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Review   
Candeeplearningrevolutionizeclinicalunderstandinganddiagnosisof opticneuropathy?

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| article | info | abstract |
| *Keywords:*  Artificialintelligence  Deeplearning  Ophthalmology  Leber’shereditaryopticneuropathy Diagnosis | | Artificialintelligence(AI)basedondeeplearning(DL)hassparkedtremendousglobalinterestinrecentyears. DeepLearninghasbeenwidelyadoptedinspeechandimagerecognition,naturallanguageprocessingwhich hasanimpactonhealthcare.Intherecentdecade,theapplicationofDLhasexponentiallygrowninthefield ofOphthalmology.Thefundoscopy,slitlampphotography,opticalcoherencetomography(OCT),andmagnetic resonanceimaging(MRI)wereemployedforclinicalexaminationofvariousocularconditions.Thesedataserved asaperfectplatformforthedevelopmentofDLmodelsinOphthalmology.Currently,theapplicationofDLinoc-ulardisordersismajorlystudiedinDiabeticretinopathy(DR),age-relatedmaculardegeneration(AMD),macular oedema,retinopathyofprematurity(ROP),glaucoma,andcataract.InOphthalmology,DLmodelsaregradually expandingtheirscopeinopticneuropathies.Glaucomaandopticneuritisareopticnervedisorders,whereDL modelsarecurrentlystudiedforclinicalapplications.ForfurtherexpansionofDLapplicationininheritedoptic neuropathies,wediscussedtherecentobservationalstudiesrevealingthepathophysiologicalchangesattheoptic nerveinLeber’shereditaryopticneuropathy(LHON).LHONisaninheritedopticneuropathyleadingtobilateral lossofvisioninearlyagegroups.Henceforearlymanagement,furtherfootstepsintheapplicationofDLinLHON willbenefitbothophthalmologistsandpatients.Inthisreview,wediscusstherecentadvancementsofAIinthe OphthalmologyandprospectiveofapplyingDLmodelsinLHONforclinicalprecisionandtimelydiagnosis. |

**Introduction**

Artificialintelligence(AI)hastakenoverhealthcarebyplayingama-jorpartinrevolutionizingdiagnosisinthepresentera.Anycomplexity inhealthcareprecision,theAImodelfindsitsapplication.Indiagnosis, AIacedinmimickinghumanbehaviourthroughmachinelearning(ML) technologytoincreaseefficiency.AIcomprehendmachinelearningpro-videstechniquesoralgorithmsthatempowerscomputerstomakeeffec-tivepredictionsorjudgementusingavailableinputdata.Itrequiresa largenumberoftrainingdatatobuildanexactmodel[1].Deeplearn-ing(DL)isasubgroupofMLwhichhassignificantaccuracyinmany domainsincludingnaturallanguageprocessing,recommendersystems, soundrecognition,andimagerecognition.Itcanalsorecognizecom-plex,unstructured,andinterconnecteddatawithfairaccuracy[2]. Gulshanetal.[3]firstintroducedthealgorithmofDLindiabetic retinopathy(DR).SoonafterthedevelopmentofDLinDR,researchers wereinterestedtoworkondifferentalgorithmsandsuccessfullydevel-opedDLmodels,thatcoulddetectandmoderateocularconditionslike

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Age-relatedmaculardegeneration(AMD),glaucoma,retinopathyofpre-maturity(ROP),andcataract[4].Todate,twocompletealgorithmshave beensuccessfullyapprovedbytheFDA.Amongstthem,IDx-DRisadig-italdiagnosissystemforDR.TheotheroneisViz.AI,whichanalysesim-agesindicatingastroke.Thesedevicesaretermed“Lockedalgorithms”[5].ThesealgorithmsforMLhavethepotentialtoevolvecontinuously andarehighlyadaptiveintheapplicationofotherfields.

ArtificialIntelligenceinneuro-ophthalmologyisanemergingfield andAIalgorithmshaveshownhighaccuracyindetectingneuro-ophthalmicdiseasesinpapilledemaandglaucoma.AlgorithmsinAI aredevelopedfordetectingneuro-ophthalmicdiseasesthroughmoni-toringretinalnervefibrelayer(RNFL)thicknessandopticdiscalter-ationsusingfundusandOCTimages[6].Thisemergingtechnologyin neuroOphthalmologyfurthersignifiesinsighttoexpanditsapplica-tionininheritedopticneuropathyespeciallyLHON.Thisreviewdis-cussesthecurrentapplicationandrecentinnovationsofAIinOph-thalmology,andthepossibleroleofAI-basedmodelsininheritedoptic neuropathy.

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**PotentialofAIinhealthcare**

ThemajorreasonfortheexponentialgrowthofAIworldwideisdue todemandinbigdataprocessingandtoenhancehumanworkinhealth-carediagnostics[7].Atpresent,tremendousgrowthindiagnosticsand imagingisbenefitingradiologists,ophthalmologists,andothertreat-mentmanagingsectors(Fig.4).Therefore,AImodelsinthefieldof Ophthalmologyarerapidlyincreasing[8].DeepLearningisemployed inseveralmedicalimagingofdiseaseconditionsliketuberculosisfrom chestX-rays[9],malignantmelanomaonskinphotography[10],lymph nodemetastasestobreastcancerfromtissuesections[11],lungcancer usingchestimages[12],cardiovascularriskusingcomputerCT[13], PulmonaryembolismusingCTangiography[14],polypsusingvirtual colonoscopy[15],gliomausingMRI[16],Alzheimer’sdiseasedetection usingfunctionalMRI[17].

Ophthalmologyinvolvesthelatestelectrical,acoustic,mechanical, andopticalimagingtechniques.Therefore,theapplicationofAIinOph-thalmologyiswidelyimplementedandaccepted.UsingadvancedDL models,AIclassifiesimagesbasedonpatternrecognition[8].Incollab-orationwiththeopticsystem,differentmodelsofDLalgorithmslike neuralnetworkingaresuccessfullyappliedinvariousdiseasediagnoses andit’sprogression[18].InDR,continuousmonitoringisrequiredto observethediseaseprogression.However,theintroductionofAIhas madeitpossibletoimagethefundusofpatientswithearlyDReffi-ciently.Inthefuture,requirementsforcontinuousmonitoringofDR patientsmaybecompromised,asAIcandemonstratethedevelopment andprogressionofthedisease[19].

**AIalgorithmsfordiagnosis**

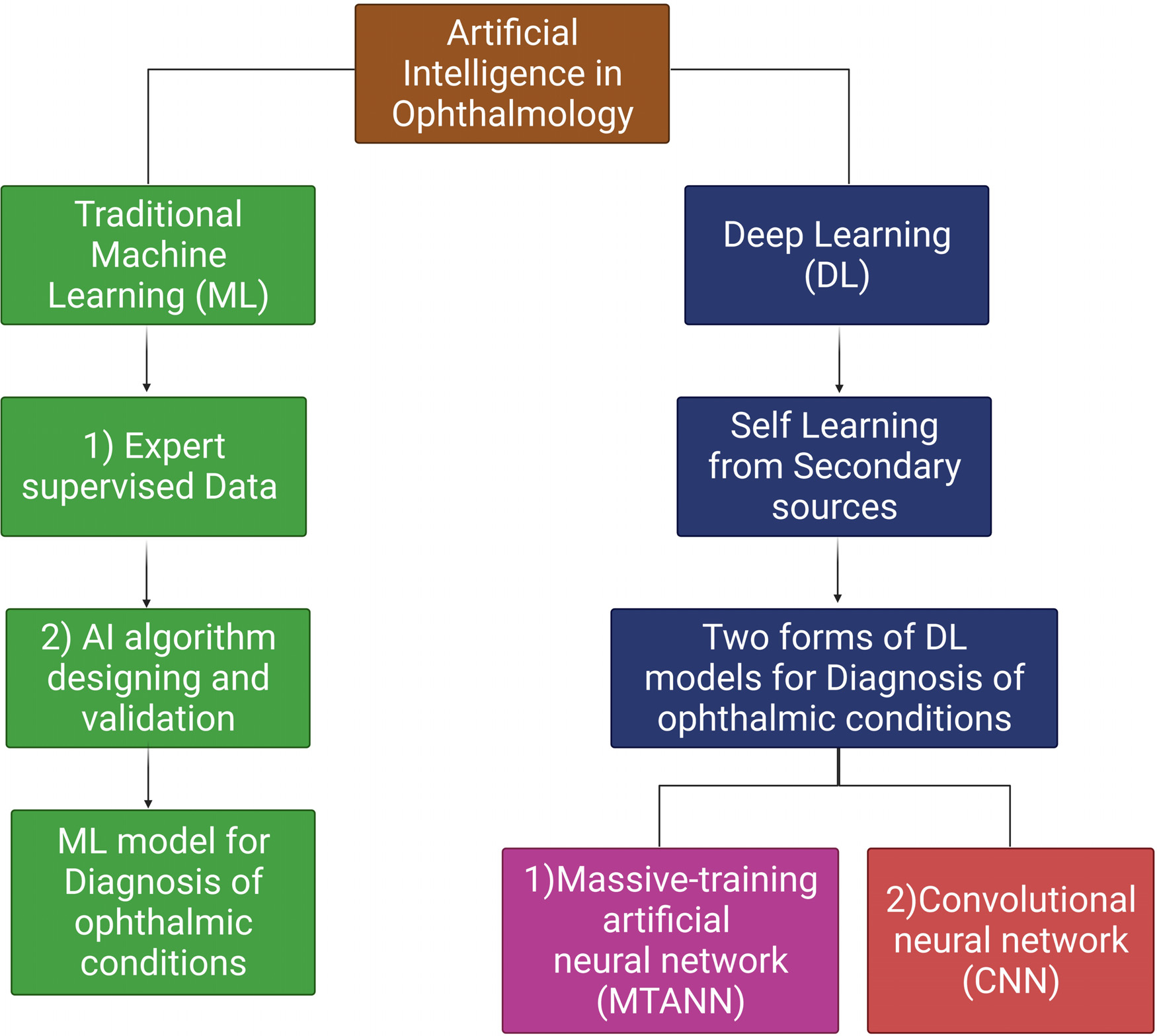
Inophthalmology,MLrequiresalgorithmswithhugeinputdata totrainforpredictingocularconditionsandtostandardizeitsperfor-mance.BuildingastructuredalgorithminMLisacrucialstepforde-velopingAImodelsfordiagnosis.Fundusimagesoftheopticconditions serveasthemajordatabaseforbuildinganAIalgorithminOphthal-mology[20].Otherthantraditionalfundusphotography,opticalco-herencetomography(OCT)scanscanalsobeusedfordevelopingal-gorithms[21].Combingboththe2-dimensionalfundusimagesand3-dimensionalOCTcanimprovethesensitivityandspecificityoftheAI algorithm.Thesedatabasesarefedintosystemswithappliedlogarithms fordecision-makingthroughAI[22].

ThetwoformsofAIaresupervisedlearningandunsupervisedlearn-ing.SupervisedlearningisthetraditionalMLmethod.IntraditionalML, expertknowledgeisutilizedtolabeltheclinicalfeaturesandprogno-sisofophthalmicconditions.Thesortedimagesrepresentingtheclin-icalseverityarethenusedforclassificationbytrainedMLmodels.To buildapreciseMLmodel,alargernumberoflabelleddatabyexperts shouldbefedtotrainandvalidatethealgorithm[23].Someofthepop-ularAIalgorithmsusedforMLinOphthalmologyincludedecisiontree, Bayesianclassifiers,randomforests,supportvectormachines,k-means, k-nearestneighbors,discriminateanalysis,andneuralnetworks[19]. Inunsupervisedlearning,DLisappliedwhichenablestoskipthestep involvingthesupervisionoftheexpert.InDLtheauthorizedinputdata fromclinicaldiagnosisareextractedfromsecondarysourceslikepub-lisheddata,medicalrecords,etc.forself-learningandtoclassifythe ophthalmicconditionsbasedonthediagnosisandseverity[22].The twopowerfulDLClassificationsystemforidentificationincludescon-volutionalneuralnetwork(CNN)andmassive-trainingartificialneural network(MTANN)[23].ThecharacteristicsoftheAIsysteminOph-thalmologyarepresentedinFig.1.

ForbuildingAIalgorithmsforOphthalmology,therawimagedata mustbesorted,validated,andpre-processed.Thesestepsinvolvehuman intelligencetovalidateanalgorithmanditalsoreflectsonthesensitiv-ityandspecificityoftheAIsystem.Pre-processingoftheimageincludes noisereduction,integration,andselectionofthemostrelevantdata. Thiswillimprovetheefficiencyofimageprocessingfortheoutcome.

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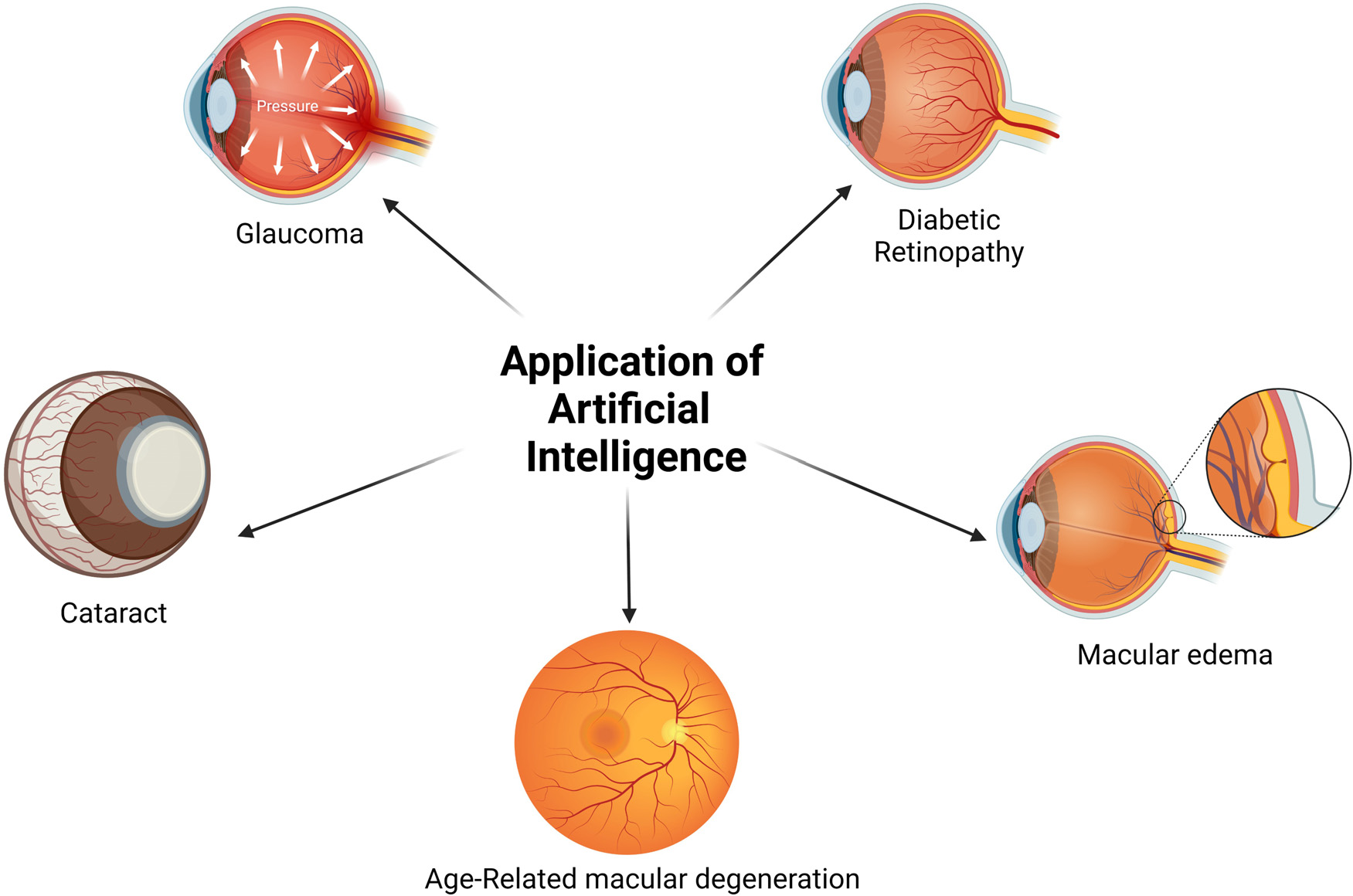
**Fig.1.**AIalgorithmsinthetraditionalMLandDLmodelsforthediagnosisinOphthalmology.

DLapplicationintheAMDarepreliminary,manystudiesandclinical trialswithgreaterstudygroupsareongoingforsuccessfulapplication [40,41].Fromtheobservedstudies,thetestsensitivityofDLinAMDis *>*87%[42].ButtheapplicationofOCTimagesofAMDintheDLmodel increasedsensitivity,specificity,andaccuracy[43].TheOCTenables theDLtodetectthevariationsinmorphology,intraretinalorsubretinal fluidaccumulations.TherecentevaluationofOCTimagesobtainedfrom thelargerpatientgroupstodeveloptheCNNplatformintheDLmodel fordiagnosishasshownaccuracygreaterthan90%[44,45].Bogunovic etal.testedanalgorithmtoobservetheanti-VEGFtreatmentrespon-dersusingOCTimages[46].IncorporatingMLinOCTimagespredicts thepossibilityofretreatmentanditachievessignificantperformancein predictinglowandhighretreatmentrequirements[47].Anotherstudy reportedadeepconvolutionneuralnetwork(DCNN)usingOCTimages fordecisionmakingonanti-VEGFinjection[48]andthesestudiesare importantintheimage-guidedpredictionoftreatmentintervalsinthe managementofAMD.Recently,scientistscreatedandvalidatedanAI modelforAMDscreeningandpredictinglatedryandwetAMDprogres-sion.Thismodelhas99.2%accuracyforAMDscreening[49].

Cataractcausesopacificationofthelensintheeyewithapromi-nentcloudyappearance.Theearlydiagnosisofcataractsiscrucialfor management,whichisachallengingtaskthroughclinicalobservation. HencetheDLfindstheapplicationincataractsbythedevelopmentof CNNalgorithmsforslit-lampimagesfordiagnosisoftheearlystageof cataract.TheperformanceoftheDLmodelincataractscomparedtothe traditionalclinicalgradingwasachievedonly70%[50].AnotherDL

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**Fig.2.**ThemajorareasofapplicationofAImodelsinOphthalmology.

nessbasedonsegmentationtechniqueusingOCTimagesanditshowed 87%accuracy[55].Anotherstudydesignedafullyautomatedmodelto classifyangle-closureglaucomausingOCTscansanditreported89.2% accuracy[59].StudieshaveevaluatedtheDLalgorithmtodetectglauco-matousopticdiscchangesusingfundusimagesanditshowshighsensi-tivityandspecificity[60,61].Visualfieldsareverydifficulttointerpret andAIintheinterpretationofvisualfieldhavebeenreportedusing afeed-forwardneuralnetworktoidentifypre-perimetricvisualfields [62,63].

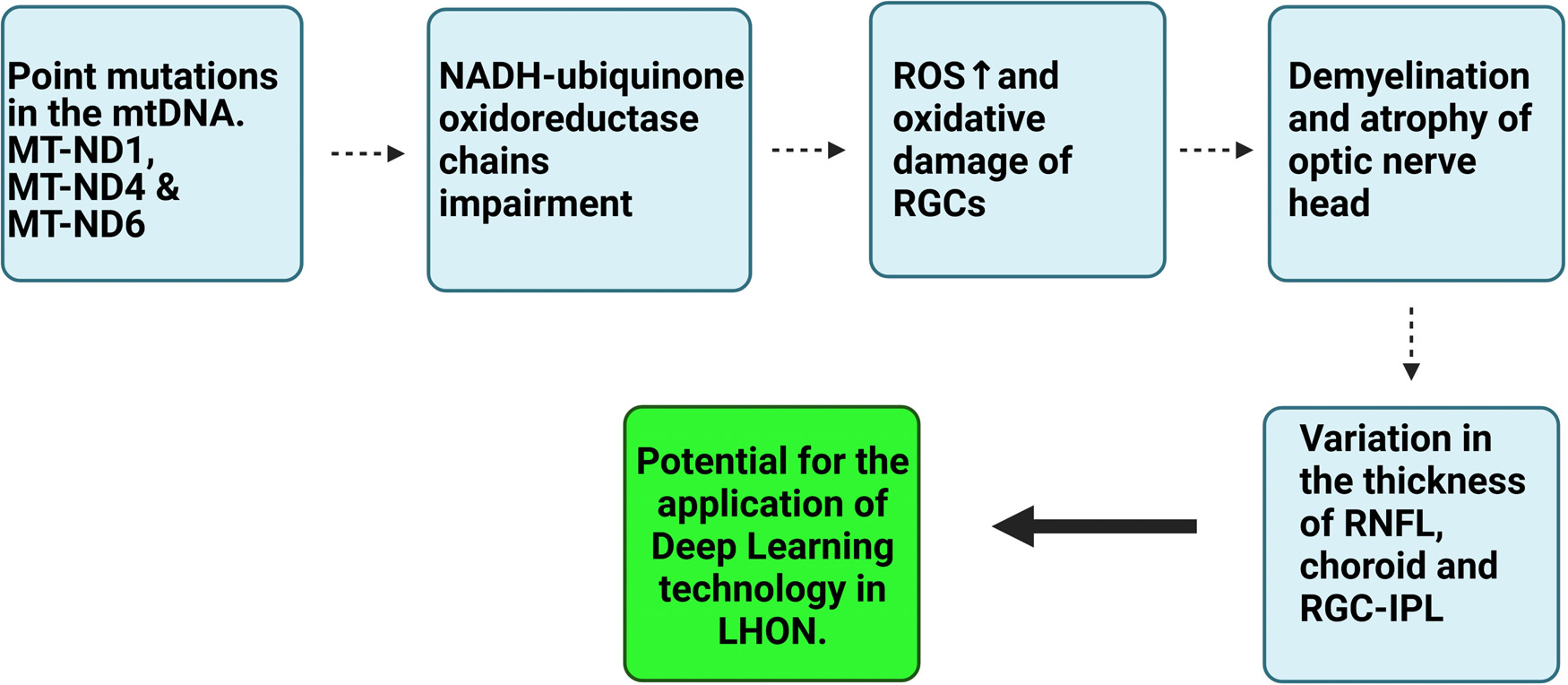
Inotheroculardiseases,Ohsugietal.developedDLwhichcande-tectrhegmatogenousretinaldetachmentfromultra-wide-fieldfundus imageswithhighsensitivityandspecificity[64].Xuetal.designed adual-stageDLsystemtoidentifypigmentepithelialdetachmentin polypoidalchoroidvasculopathy(PCV)fromOCTimages[65].Another studyfromretinitispigmentosaandLebercongenitalamaurosispatients hasemployedanML-basedapproachtopredictperimetryfromOCTim-ages[66].TheMLdecisiontreemodelhasbeenintroducedtopredict thecomplexityofreconstructivesurgeryaftertheexcisionofperiocular basalcellcarcinoma[67].InOphthalmology,AIholdsmanyadvantages likecornealtopography,IOLpowerprediction,predictingtheoutcome ofthetreatment,screening,anddiagnostics.ArtificialIntelligencehas notonlyproventobeefficientandstructuredbutalsocost-effective whencomparedtohigh-endscreeninganddiagnostictechniques[68].

**CurrentstatusofAIinthediagnosisofopticneuropathy**

Opticneuropathyoccurswhentheopticnerveisdamagedcausing structuralchangesintheeyeandvariationsinthebloodflow[69].In mostcases,opticneuropathyleadstovisionlossstartingwithfading ofvision,lossofcolourvision,blurriness,peripheralvisionloss,and clouding.Itisimportanttodetectopticnervedamageearlyandtreat it.Researchersaretryingtostudyvariousmethodstoderivebetterand quickdiagnosesusingAI.[70].Currently,somestudiessupporttheuse ofAIinvariousdiseasesrelatedtoopticneuropathy.Recentstudieson MLsystemattemptsindetectingopticdiscabnormalitiesthroughreti-nalfundus,focusingonopticdiscatrophyandpapilledema.Thecom-

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**Fig.3.**StepwisepathophysiologicalchangesinLHONfrommtDNAmutationleveltoopticnerveatrophyforunderstandingDLapplication.

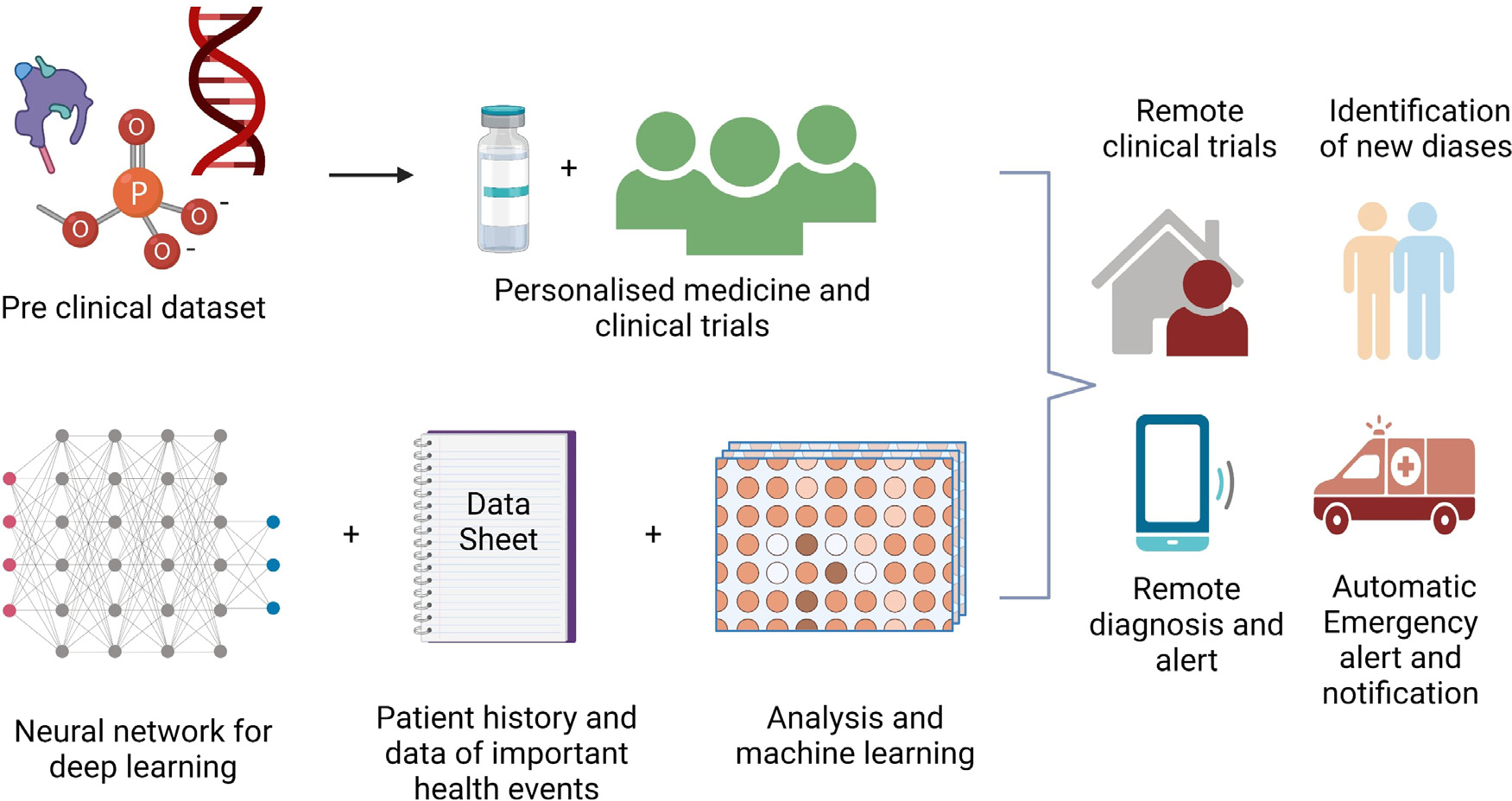
ageofthecells[80].Asthenervecellsarevulnerabletomitochondrial dysfunction,theretinalganglioncells(RGC)intheaxonalregionof theopticnervediscdegeneratesduetoapoptosis[81,82].Thiscauses opticneuropathyandaffectsthevisualpathwayforimageperception. Thefollowingeventscontributetobilateralvisuallossintheindividual andpathologicalchangesobservedattheopticnerve.Thepathophysi-ologicalchangesattheopticnervediscincludedemyelinationandat-rophy.Intheacutestage,theRNFLswellsintheareasurroundingthe opticnervehead.Itisthenfollowedbypersistentthinningoftheselay-ersduetocompensatoryresponseinthechronicLHON.Thesechanges werestudiedinOCTimaging[83].Fewstudiessuggestedthat,inacute LHON,bothRNFLandchoroidalthickeningwereobserved.Ontheother hand,inchronicLHON,bothRNFLandchoroidalbecomethin[84]. ThepathologicalchangesintheRGCsaffectthevascularityofthereti-nalganglioncell-innerplexiformlayer(RGC-IPL).Boththemacularand peripapillarychoroidthinninginprogressedLHONcorrelateswiththe RGC-IPLthickness[85].EvaluationofretinalvasculatureinacuteLHON usingOCTangiography(OCT-A)outlinesthemarkedvasculardilatation andtortuosityclinically.Infundusexaminationafterdilation,peripapil-larytelangiectasiaswithhyperaemicopticnerveareobservedandserve forclinicaldiagnosisofLHON.Inthechronicstage,opticatrophyis seenatthenervehead[83].Toexcludetheothercausesofdemyeli-nationandcompressivelesionsfromLHON,Magneticresonanceimag-ing(MRI)aidstonarrowdownthedifferentialdiagnosis.InLHON,in-creasedT2signalsarenotedinthechiasmandopticnervetract.Optic nerveandchiasmalenhancementsmimicopticneuritisinMR.Follow-ingpathologicalchangesobservedonLHONincomparisonwiththe healthyindividualanditmayserveasatoolfortheapplicationofDL infaceofLHONdiagnosis(Fig.3).

**PotentialofDLinthediagnosisofLHON**

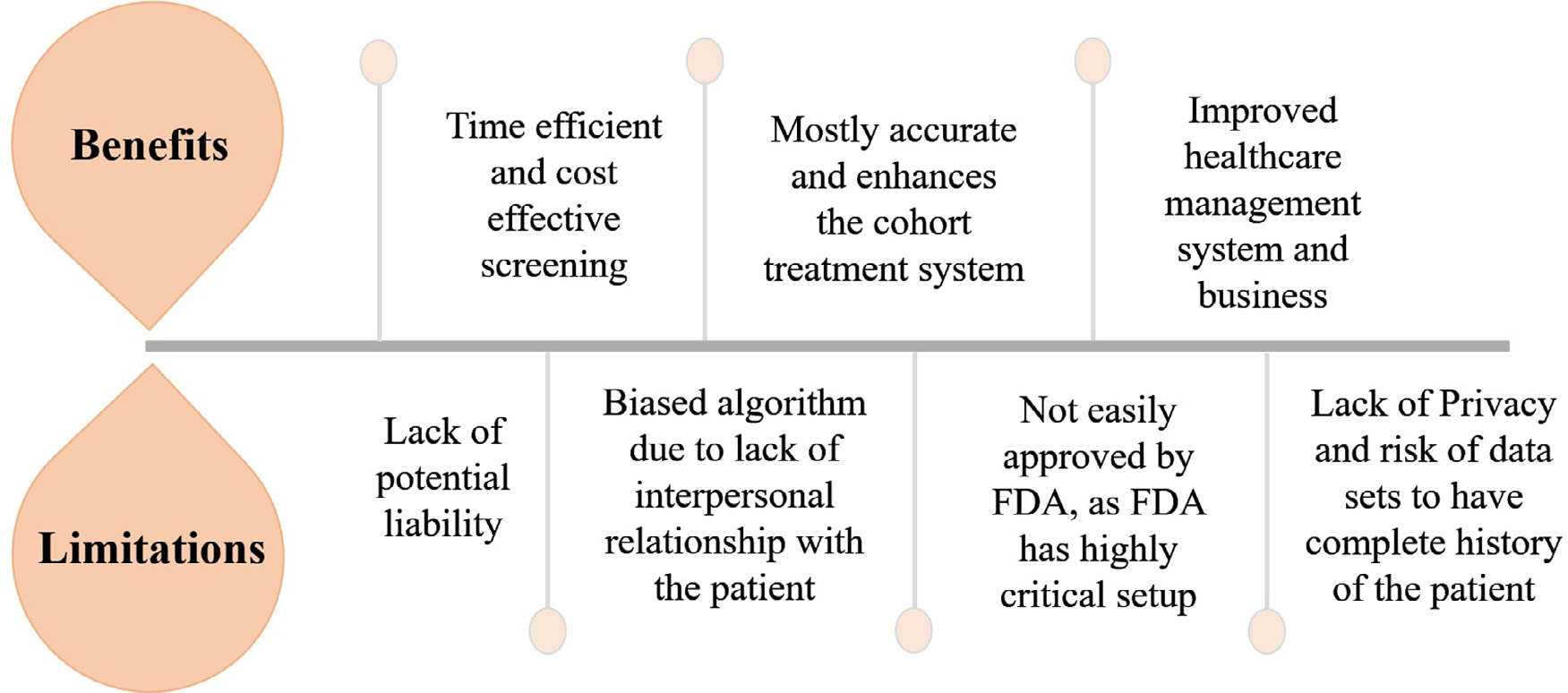
Currently,DLmodelsarewidelyusedonlyinthediagnosisofDR, AMD,cataract,andglaucoma[86,87].Itsapplicationisnotyetinves-tigatedinLHON.Althoughthedemandforthedataexiststotrainthe DLmodels,sinceLHONisararedisease,atargetedmulti-centricstudy canprovideenoughinformationtofeedtheDLsystem.Successfulap-plicationofDLinLHONwillrevolutionizethediagnosisandprecision inneuro-ophthalmology.Inrecentyears,DLtechnologyiswellestab-lishedespeciallyintheDR,andenablestheclassificationofthembased onthetypesandseverity[88].InDR,fundusexaminationshowsmicro-aneurysms,dothemorrhages,intraretinalmicrovascularabnormalities, neovascularizationwhichservesasanessentialtoolforclinicaldiag-nosis[89].Thecolourfundusimagesdisplayingthesepeculiarchanges inDRaretakenintoconsiderationbytheDLalgorithmtoformCNN

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**Fig.4.**RemoteassessmentinOphthalmology.TelemedicineemployingAItechnologyasaprospectiveforlongitudinaldiagnosisofocularconditions.



**Fig.5.**ThisfiguredepictsthemajorbenefitsandlimitationsofAIinhealthcare.

*vitro*studiestotrackdownthemorphologicalchanges,progression,and understandingofLHON.

**AdvantagesofemployingtelemedicineinOphthalmology**

TrialsareongoingtoexpandAIplatformsviadigitalinnovations intheinternetofthings,5thgenerationtelecommunicationnetworks, andthecreationofanecosystemthatisself-dependantandprovides theprospecttoadvancethelatestmodelsrelatedtoOphthalmologyad-dressingvariouschallenges[94].Oneofthemajoradvantagesofusing telemedicineisthatitmadepossibleforclinicianstoevaluatethepa-tientfromanygivenlocation.Replicatingroutineclinicalexamination, AIandtelemedicineareimprovisingtobebetterbyincorporatingvast informationabouttheprogressionofdiseases,longitudinaldatausage, andreal-timecalculationofincidencesinthereal-world[95,96].The applicationofAIcanmakedatacollectionpossibleandstorebigdataof patients.Manydigitalinnovationsrunfromdiagnosticstohelpinginthe treatmentofeyediseases.Screeningofeyediseaseswasmajorlycarried withthehelpofAI.Tele-screeningthroughAIhasexpandeditsapplica-tiontowardsophthalmologicalissueslikeDR,ROP,glaucoma,myopia,

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beenapprovedbytheFDA,whichhascriticalacceptancecriteriafor themajorityofthesystemsincludingclinicaltrialsandtransparency. ThereareslightchancesthatAIcommitsminorerrorswhichmay beahindranceintheprocessofoperationsanddiseasediagnosiscon-siderably[99].Tooriginatevariouswaysforgatheringdataaswellas analysingthemconsideringthelegalformalityisoneamongsttheprin-cipalchallengestobeconfrontedbytheupcomingAIsystem.Artificial Intelligenceusesdifferentapproachestoassigngroundlabelswhichare AIreferencestandards,andtheyaresubjectedtohumanerror.With evidence,itcanbeeasilystatedthatthereisahighriskofAIsystem producingbiasedassessmentbythemethodologicalindexfornonran-domizedstudies(MINORS),whichisyettobeusedcompletelyasan applicationduetotesting[100].Everynewsystemandalgorithmmust gothroughalargeamountoftestingandtrialswhichistime-consuming asitmustcrossmanyapprovals,asthewholesystemisdependantona trial-and-errorprocedure.

NeuralnetworkinginDL,alsoknownasAIparadigms,trainsdataset dependingontheinputfed.Insomecases,thevariabilitymayoccurin theoutputdatawhichistermedasablack-boxproblem[101].TheAI wouldefficientlyworkonlyifthedatabasehasallthesufficientinfor-mationtounderstandtheparticularcondition[102].Thebiasedalgo-rithmisnotaverycommonmistakeofAIbutoccursinthreediffer-entformsofcomponentsnamelyModelvariance(Insufficientdataset), Modelbias(selectedmajorityandunder-representedgroups),andout-comenoise(Interactionthroughmodelpredictionsunaffectedbysub-population)[99].Despitevariouschallengesandrisks,AI/DLsystemis stillchangingthefaceofthehealthcareecosystemuniversally(Fig.5).

**Conclusion**

Accurateandefficientimageinterpretationandsatisfactoryprelim-inaryoutcomeofAIhaveasignificantimpactonOphthalmology.The fusionofautomaticdiagnosticsthroughAIwiththetraditionalsystem ofOphthalmologywouldhelpophthalmologistsinunderstandingthe pathophysiologyofocularconditions.DiagnosisofLHONrequirescom-plexgenetictastingswhichistime-consuming.Therefore,theapplica-tionofAIintheobservationofclinicalimagesincreasesprecisioninthe provisionaldiagnosisandhelpsintheearlymanagement.

**DeclarationofCompetingInterest**

Theauthorsdeclarethattherearenoconflictsofinterest.

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