VEGF injections.

4. Using ML models to predict visual function based on structure

There is a preference from regulatory agencies for functional over structural outcomes for drug approval in AMD clinical trials.(Csaky et al., 2018) Functional endpoints may include visual acuity, visual field defects, contrast sensitivity, as well as other light sensitivity measures such as dark adaptation. However, measuring visual function is time-consuming, subjective, and might vary depending on the disease. Regulatory agencies, in certain

circumstances, accept surrogate anatomic endpoints especially in clinical trials for diseases leading to central vision loss and where there are difficulties in obtaining accurate functional measures, such as in atrophic AMD.(Csaky et al., 2018) After proper validation, ML models may assist in correlating function with structure, potentially overcoming the need for functional endpoint collection. Trained ML models already exist in other retinal diseases for this purpose. Using a cohort of macular telangiectasia type 2 patients, Kihara *et al.* have demonstrated that deep learning models are able to estimate microperimetry sensitivity based on OCT scans alone.(Kihara et al., 2019) Likewise, Sumoraka *et al.* developed a model that predicts the light sensitivity of cone photoreceptors to retinal structure in patients with Leber congenital amaurosis and subsequently estimates the treatment potential for such cases.(Sumaroka et al., 2019) Interestingly, the model trained to predict visual function in Leber congenital amaurosis patients was trained on a retinitis pigmentosa data set.(Sumaroka et al., 2019) This exemplifies a unique advantage of ML models: the ability to modify, re-train, and re-use models for diseases that share similar pathophysiologies, such as retinal degeneration in retinitis pigmentosa and Leber congenital amaurosis. In the case of AMD clinical trials, models trained to predict visual function in MNV patients based on a set of anatomical biomarkers, and if proven to be sufficiently accurate, might be used to predict visual function in patients with GA.

5.   Ethical concerns

A major ethical concern with ML algorithms involved in patient recruitment for clinical trials is the risk of creating inequity in the use of the technology once the model is deployed in the market and widening a preexisting inequality in the healthcare system.(Dickman et al., 2017; Krouse, 2020) Inequity might arise at two levels: 1- when selecting patients to train the model and 2- when the model predicts which patients are eligible to be enrolled in a clinical trial based on the training process data feed. To prevent inequity at the training level, investigators have to make sure to include underrepresented minorities and diversify the training data sets thus minimizing algorithmic bias. Algorithmic bias arises when the training data for the algorithms are more representative of certain groups over others, leading to both biased conclusions and 'harms of representation' in the use of the resultant technology.(Buolamwini and Gebru, 2018; Dwork et al., 2011; Ryu et al., 2018; Zhang et al., n.d.) Minimizing algorithmic bias and maximizing generalizability require proper data infrastructure to allow data from low- and middle-income countries to be collected, stored, and used to train current and future ML models.(McDermott et al., 2021) To prevent inequity at the market deployment level, there needs to be constant assessment of fairness of the algorithms to not marginalize individuals belonging to certain sociodemographic/socioeconomic groups, but rather understand and address the reasons behind discrepancies in

eligibility and access to clinical trials to ensure inclusion, diversity, and generalizability in future trials.(Soares et al., 2021)

Another ethical concern is the 'black box' feature of ML algorithms characteristic of deep learning algorithms, which precludes the understanding of how a model reached a certain outcome.(Castelvecchi, 2016; "Our Machines Now Have Knowledge We'll Never Understand | WIRED," n.d., "The Dark Secret at the Heart of AI | MIT Technology Review," n.d.) This carries the potential for investigator exploitation to push the tested drug to the market. In addition to implementing regulatory measures to test for such hidden incentives by an assigned ethics committee, upgrading the models to generate heat maps giving clues about the decision-making process may be helpful. Another way to overcome the 'black box' issue is to give more weight to concrete attributes when training a model so that the decision-making be more objective as opposed to depending on less tangible data points. For example, when training a DL model that screens for the potential eligibility of intermediate AMD patients, giving more weight to clinical features such as drusen size would make the decision-making process more transparent as opposed to giving more weight to demographic features such as sex and race or a family history of intermediate AMD.

Last, but not least of the concerns, is patient privacy and security of patient data. Artificial intelligence models rely on large data collected over long periods of time. Secure storage and protection of data from potential hacks is critical, as a single breach can instantly expose and compromise the protected health information of thousands of patients.(Jiang and Bai, 2020) Moreover, the need of ML models for large datasets for training that require transferring images between institutions adds another layer of data security concerns. Some authors have described alternatives to those issues, such as transfer learning with a "model-to-data" approach to avoid transferring images between institutions,(Mehta et al., 2020) and the use of deep generative models to train ML models using realistic synthetic fundus images and OCT scans that would serve as proxy datasets for real patient images.(Burlina et al., 2019b; Zheng et al., 2020)

6. Regulatory concerns

With the increasing use of AI in medicine, concerns are raised about its safe use in a clinical setting, especially when its outcomes directly impact clinical judgment and management.(Topol, 2019) According to the 21st Century Cures Act, "a medical device is an instrument or other tool intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of many or other animals."("Artificial Intelligence and

Machine Learning in Software as a Medical Device | FDA," n.d.) Any of the abovementioned clinical trial-related ML algorithms fall within this definition and will thus be regulated by the FDA as stated by the Federal Food, Drug and Cosmetic Act.("FD&C Act Chapter V: Drugs and Devices | FDA," n.d.) Recently, the FDA laid out a new regulatory framework for ML-based software as a medical device (SaMD) that consists of a premarket review to assess the algorithm's safety and efficacy as well as continuous post-market evaluation of its performance in order to parallel the self-taught, iterative nature of the technology.("Artificial Intelligence and Machine Learning in Software as a Medical Device | FDA," n.d.) More recently, the International Coalition of Medicines Regulatory Authorities (ICMRA) published a report that discussed the regulatory concerns and initiatives taken by regulatory agencies across the world including Canada, Japan, Europe, Switzerland, and Australia.("ICMRA Informal Innovation Network Horizon Scanning Assessment Report-Artificial Intelligence," 2021) Despite differences in the legal systems where these regulatory bodies are located, there's a consensus to develop guidelines and regulations that prioritize patient safety and ensure the robustness of the algorithms at hand, their ethical use, and their efficacy in improving patient outcomes.

Another area of concern is informed consent. Machine learning algorithms require huge data sets for training, often requiring the repurposing of data collected for clinical purposes. Patients should be made aware that their data can potentially be used for training ML algorithms, and that this data might not directly impact their clinical management as initial consent for data collection does not ensure continued consent for other purposes.(Botkin et al., 2013)

It is worthy to note that the regulatory measures might differ depending on whether the ML assisted in a clinical trial pre- or post-randomization. Regulatory measures would be less strict if the ML model were deployed during the pre-randomization phase of a clinical trial, as the investigated drug or placebo would still be applied in the traditional manner and endpoints would not be disturbed. On the contrary, if the ML model were deployed during the post-randomization phase, the ML may influence the trial's endpoint and raise skepticism among regulatory bodies during the approval process to release the drug to market. This hesitancy to accept new technologies is not new to science in general and medicine in particular. One solution suggested by Lee *et. al* would be to slowly integrate ML models in clinical trials and prove their efficacy in multiple trials before allowing independent decisions.(Lee and Lee, 2020) One such method is using ML models to create a third synthetic control arm that would be used in parallel to the usual study and control arms. This novel, AI-generated control arm would predict the course of participants had they not received the investigated drug.(Lee and Lee, 2020)

7. Challenges of ML models

In addition to the aforementioned ethical and regulatory concerns, the nonperfect accuracy of the described ML models poses its own challenge. In general, the more complex the task, the more data is needed to achieve higher accuracy rates. For *classification* models where the decision is binary (e.g. normal vs. AMD or presence/absence of retinal fluid), accuracy rates are highest, but there's still a 5-10% error rate that has to be taken account for. For *segmentation* models (e.g. segmenting intraretinal and subretinal fluid), the model's performance drops with scans of abnormal retinal architecture. For *predictive* models, accuracy rates are the lowest of all three with error rates still in the 15-20% range. The accuracy of these three types of models will likely increase with time if the models are trained on larger and more diverse datasets. For the time being, ML models have to be regarded as one of the many tools available in a clinician's arsenal to diagnose and treat disease rather than be regarded as a magic bullet.

In summary, ML holds huge promise in offering an unbiased way of enriching patient populations in AMD clinical trials by predicting and helping enroll participants that are less likely to drop out of a trial, more likely to demonstrate disease progression, and more likely to respond to an investigative drug. Trained models can also be used to grade clinical images, measure imaging outcomes, and predict visual function from structure. However, ML models have to comply with rules set by emerging regulatory bodies and be used with caution to prevent bias and inequality of use of the technology.

Figure legends

Figure 1. Map showing the worldwide distribution of active AMD clinical trial studies. Note that studies with multiple locations are counted more than once. (*Adapted from clinicaltrials.gov*)

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Colors indicate the number of studies with locations in that region.

Least ▭ Most

Labels give the exact number of studies