Future Of Medicine and Ophthalmology: *Convergence of Artificial Intelligence, Innovation and Microelectronics*

CCTS Annual Scientific Meeting,
Ohio State University, December 3rd, 2019

Dimitri T. Azar, MD, MBA
Senior Director of Ophthalmic Innovation, Google Verily Life Sciences

Distinguished University Professor and
B.A. Field Chair of Ophthalmologic Research,
Former Dean, College of Medicine,
Professor of Ophthalmology, Pharmacology, & Bioengineering,
University of Illinois at Chicago

Acknowledgement-
Potential Conflicts of Interest

- Board of Directors:
  - Novartis (2012-2019)
  - Verb Surgical
- Alphabet/Verily
- NIH (Current funding):
  - NEI: R01EY10101

Opinions in this talk reflect opinions of D. Azar (and not necessarily those of UIC, Verily, NEI or other affiliated entities)…

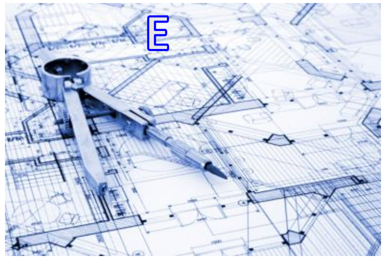
“Medicine is art based on science”

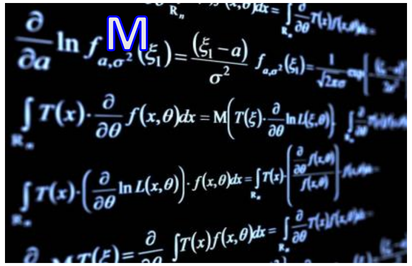
Sir William Osler,
Founding Professor and first Physician-in-Chief of
Johns Hopkins Hospital

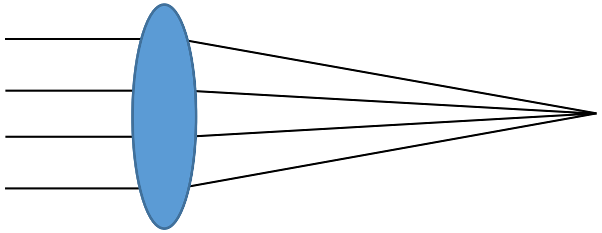
Overview

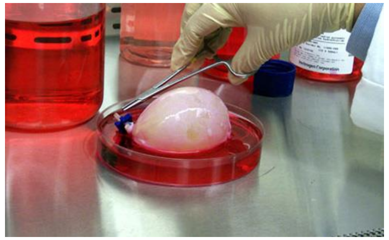
- **Pillars of Medicine**
  - **Convergence of Engineering and Medicine**
  - **Humanistic Medicine**
- **Artificial Intelligence and Machine Learning in Medicine**
- **Artificial Intelligence in Ophthalmology**
- **Summary/Conclusions**

Pillar I. CONVERGENCE









Artificial Bladder

http://dc.mit.edu/sites/dc.mit.edu/files/MIT
White Paper on Convergence.pdf

THREE REVOLUTIONS Since the 1910 Flexner Report:

- MOLECULAR BIOLOGY
  - 1950s
- GENOMICS
  - 1980s
- CONVERGENCE and AI
  - 2000s

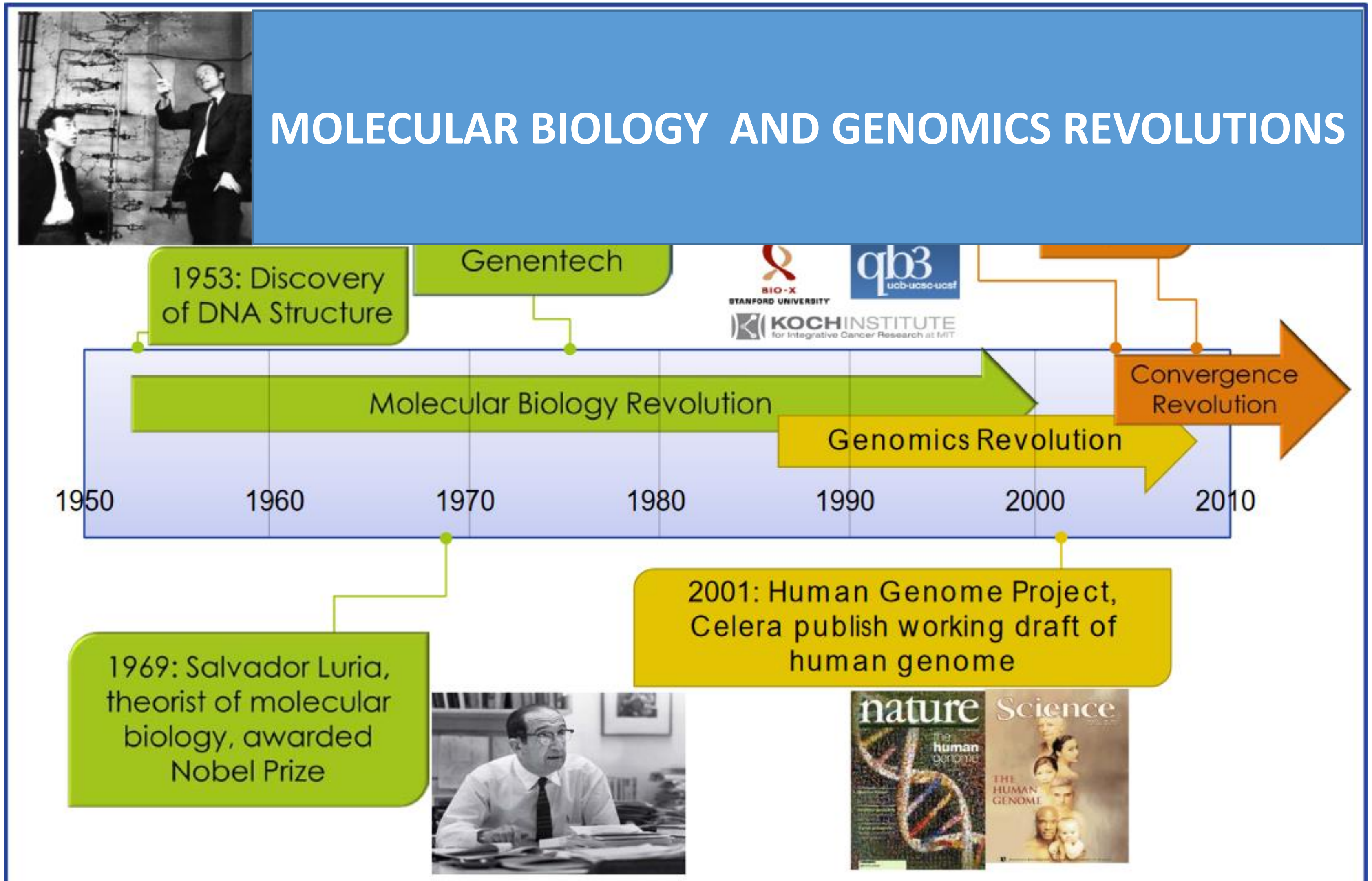
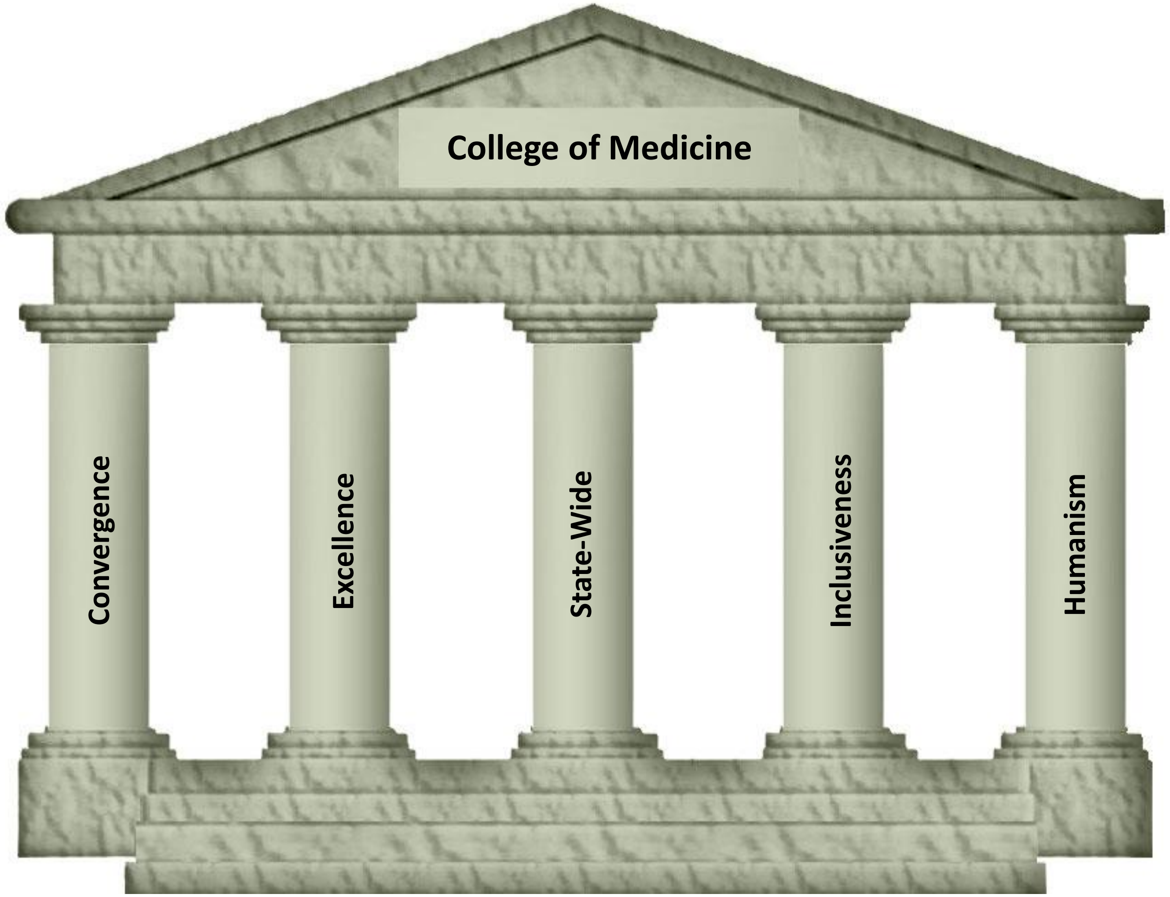


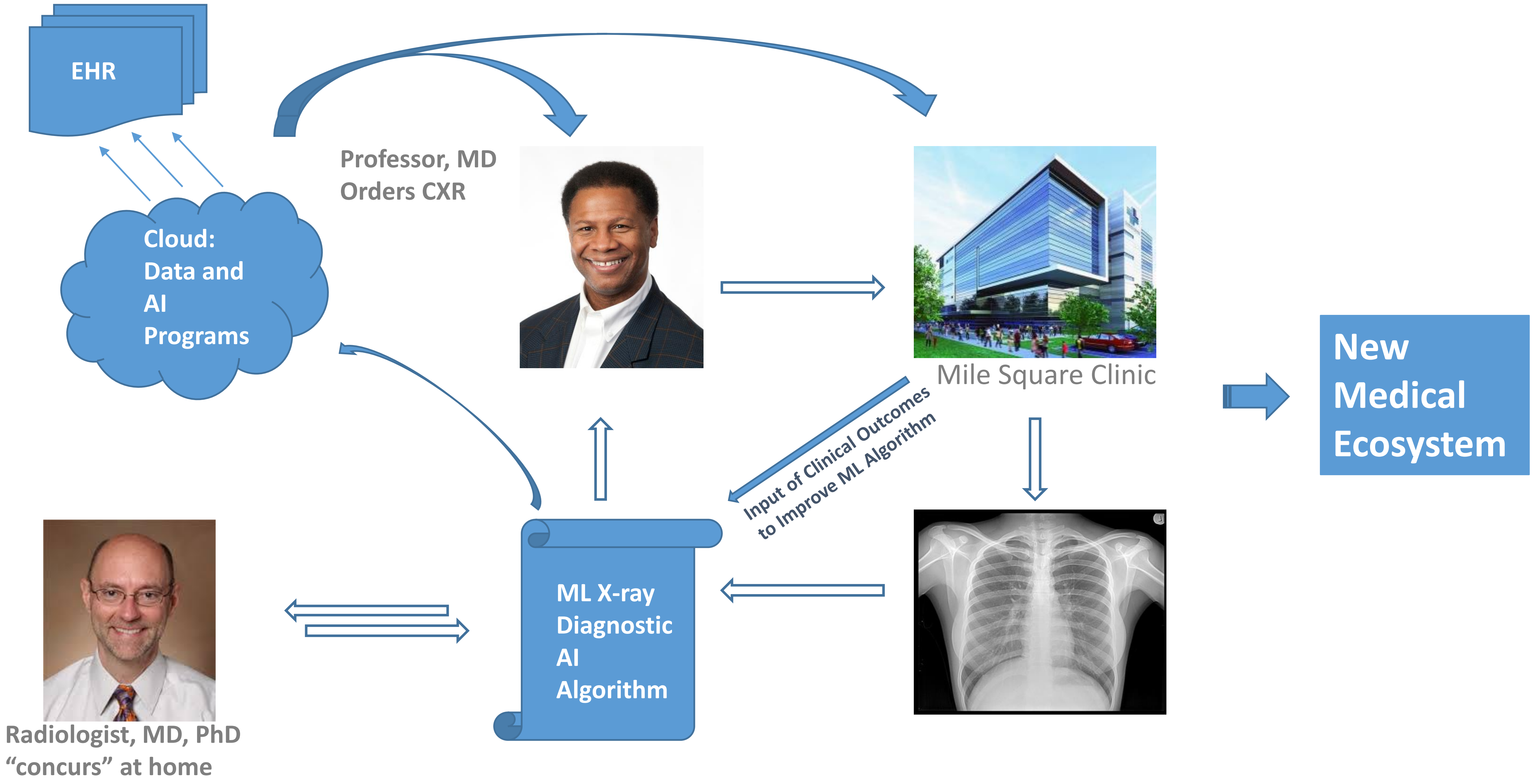
Image and info credits (clockwise from top-left): DNAmazing.com, Gene.com, BioX.stanford.edu, qb3.org, mit.edu/ki, nap.edu, sciencemag.org, nature.com, nlm.nih.gov

Convergence of Engineering, AI and Data Science with Medicine:

- Contributes to the *excellence* in clinical care, research and education
- Broadens the impact and *scope* of medical care
- Requires renewed focus on *humanism in medicine* to address technological downsides
- *Enhances* the *diversity* mission

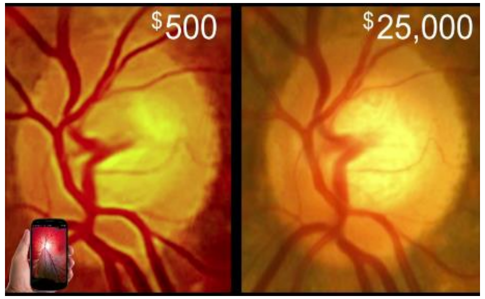


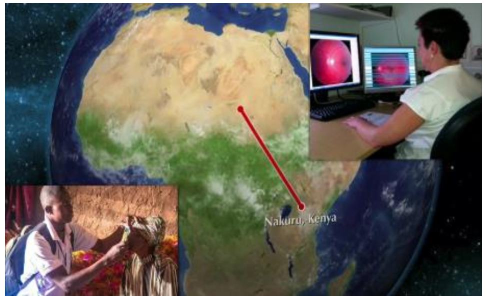
Unmet Patient Needs: Telemedicine/ Future Medicine



Convergence Goes Global:

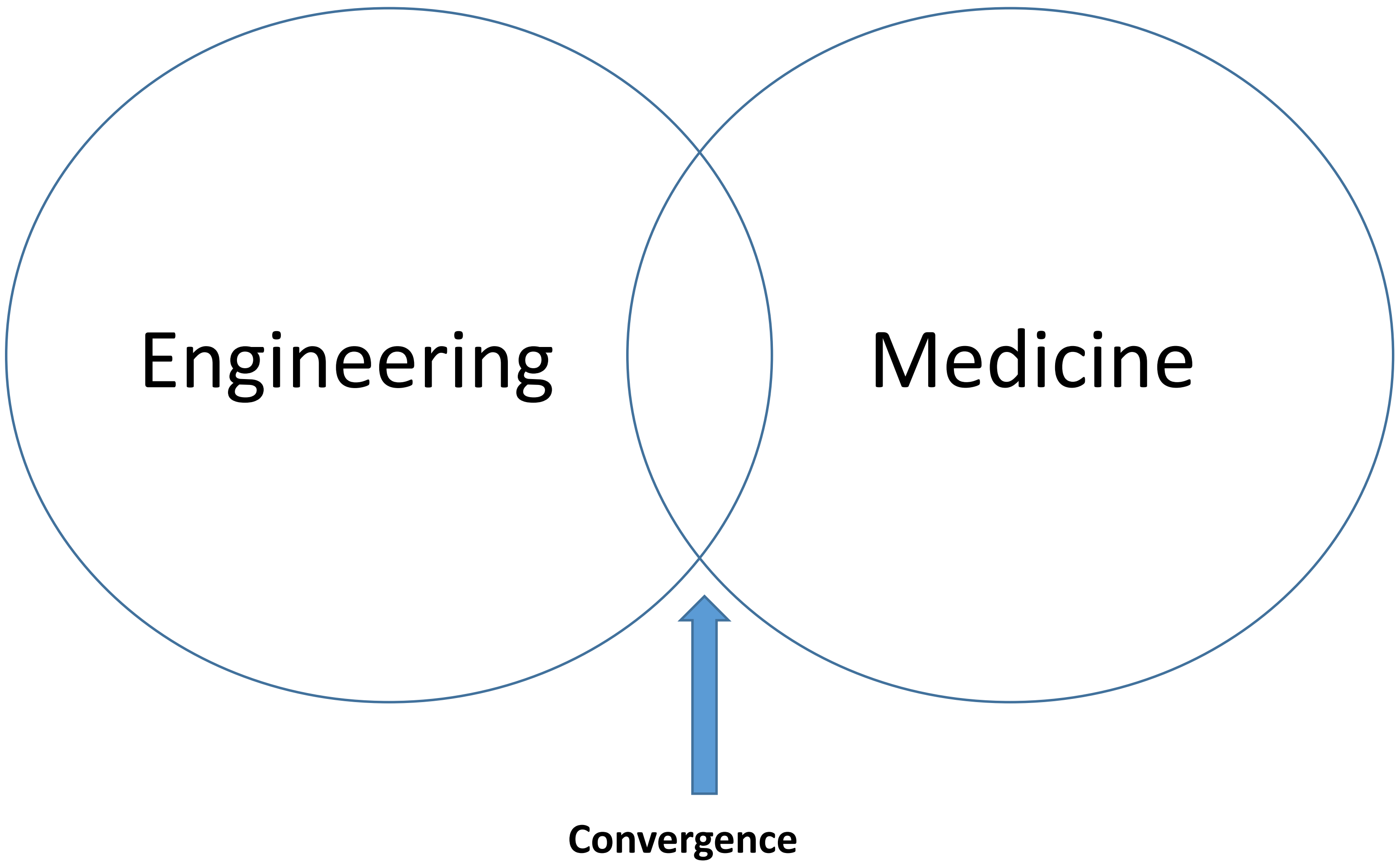
Beyond National Borders…





From: Andrew Bastawrous' **Get your next eye exam on a Smartphone**

Innovation-Med (I-Med) Program



Medical Education

R-MED

U-MED

Global Med

MD/PhD

I-Med

Bioengineering: Majority of 200+ MD/PhD students

96 MD students in I-Med track: Working with design, engineering and business students

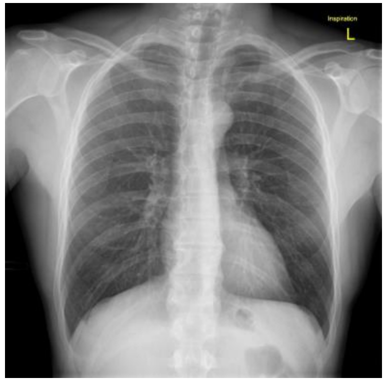
Integrate STEM Disciplines throughout UI COM Educational Programs
Expand Dual Degree Programs and Post-doctoral Fellowships.

Pillar II. Humanistic Medicine

- **Compassion**
- **Professionalism**
- **Ethics**
- **Communication**
- **Team spirit**
- **Helping those most in need**

*"**Durch Mitleid Wissend**" – Amfortas, Wagner's Parsifal*

Medicine in the XX Century:
Big devices, small data



negative!

D. Azar, personal opinion

FROM SOPHISTICATED OPHTHALMIC EQUIPMENT to MICROELETRONICS AND AI

AFFERENT ARM **EFFERENT ARM**

+

Corneal Topography/ Wavefront Analyzer + Scanning Laser

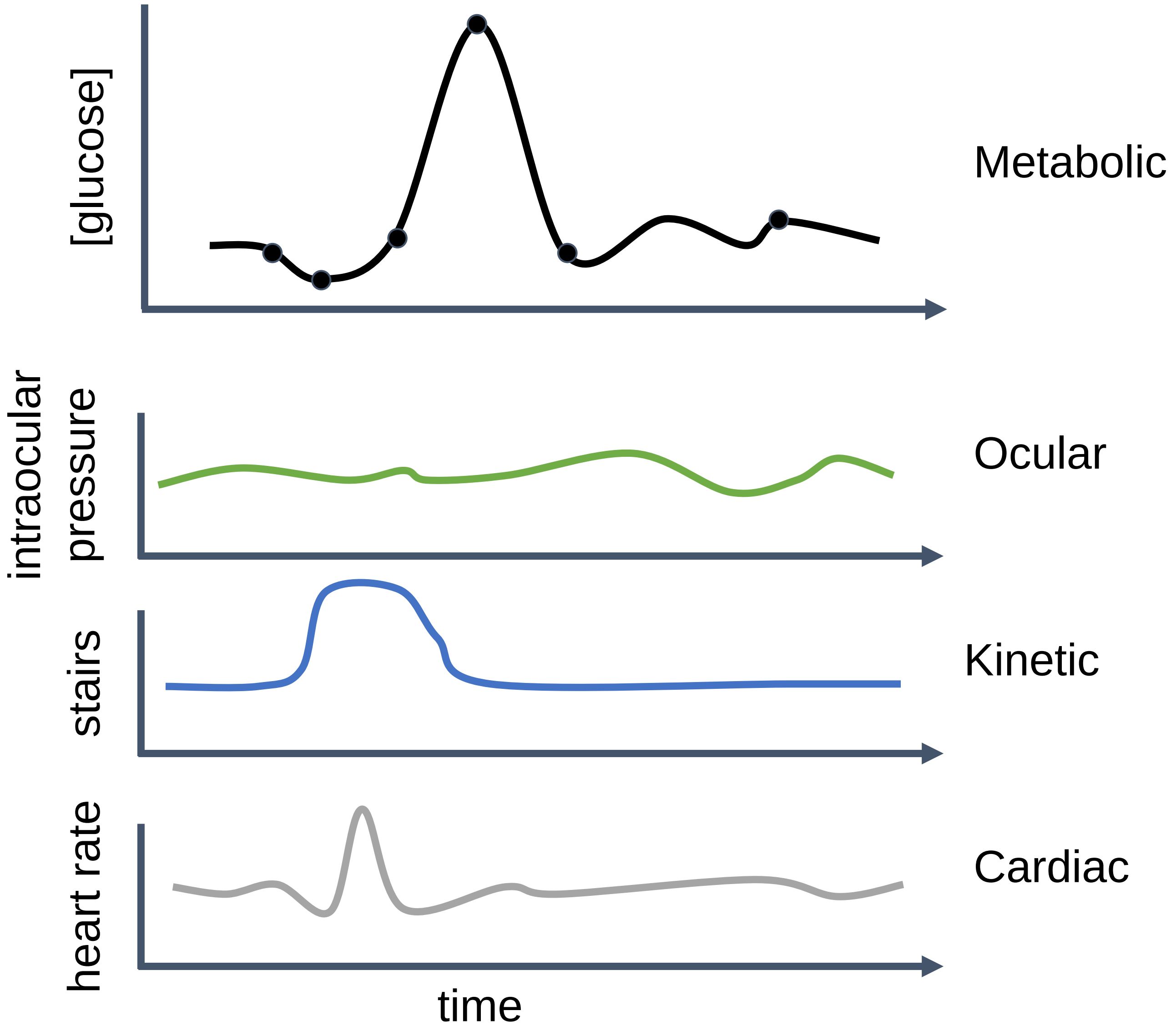
Time between doctor visits is more relevant for disease prevention

D. Azar, personal opinion

Time between doctor visits is more relevant for disease prevention

D. Azar, personal opinion

Cloud connectivity offers multidimensional data



Simulated graphs, not actual patient data

D. Azar, personal opinion

Small Devices; Big Data; Cloud Connectivity

Hardware is catching up to the nanometer scale

D. Azar, personal opinion

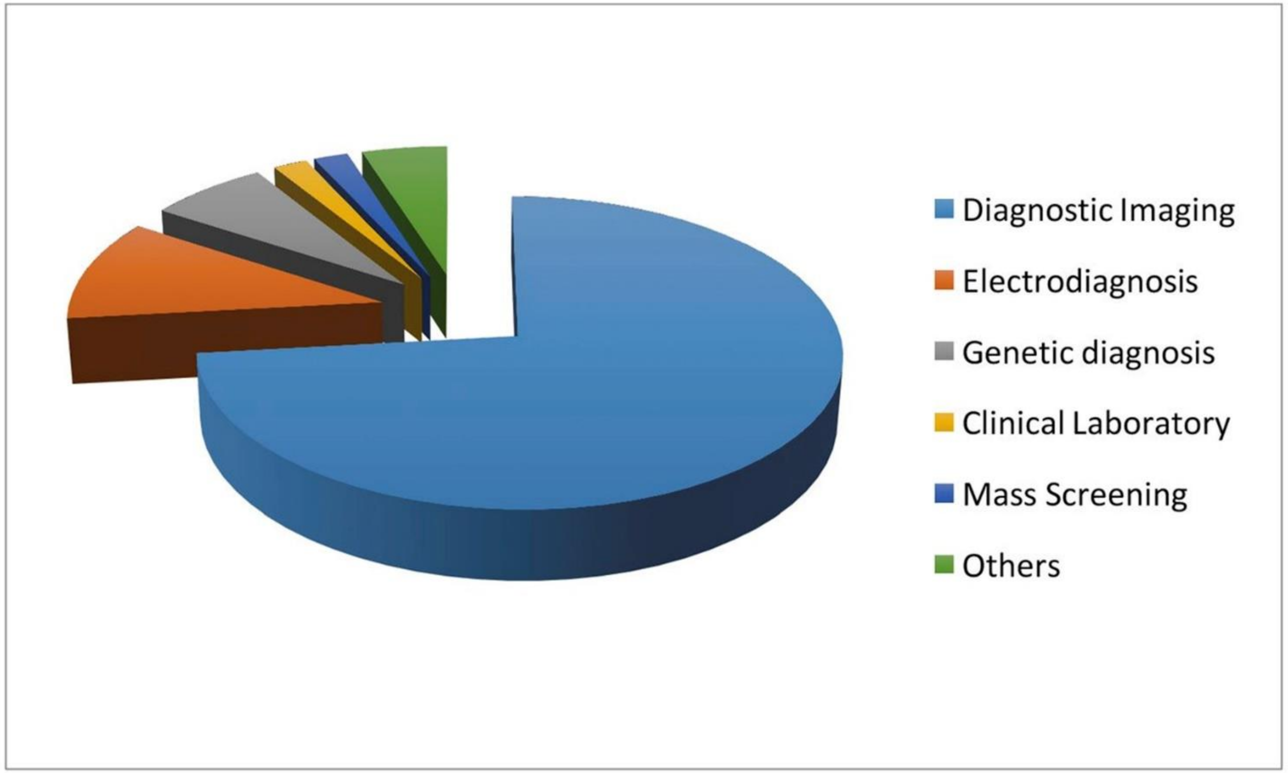
Miniaturization

- **Computation**
- **Form-factor**
- **Batteries**
- **Pumps**
- **Protection of Microelectronics**
- **Therapies enabled: The inflection point for technology miniaturization needs to be guided by the medical** profession

Overview

- Pillars of Medicine
  - Convergence of Engineering and Medicine
  - Humanistic Medicine
- **Artificial Intelligence and Machine Learning in Medicine**
- Artificial Intelligence in Ophthalmology
- Summary/Conclusions

Applications of AI-based Analyses



Diagnostic imaging is currently the highest and most efficient application of AI-based analyses and will likely further expand as imaging modalities become advanced and multi-modal.

Jiang F, Jian H, Dong Y, Li S, Wang MY, Dong Q, Shen H, Wang Y. Artificial intelligence in healthcare: past, present and future. Stroke Vasc Neurol. 2017. 2; 230-243.

How Can AI Help?

*Artificial Intelligence (AI) has already demonstrated proof-of-concept in medical fields such as: **radiology, pathology and dermatology**, which are deeply rooted in diagnostic imaging.*

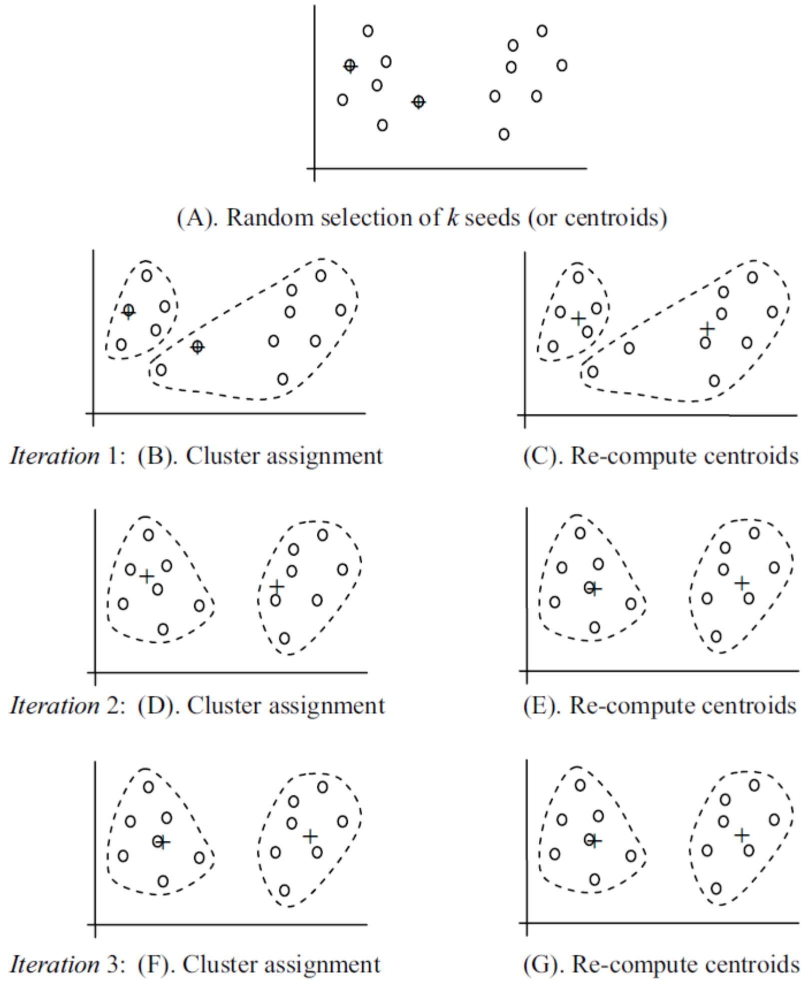
- AI-based grading algorithms can identify **which patient should be referred** to an ophthalmologist for management
- Workload reduction; **increase in efficiency** of limited healthcare resources
- Algorithms can be run on **PC or smartphone** with average processors
- AI can improve the sensitivity and specificity of **at-risk patient detection**
- AI will promote **personalized medicine**
- AI can recognize **disease-specific patterns** and correlate novel features to gain innovative scientific insight

Schmidt-Erfurth U, Sadeghipour A, Gerendas BS, Waldstein SM, Bogunovic H. Artificial intelligence in retina. Prog Retin Eye Res. 2018 Aug 1. pii:S1350-9462(18)30011-9.
The future of artificial intelligence in opthahlmology. Clinical Education. American Academy of Ophthalmology. 2018 May.

AI Learning Algorithms

- **Unsupervised**
  - Clustering (k-Means)
  - Visualization and dimensionality reduction (Principal Component Analysis)
- **Supervised** (main learning tasks: Classification and Regression)
  - Linear Regression
  - K-Nearest Neighbors (KNN)
  - Logistic Regression
  - Support Vector Machine
  - Decision Trees and Random Forests
  - **Neural Networks**
    - **Simple**
    - **Deep Learning CNN**
- **Semi-supervised**

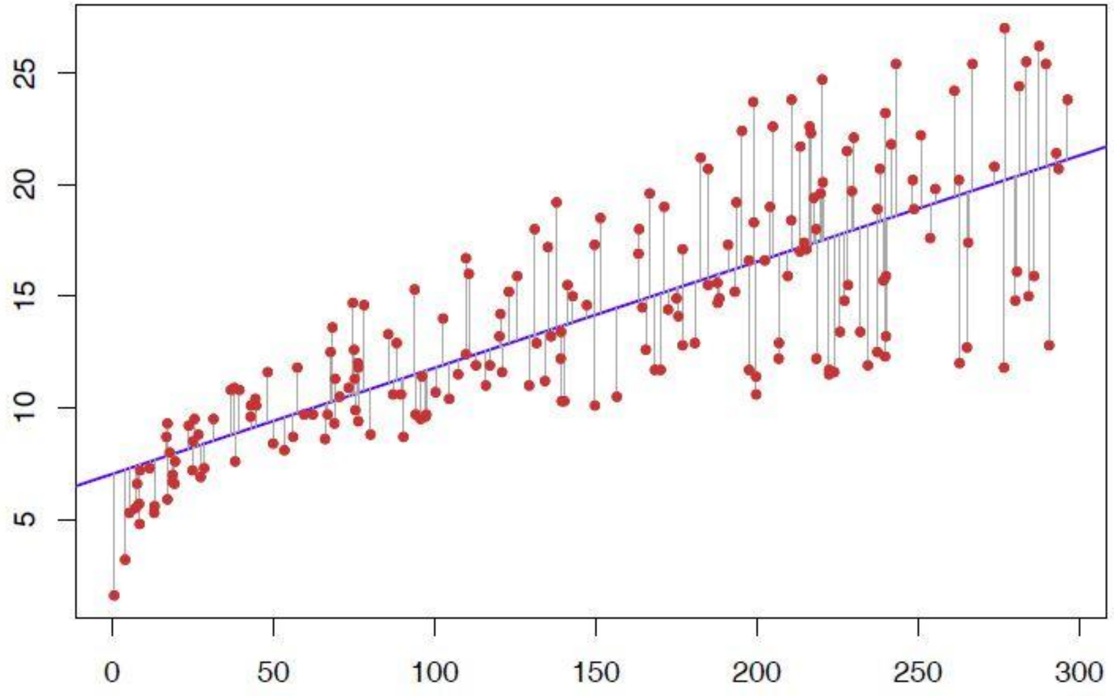
Unsupervised Learning: Clustering



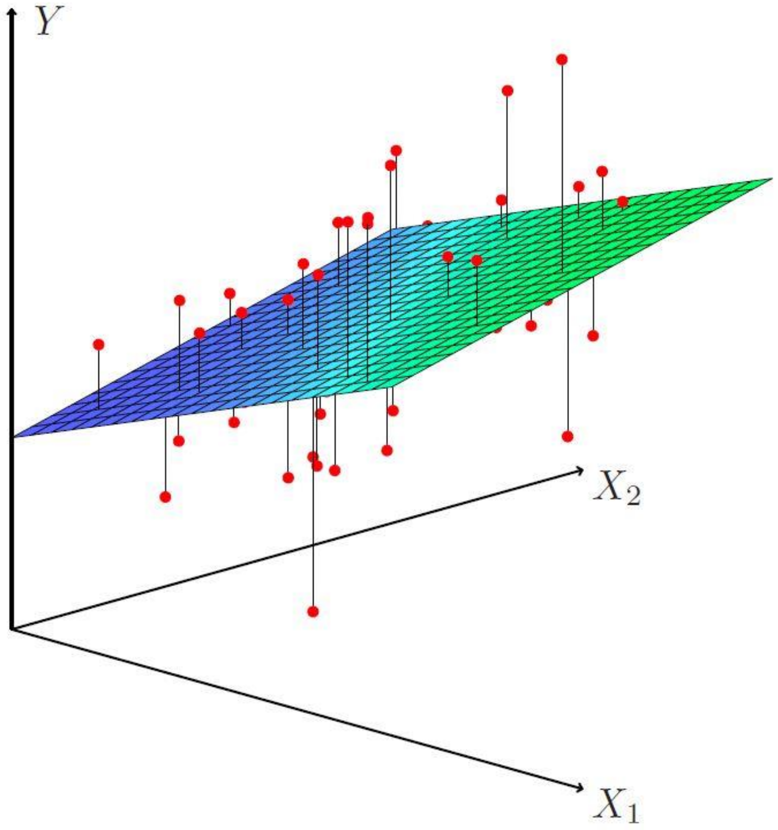
Bing Lui. Web Data Mining: Exploring Hyperlinks, Contents, and Usage Data

Supervised Learning: Regression

Simple Linear Regression
$Y = \beta 0 + \beta 1X + \varepsilon$



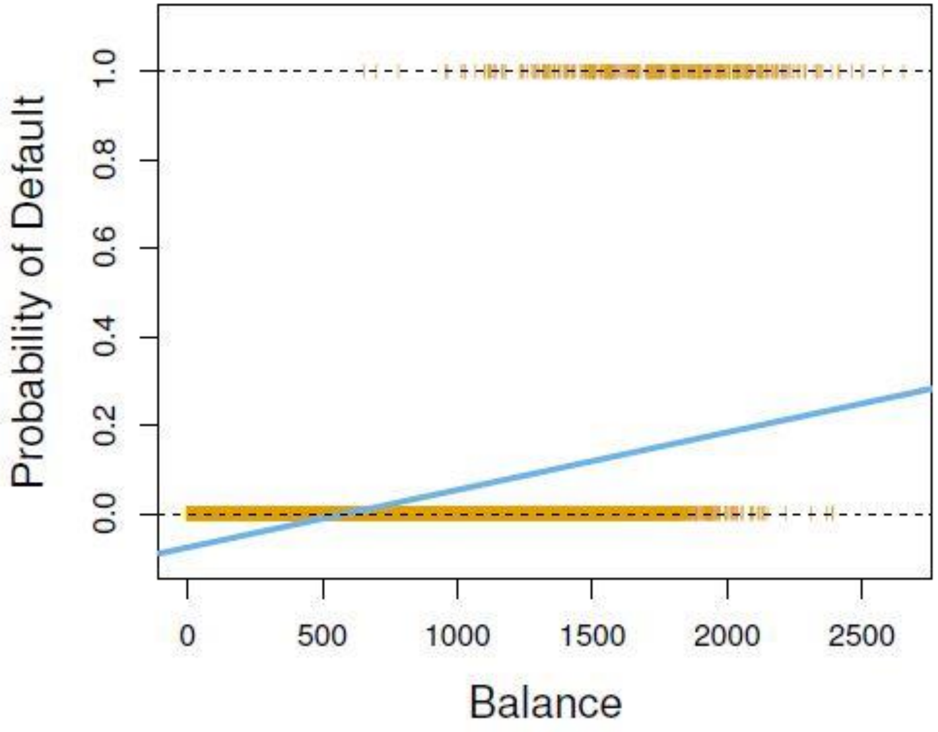
Multiple Linear Regression
$Y = \beta 0 + \beta 1X + \beta 2X + \varepsilon$

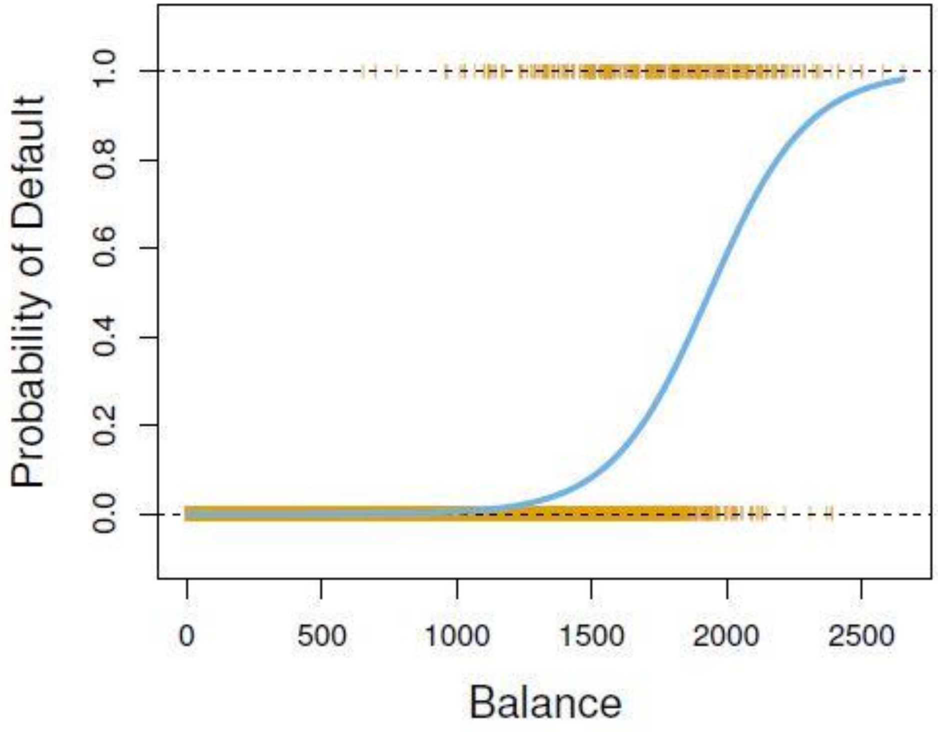


G. James, D. Witten, T. Hastie, and R. Tibshirani, An introduction to statistical learning (Springer, 2013), Vol. 112.

Supervised Learning: Logistic Regression

$$\log\left(\frac{p(X)}{1-p(X)}\right) = \beta_0 + \beta_1 X$$



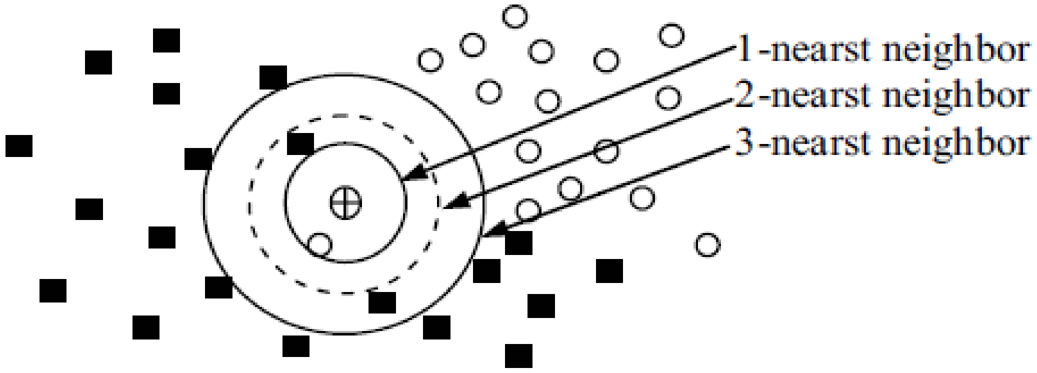


Logistic regression ensures that our estimate for *p(X)* lies between 0 and 1. It is very popular for classification, especially when *K=2*.

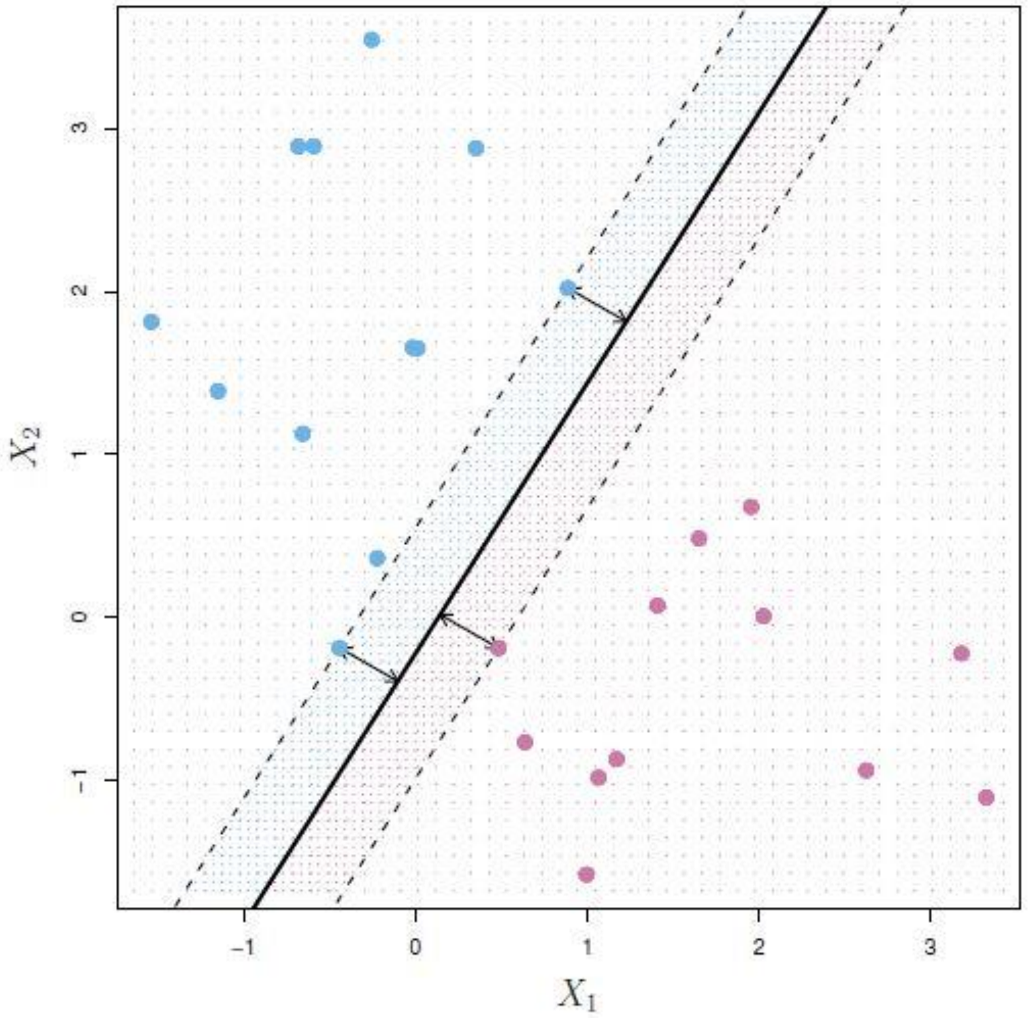
G. James, D. Witten, T. Hastie, and R. Tibshirani, An introduction to statistical learning (Springer, 2013), Vol. 112.

Supervised Learning: K-Nearest Neighbors (KNN)

Simplest form of machine learning for classification



Supervised Learning: Support Vector Machines

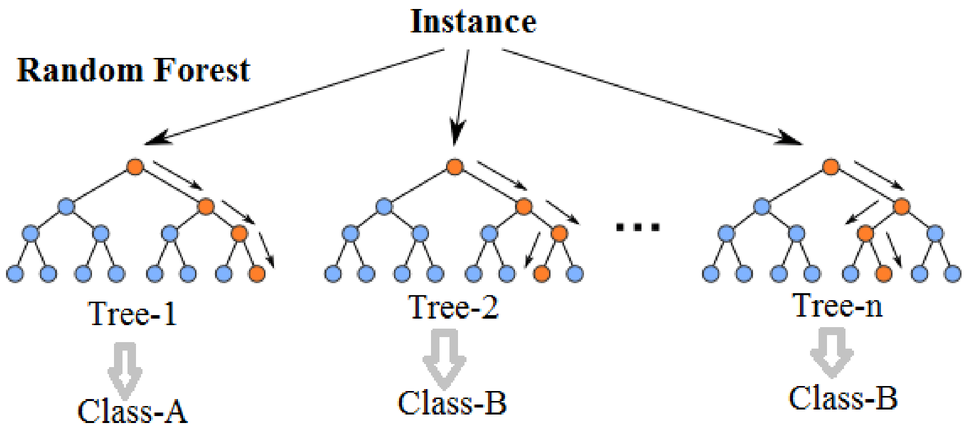


Support Vector Machines: Finds the plane that separates the classes in feature space

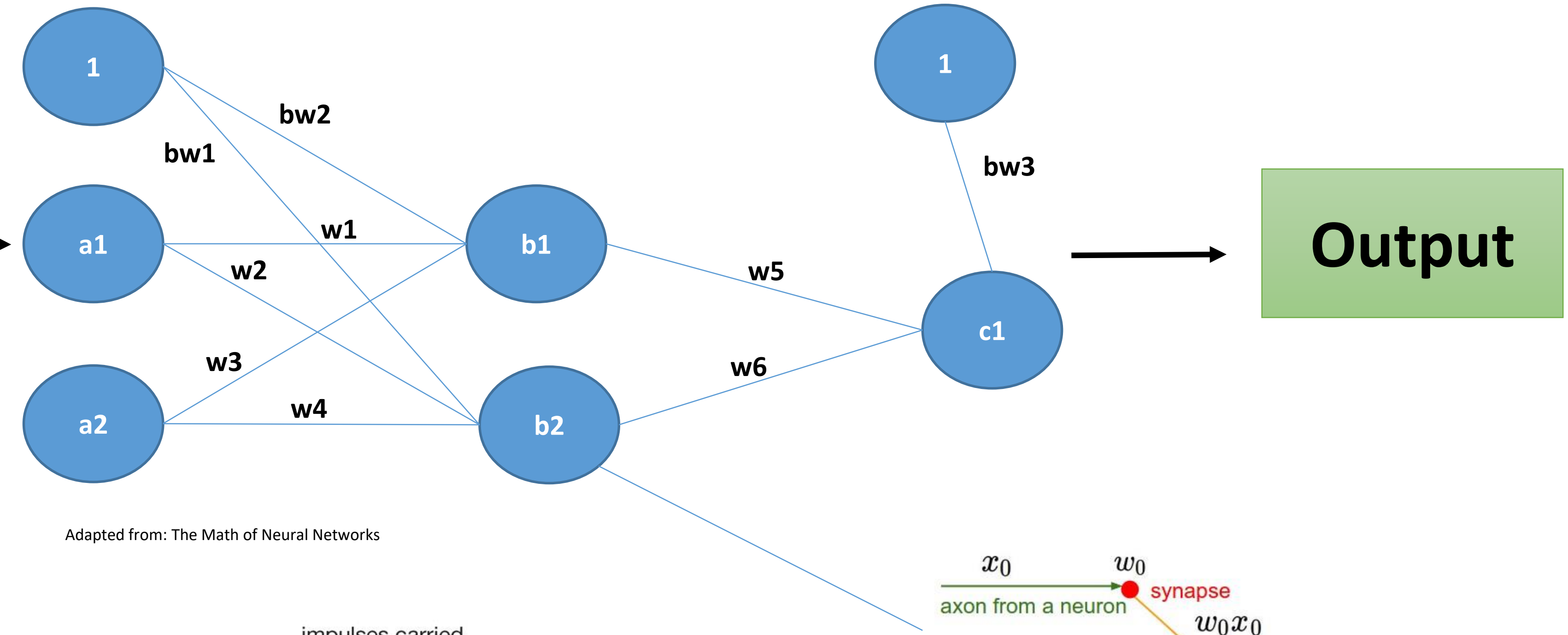
G. James, D. Witten, T. Hastie, and R. Tibshirani, An introduction to statistical learning (Springer, 2013), Vol. 112.

Supervised Learning: Random Forests

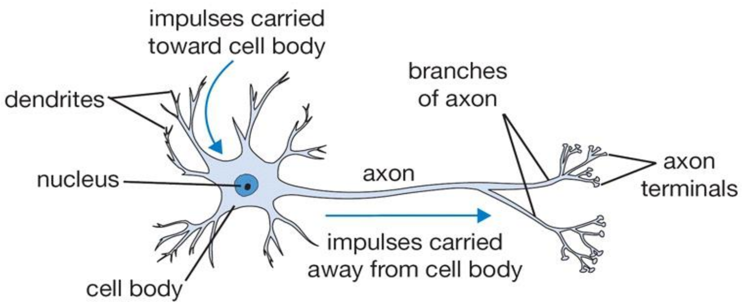
An ensemble of random decision trees
to predict a result



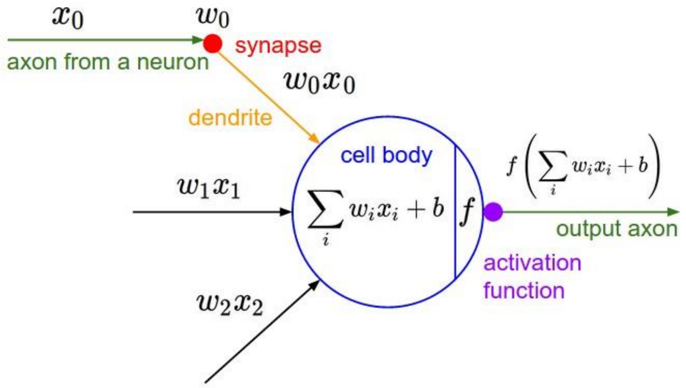
Supervised Learning: Neural Networks



Adapted from: The Math of Neural Networks



Stanford cs231 http://cs231n.github.io/neural-networks-1/



Stanford cs231 http://cs231n.github.io/neural-networks-1/

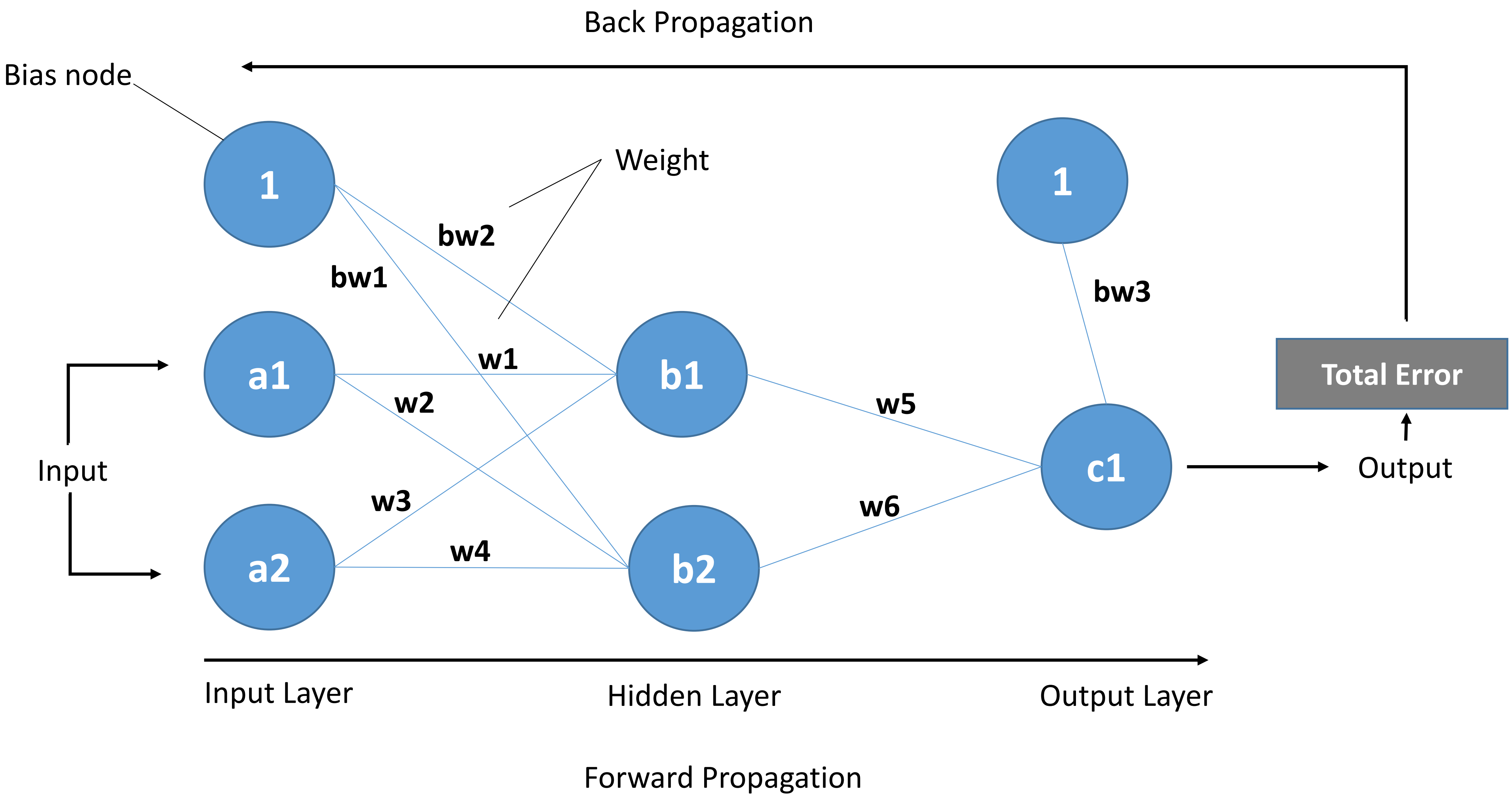
Convolutional Neural Networks

e.g. Learning to interpret medical images

As training commences, neural networks start off without any fine tuning and return random results.

The neural network progressively learns the combinations and permutations of important features

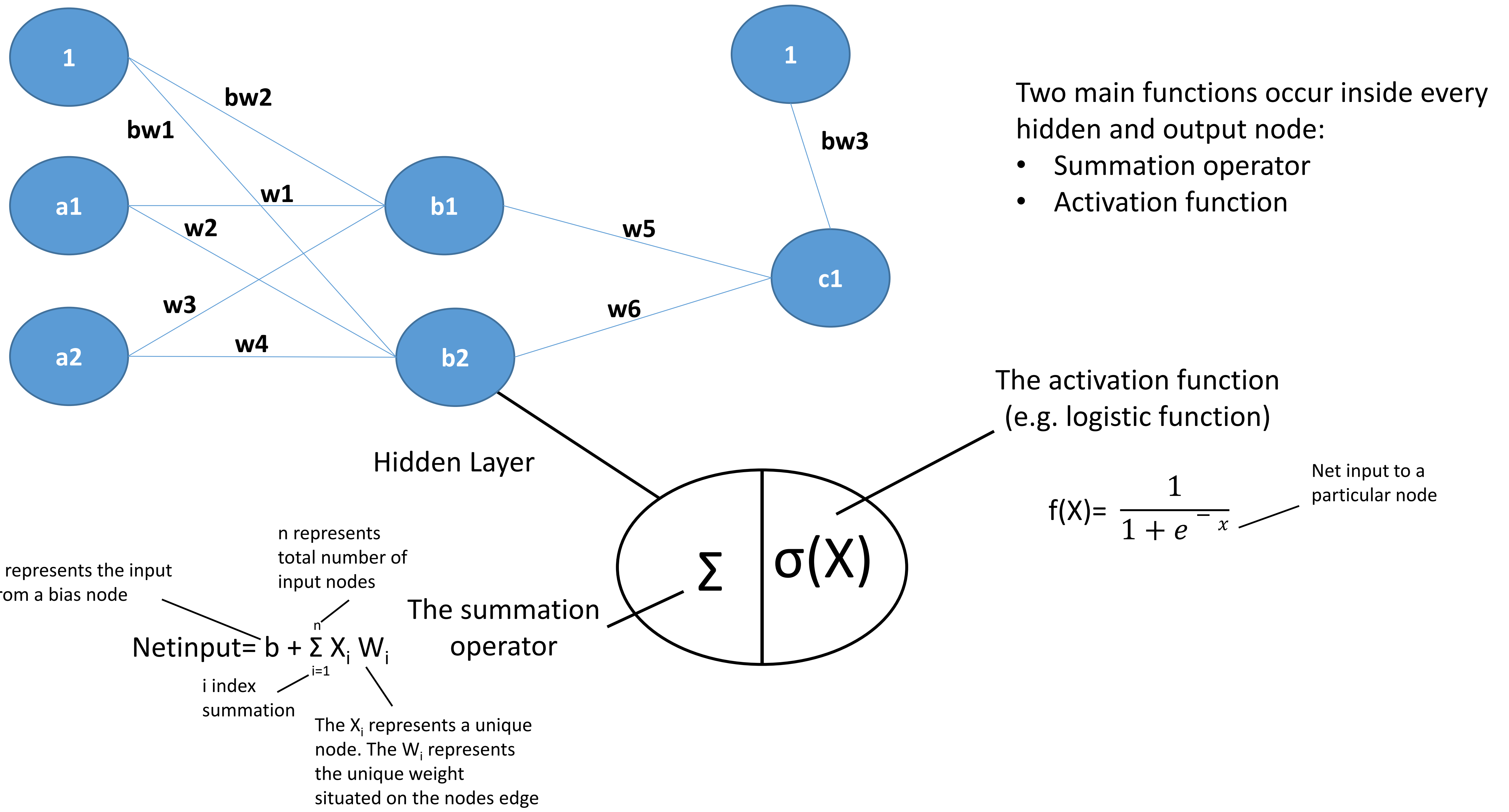
while learning to ignore unimportant features in order to make the diagnosis.



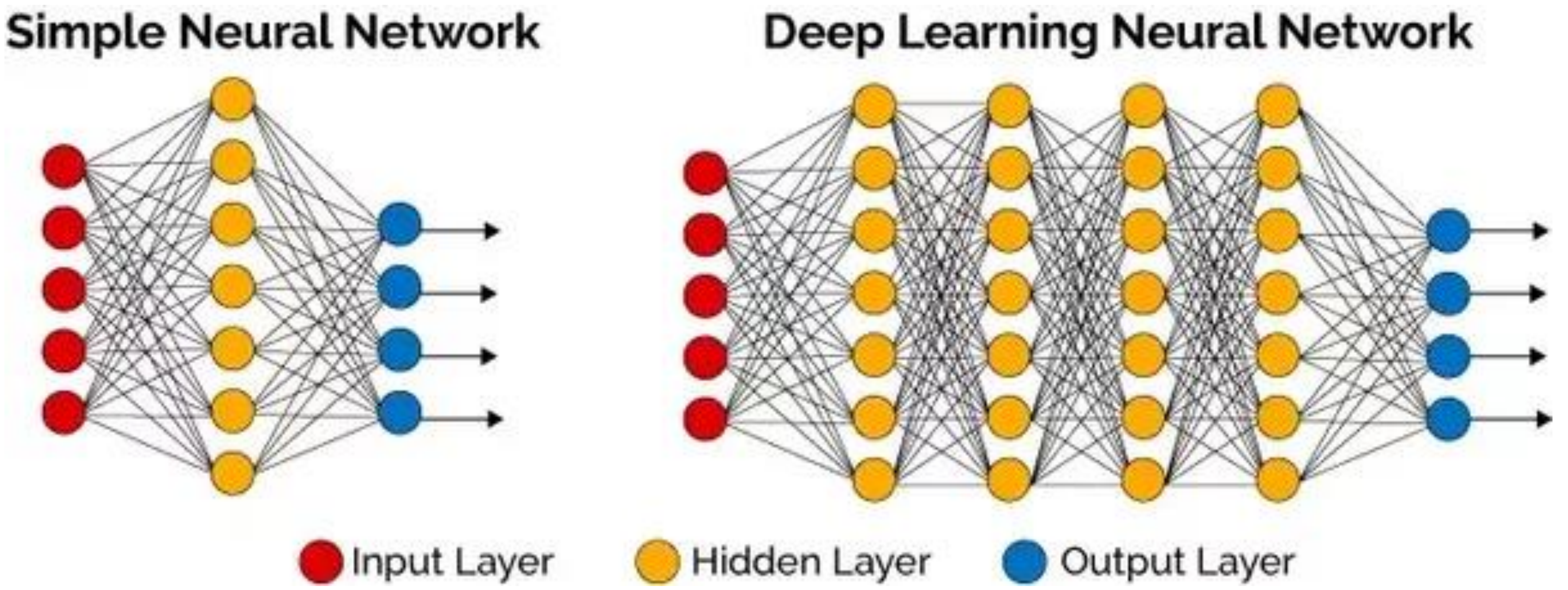
Adapted from: The Math of Neural Networks

Neural Networks

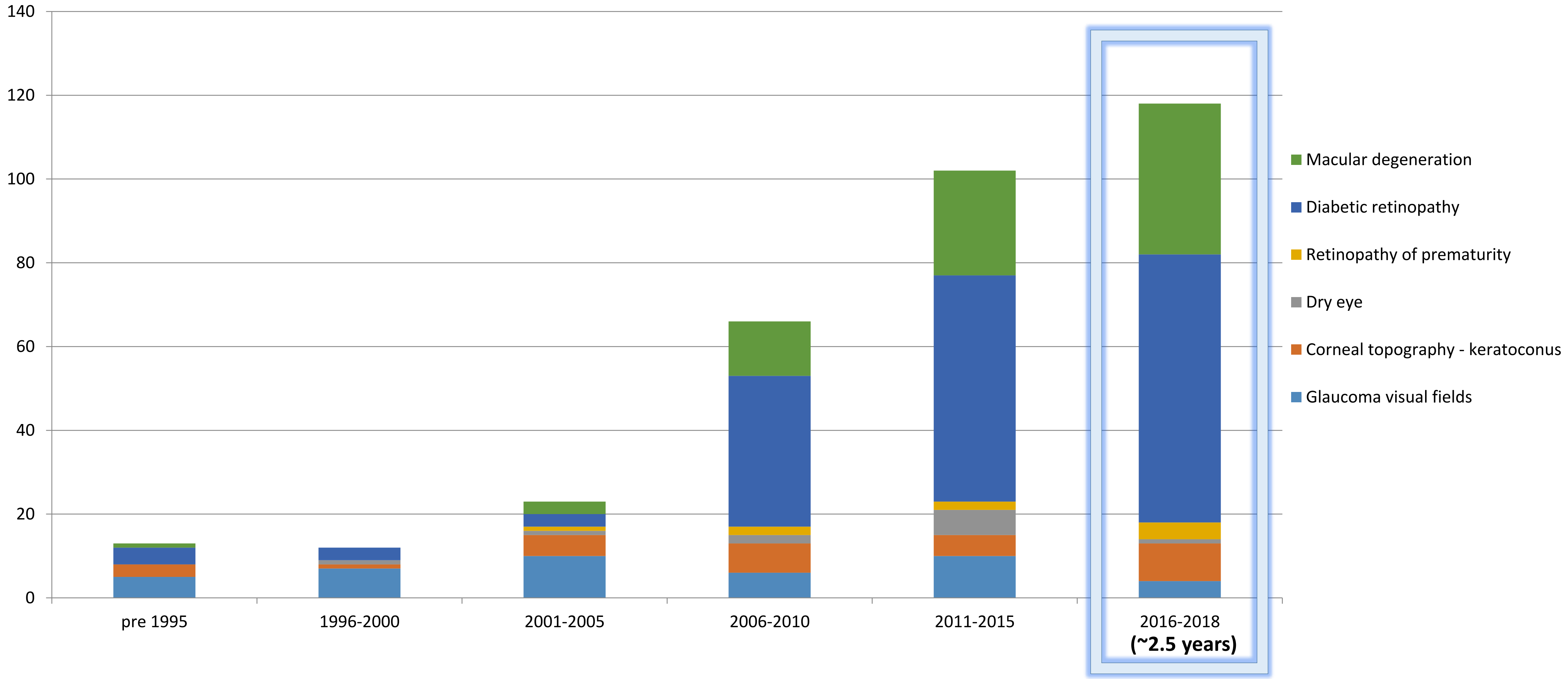
- Define the neural network that has some learnable parameters (weights)
- Iterate over a dataset of inputs
- Process input through the network
- Compute the loss (how far is the output from being correct)
- Propagate gradients back into the network’s parameters
- Update the weights of the network, typically using a simple update rule: weight = weight - learning_rate * gradient



Adapted from: The Math of Neural Networks


Simple Neural Network
Deep Learning Neural Network
Input Layer
Hidden Layer
Output Layer

AI Publications in Eye Care



AI Applications

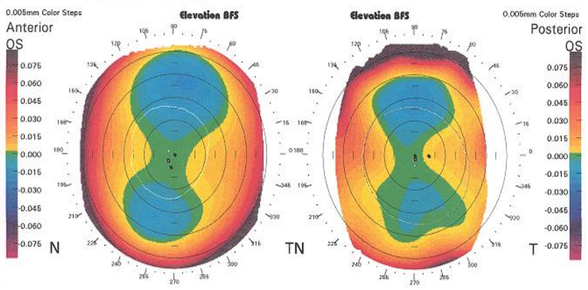
- Corneal Topography
- Dry Eye Diagnosis
- Smart Intraocular Lenses
- Glaucoma Diagnosis
- Fundus Photography:
  - Refractive Error Prediction
  - Identification of retinal lesions
  - Diabetic Retinopathy
- OCT:
  - AMD Progression Prediction
  - Diagnosis and Referral

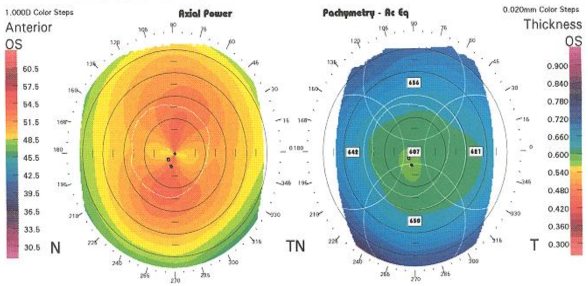
AI Applications

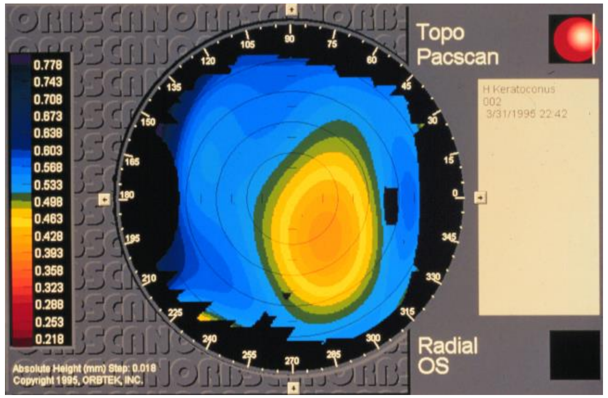
- Corneal Topography
- Dry Eye Diagnosis
- Smart Intraocular Lenses
- Glaucoma Diagnosis
- Fundus Photography:
  - Refractive Error Prediction
  - Identification of retinal lesions
  - Diabetic Retinopathy
- OCT:
  - AMD Progression Prediction
  - Diagnosis and Referral

Image Processing vs. Machine Learning: Corneal Topography and Tomography

- Preoperative evaluation for refractive surgery
- Topography is #1 risk for Ectasia
  - s/p PRK, LASIK
- Posterior corneal tomography
- Keratoconus classification: Normal vs. suspect

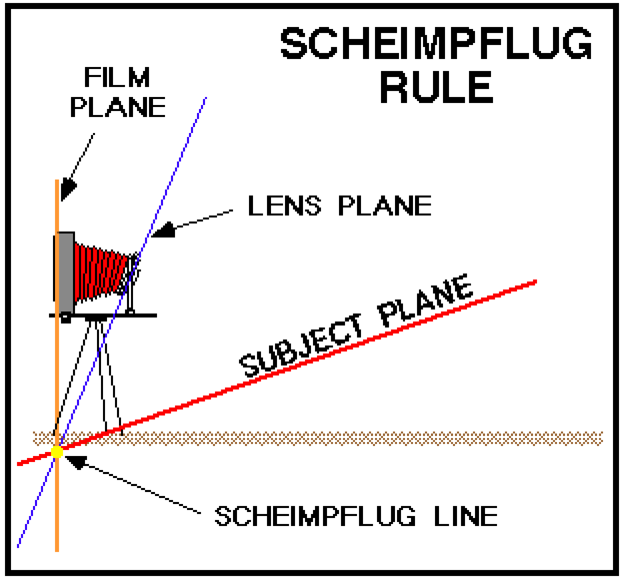






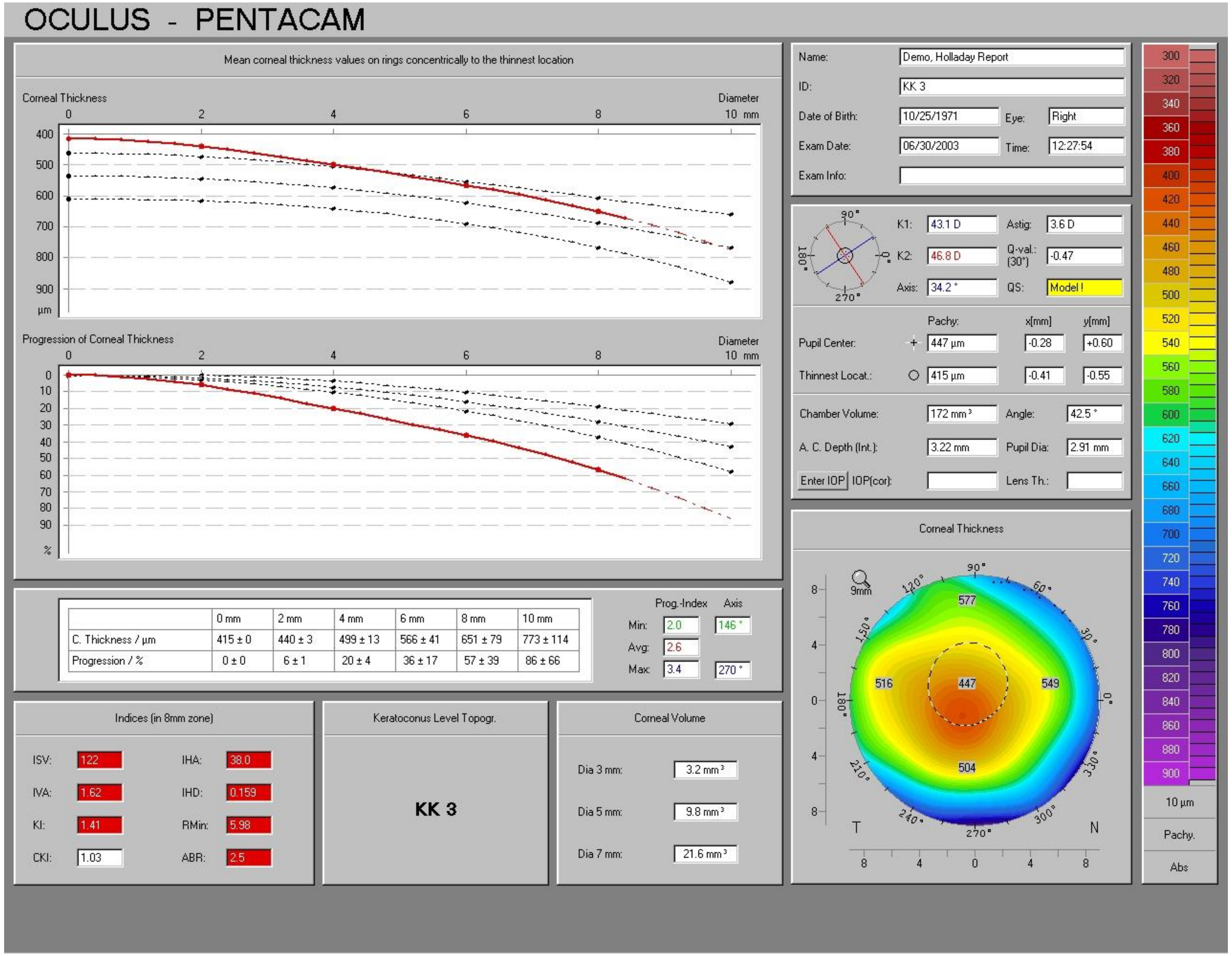
Scheimpflug Topography and Tomography

- Pentacam utilizes Scheimpflug imaging
    - Austrian Army officer flying balloons patented in 1904
- Scheimpflug imaging has the benefit of extended depth of focus
- Trade off is distortion of the image



Three planes must converge along a single line. These three planes are the film plane, the subject plane and lens plane

Keratoconus Indices Display



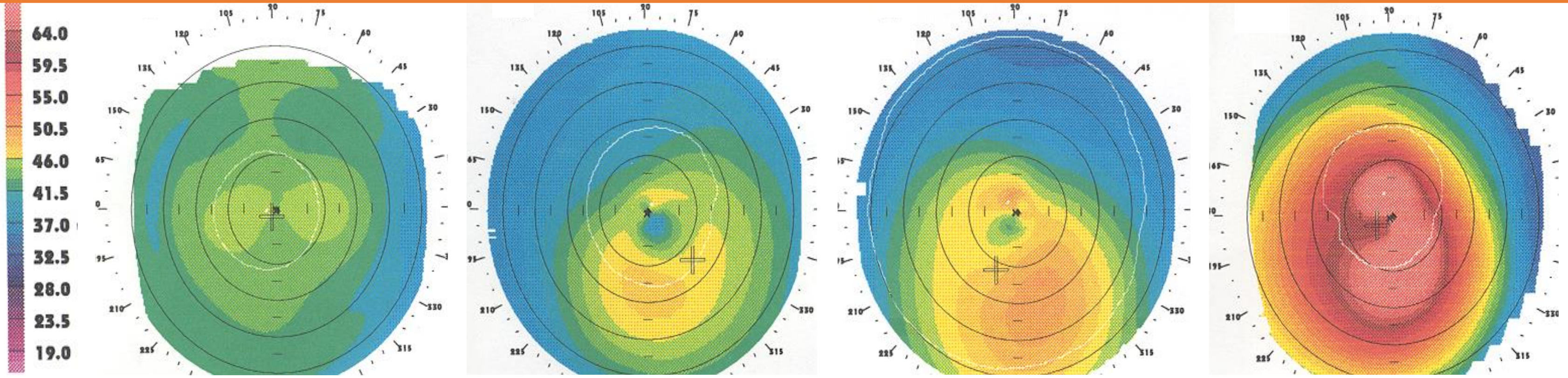
Currently the Gold Standard for Diagnosis of Keratoconus

Placido-based Axial Topography in Keratoconus

(No Pachymetry measurement)

Keratoconus Classification

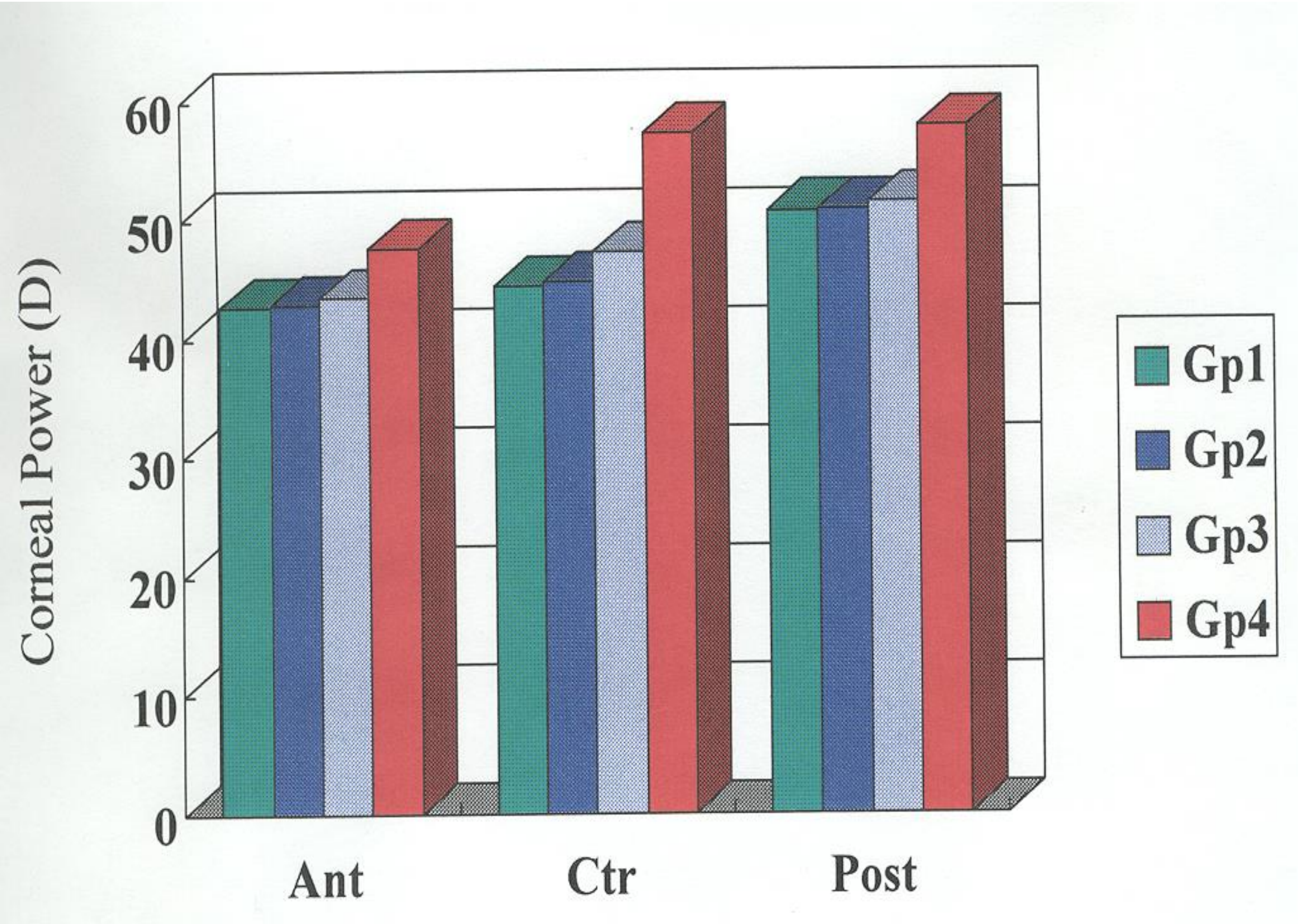
Normal	Suspect	Early KC	Advanced



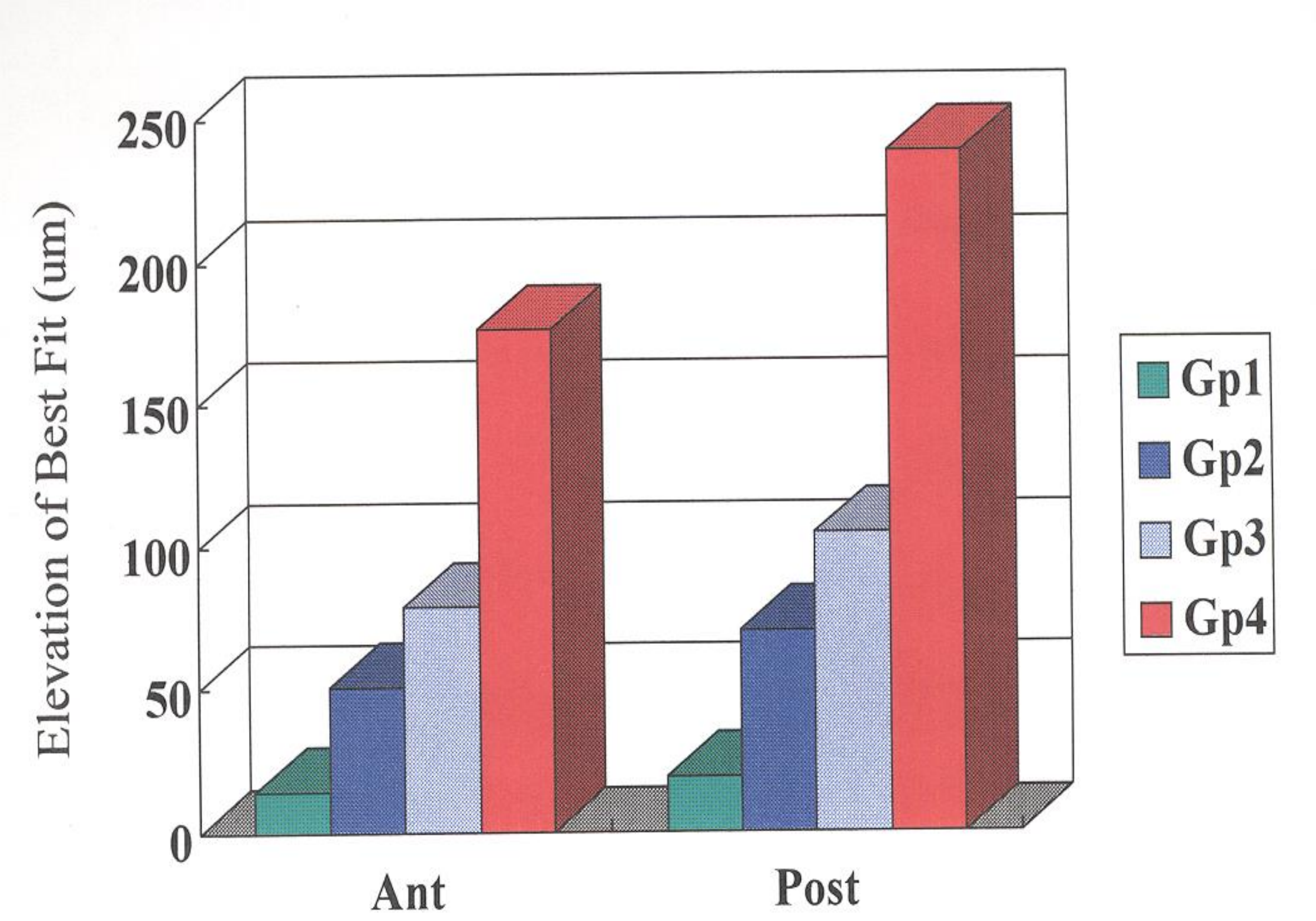
Azar-Lu MEEI Keratoconus Classification

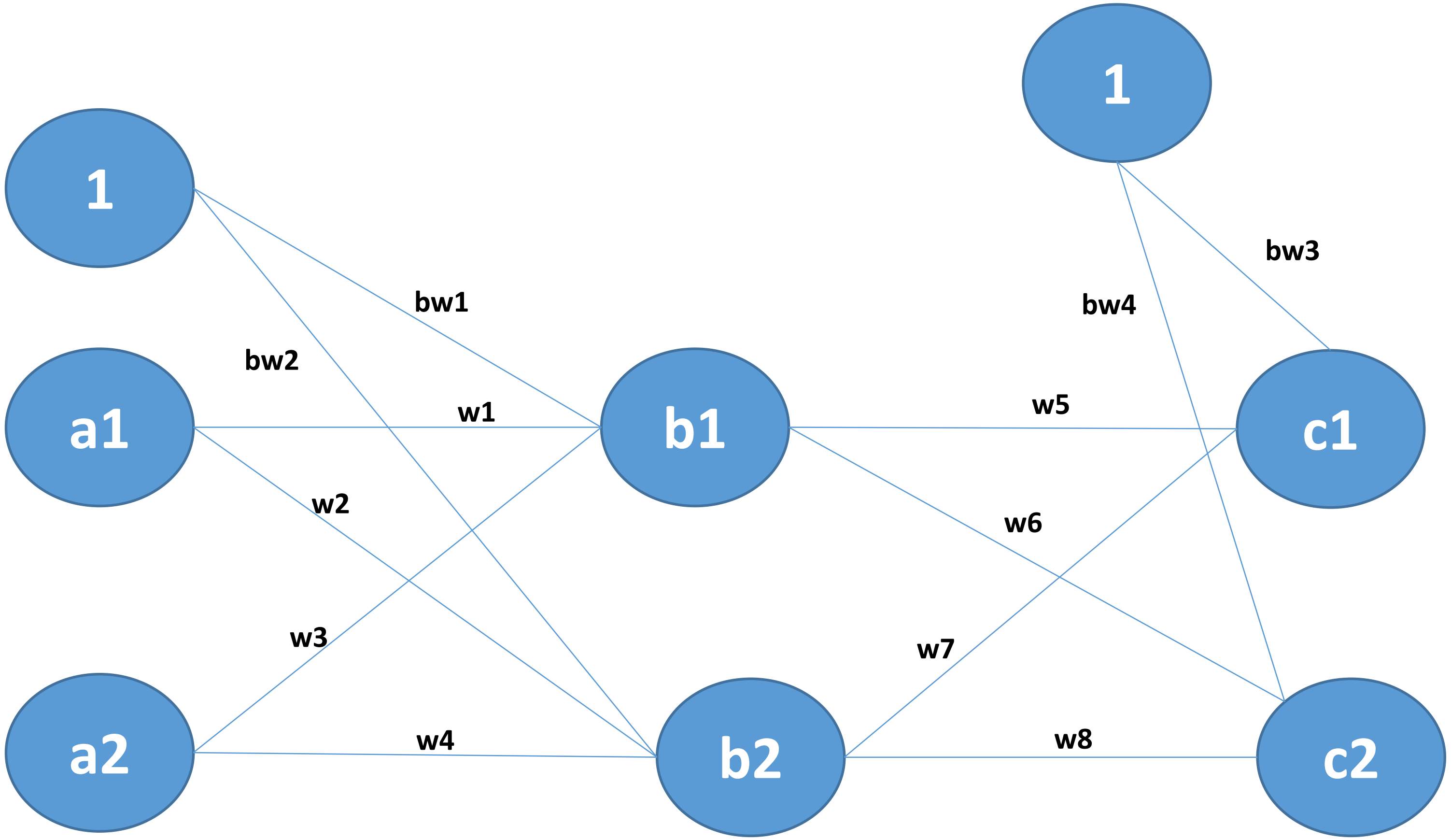
			Score
KOD-KOS	< 1.9	0	
	> 1.9	1	
KOD	< 47.2	0	
	47.2-48.7	1	
	>48.7	2	
ISOD	<1.4	0	
	1.4-1.9	1	
	>1.9	2	
≥ 2 Findings on hx (atopy, down), FH and exam (Fleisher, Vogt, Munson, nerves, scarring)	No	0	
	Yes	2	
Corneal Hydrops (by exam or hx) OD	No	0	
	Yes	2	
		Total Score	OD

Central Corneal Power



Elevation of Anterior & Posterior fit sphere





Multiple outputs. The local error of each output is calculated, and the results are summed to create a final local error

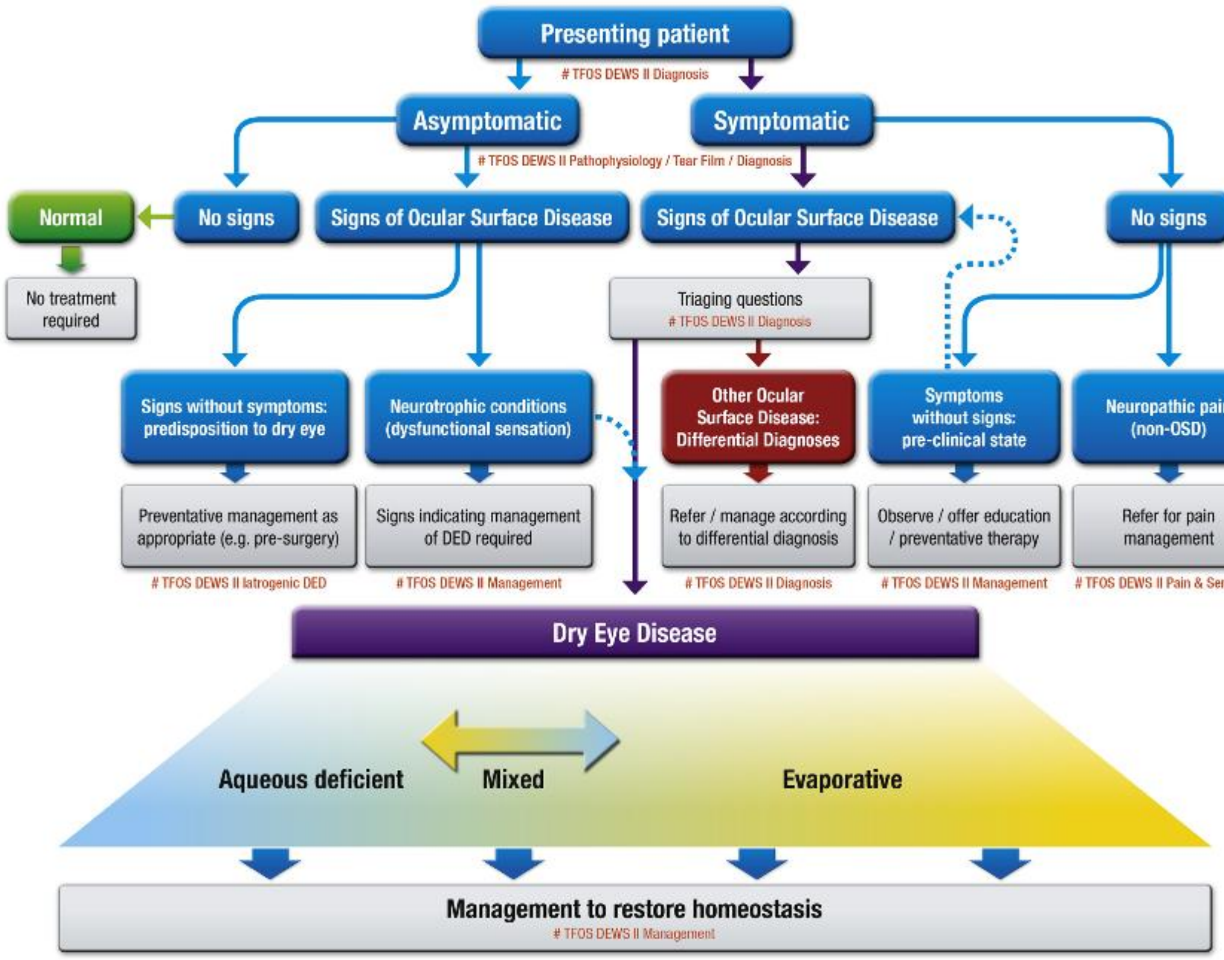
Adapted from: The Math of Neural Networks

AI Applications

- Refractive Error Prediction
- Corneal Topography
- **Dry Eye Diagnosis**
- Smart Intraocular Lenses
- Glaucoma Diagnosis
- Refractive Error Prediction
- Fundus Photography:
  - Identification of retinal lesions
  - Diabetic Retinopathy
- OCT:
  - AMD Progression Prediction
  - Diagnosis and Referral

Machine Learning: Dry Eye Disease

DEWS II Clinical Algorithm for Dry Eye Diagnosis



Dry Eye Diagnostic Tests: DEWS 2

DEQ 5

1. Questions about **EYE DISCOMFORT**:

   a. During a typical day in the past month, how often did your eyes feel discomfort?

   - 0 ☐ Never
   - 1 ☐ Rarely
   - 2 ☐ Sometimes
   - 3 ☐ Frequently
   - 4 ☐ Constantly

   b. When your eyes felt discomfort, how intense was this feeling of discomfort at the end of the day, within two hours of going to bed?

Never have it	Not at all intense				Very intense
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

2. Questions about **EYE DRYNESS**:

   a. During a typical day in the past month, **how often** did your eyes feel dry?

   - 0 ☐ Never
   - 1 ☐ Rarely
   - 2 ☐ Sometimes
   - 3 ☐ Frequently
   - 4 ☐ Constantly

   b. When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed?

Never have it	Not at all intense				Very intense
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

3. Question about **WATERY EYES**:
   During a typical day in the past month, **how often** did your eyes look or feel excessively watery?

   - 0 ☐ Never
   - 1 ☐ Rarely
   - 2 ☐ Sometimes
   - 3 ☐ Frequently
   - 4 ☐ Constantly

Score:	1a	+	1b	+	2a	+	2b	+	3	=	Total
	____	+	____	+	____	+	____	+	____	=	________

OCULAR SURFACE DISEASE INDEX©

Please answer the following questions by checking the box that best represents your answer.

Have you experienced any of the following during **the last week**:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	☐	☐	☐	☐	☐
2. Eyes that feel gritty?	☐	☐	☐	☐	☐
3. Painful or sore eyes?	☐	☐	☐	☐	☐
4. Blurred vision?	☐	☐	☐	☐	☐
5. Poor vision?	☐	☐	☐	☐	☐

Have problems with your eyes limited you in performing any of the following during **the last week**:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	☐	☐	☐	☐	☐	☐
7. Driving at night?	☐	☐	☐	☐	☐	☐
8. Working with a computer or bank machine (ATM)?	☐	☐	☐	☐	☐	☐
9. Watching TV?	☐	☐	☐	☐	☐	☐

Have your eyes felt uncomfortable in any of the following situations during **the last week**:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	☐	☐	☐	☐	☐	☐
11. Places or areas with low humidity (very dry)?	☐	☐	☐	☐	☐	☐
12. Areas that are air conditioned?	☐	☐	☐	☐	☐	☐

Scoring Instructions

Item scoring

The total OSDI score is calculated based on the following formula:

$$\text{OSDI} = \frac{(\text{sum of severity for all questions answered}) \times (100)}{(\text{total \# of questions answered}) \times (4)}$$

where the severity was graded on a scale of

- 0 = none of the time,
- 1 = some of the time,
- 2 = half of the time,
- 3 = most of the time,
- 4 = all of the time.

Interpretation

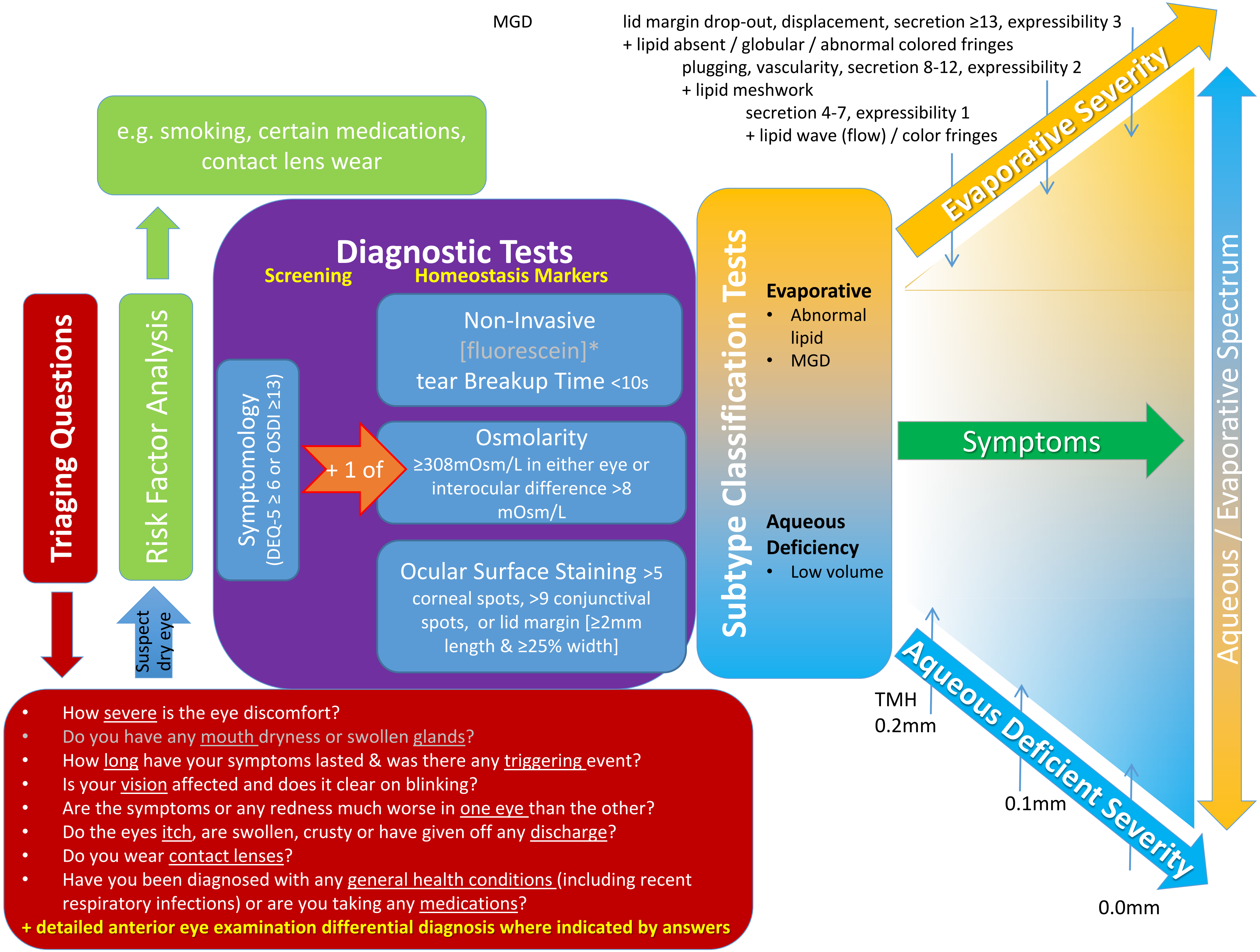
A score of 100 corresponds to complete disability (a response of "all of the time" to all questions answered), while a score of 0 corresponds to no disability (a response of "none of the time" to all questions answered). Therefore, change from baseline of −12.5 corresponds to an improvement by at least one category in half of the questions answered.

Subscale Scoring

Subscales scores are computed similarly with only the questions from each subscale used to generate its own score. Therefore, any subscales analyzed separately would also have a maximum possible score of 100.

The three subscales (vision-related function, ocular symptoms and environmental triggers) are broken out as follows:

Subscale	Questions
Vision-Related Function	4, 5, 6, 7, 8, 9
Ocular Symptoms	1, 2, 3
Enviromental Triggers	10, 11, 12



MGD
lid margin drop-out, displacement, secretion ≥13, expressibility 3
+ lipid absent / globular / abnormal colored fringes
plugging, vascularity, secretion 8-12, expressibility 2
+ lipid meshwork
secretion 4-7, expressibility 1
+ lipid wave (flow) / color fringes
e.g. smoking, certain medications, contact lens wear
Evaporative Severity
Diagnostic Tests
Screening
Homeostasis Markers
Triaging Questions
Risk Factor Analysis
Symptomology
(DEQ-5 ≥ 6 or OSDI ≥13)
+ 1 of
Non-Invasive
[fluorescein]*
tear Breakup Time <10s
Osmolarity
≥308mOsm/L in either eye or interocular difference >8 mOsm/L
Ocular Surface Staining >5
corneal spots, >9 conjunctival spots, or lid margin [≥2mm length & ≥25% width]
Subtype Classification Tests
Evaporative
• Abnormal lipid
• MGD
Aqueous Deficiency
• Low volume
Symptoms
Aqueous / Evaporative Spectrum
Suspect dry eye
TMH
0.2mm
0.1mm
0.0mm
Aqueous Deficient Severity
• How severe is the eye discomfort?
• Do you have any mouth dryness or swollen glands?
• How long have your symptoms lasted & was there any triggering event?
• Is your vision affected and does it clear on blinking?
• Are the symptoms or any redness much worse in one eye than the other?
• Do the eyes itch, are swollen, crusty or have given off any discharge?
• Do you wear contact lenses?
• Have you been diagnosed with any general health conditions (including recent respiratory infections) or are you taking any medications?
+ detailed anterior eye examination differential diagnosis where indicated by answers

Dry Eye Disease Diagnosis

- DEWS 2 rigorous approach -- (Overcomplication)

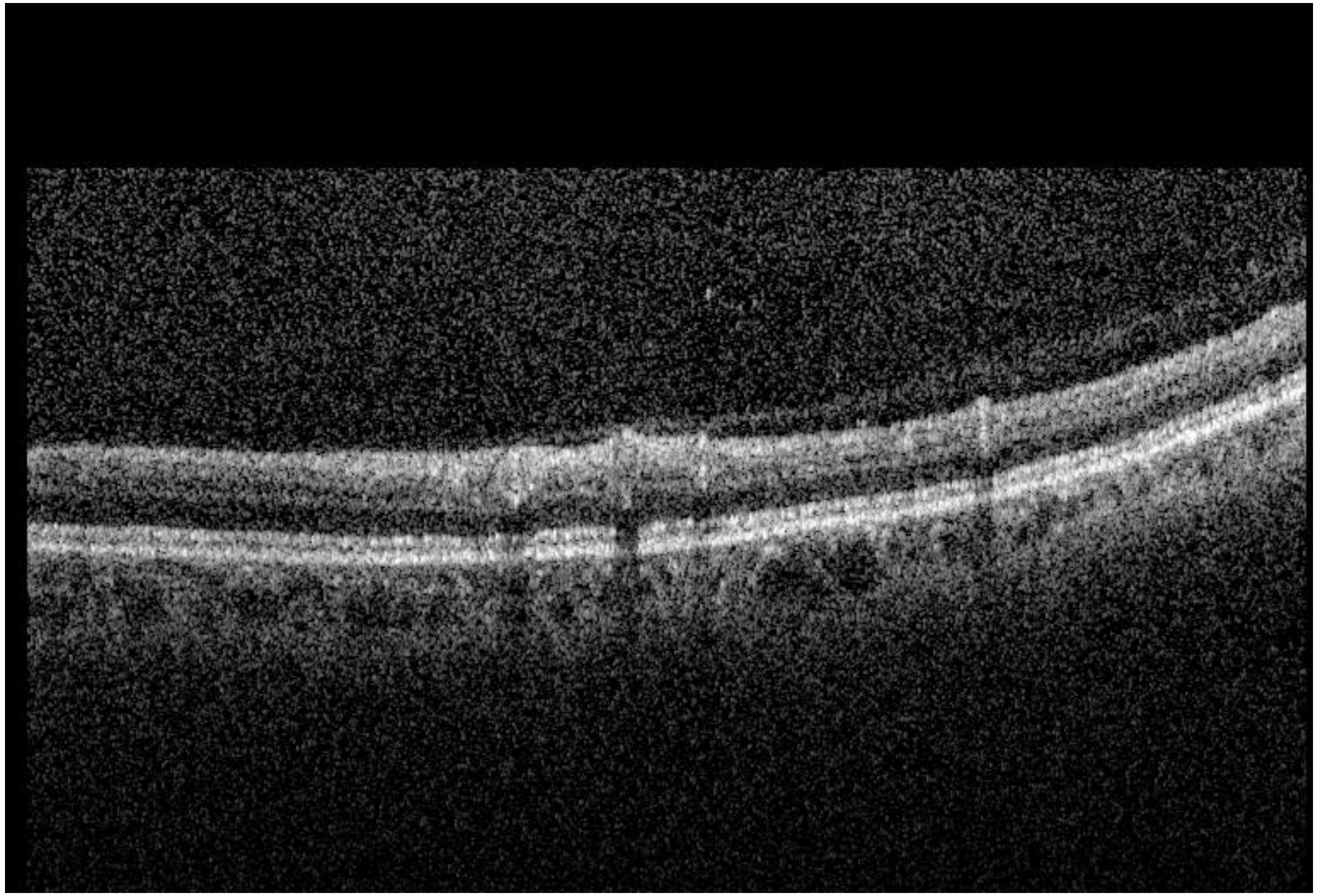
- Alternatives: (Oversimplification)
  - Do You have Dry eye?

  - ML algorithm utilizing combination of surrogate factors to diagnose DED

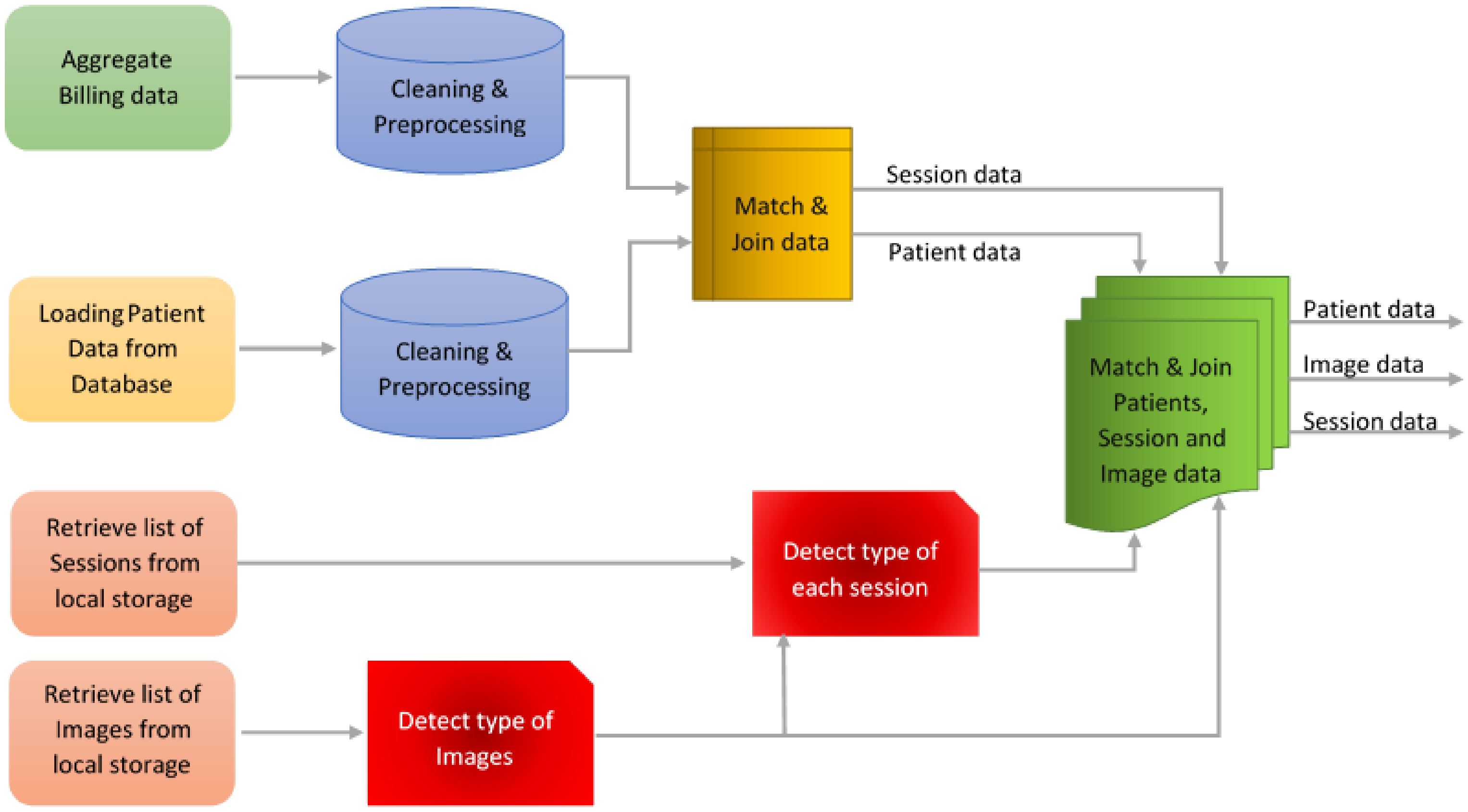
AI Applications

- Corneal Topography
- Dry Eye Diagnosis
- Smart Intraocular Lenses
- **Glaucoma Diagnosis**
- Refractive Error Prediction
- Fundus Photography:
  - Identification of retinal lesions
  - Diabetic Retinopathy
- OCT:
  - AMD Progression Prediction
  - Diagnosis and Referral

Deep Learning: Glaucoma

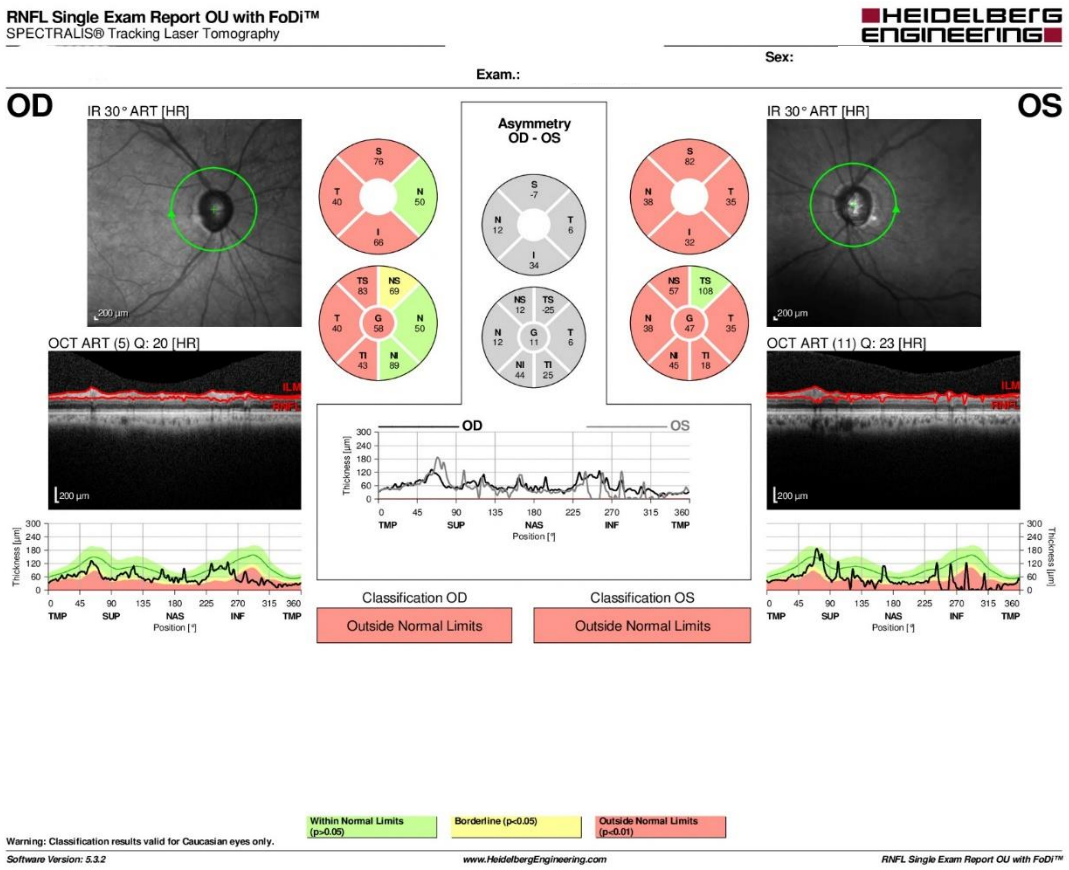


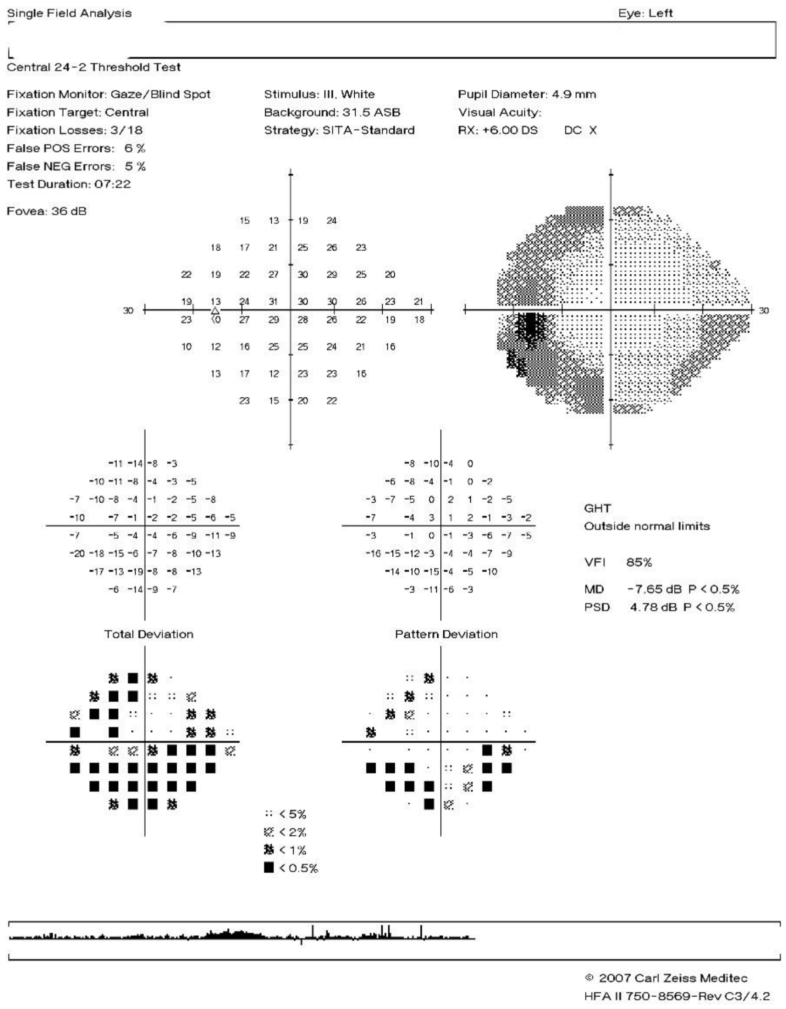
Example of Data Processing from stored servers



Hallak J, Yi D, Noorozi V, Lam C, Baker J, Mojab N, Rubin D, Azar D, Rosenblatt M. Longitudinal Data in Ophthalmic Imaging: Curation and Annotation. [ARVO Abstract]. 2018.

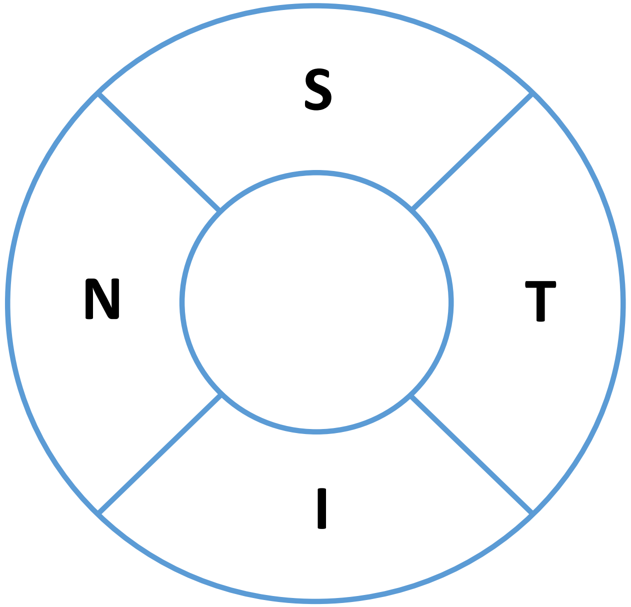
Diagnostic Tools

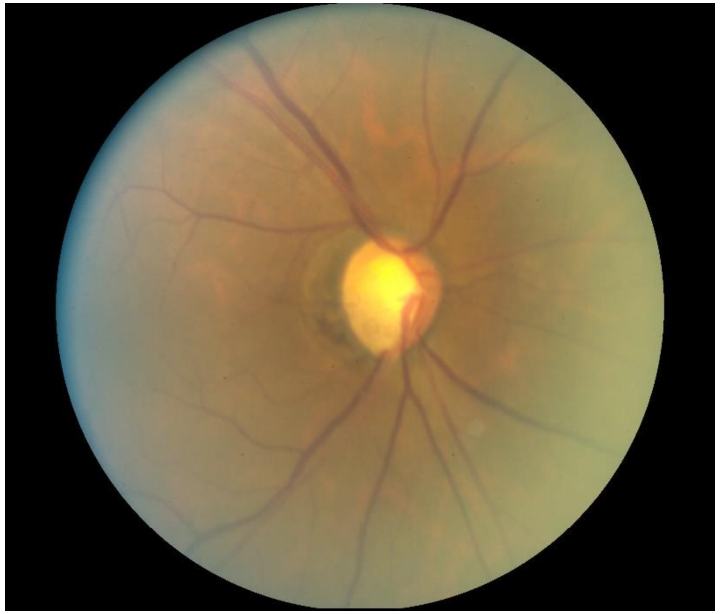




Glaucoma

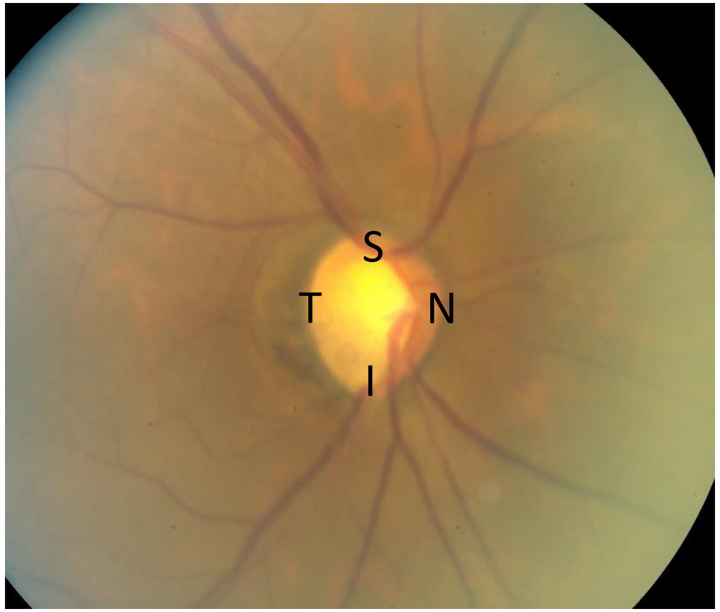
- OCT can provide analysis and thickness of the retinal nerve fiber layer (RNFL).
- RNFL in the various quadrants (ISNT) as the input (ground truth) for a deep learning convolutional network to label digital fundus photos.

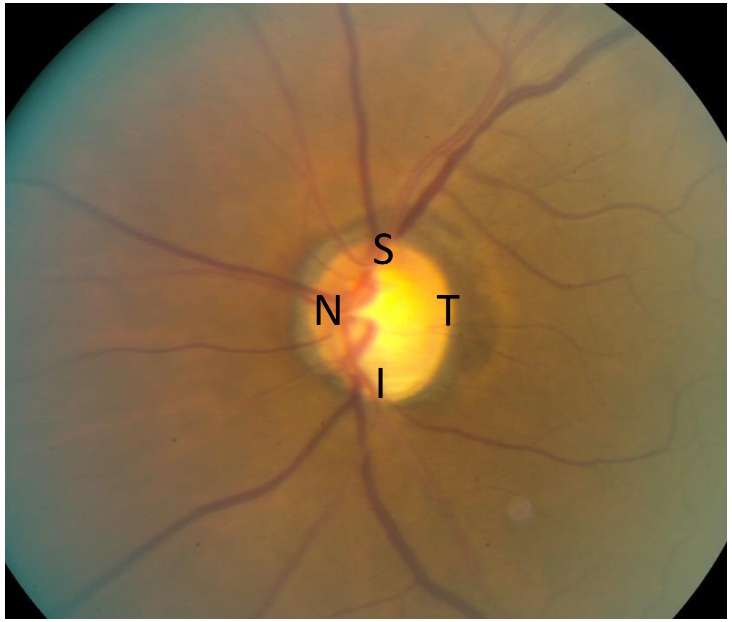




OD

OS





From the UIC Department of Ophthalmology and Visual Sciences

AI Applications

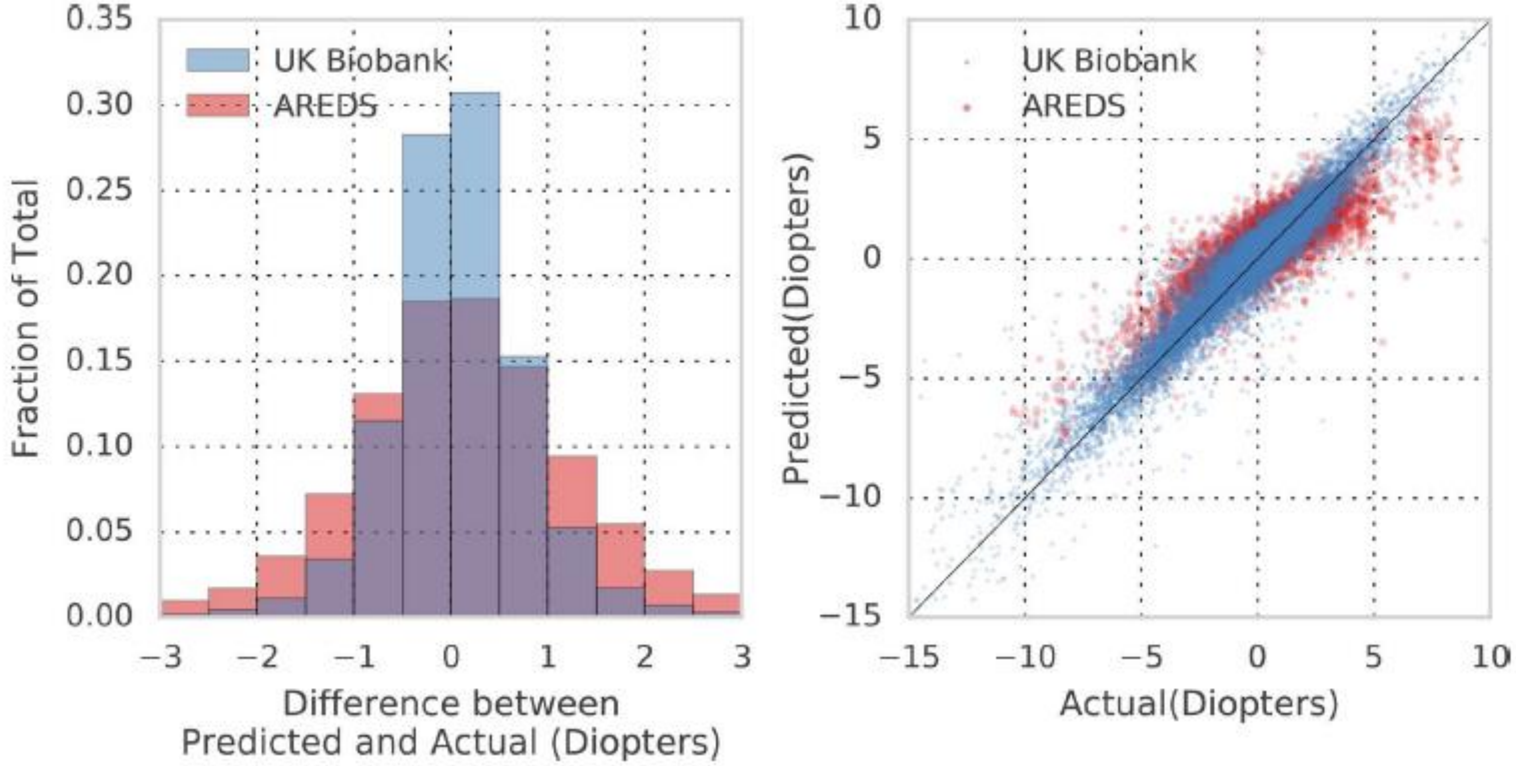
- Corneal Topography
- Dry Eye Diagnosis
- Smart Intraocular Lenses
- Glaucoma Diagnosis
- **Fundus Photography:**
  - **Refractive Error Prediction**
  - Identification of retinal lesions
  - Diabetic Retinopathy
- OCT:
  - AMD Progression Prediction
  - Diagnosis and Referral

Refractive Error Prediction from Fundus Images

- Use of retinal fundus photos to estimate refractive error with high accuracy with deep learning techniques
- Mean absolute error (MAE) of 0.56 diopters (95%confidence interval [CI]: 0.55–0.56) for estimating spherical equivalent on the UK Biobank data set and 0.91 diopters (95% CI: 0.89–0.93) for the AREDS data set.
- The baseline expected MAE (obtained by simply predicting the mean of this population) was 1.81 diopters (95% CI: 1.79–1.84) for UK Biobank and 1.63 (95% CI: 1.60–1.67) for AREDS.
- Attention maps suggested that the foveal region was one of the most important areas used by the algorithm to make this prediction, though other regions also contribute to the prediction.

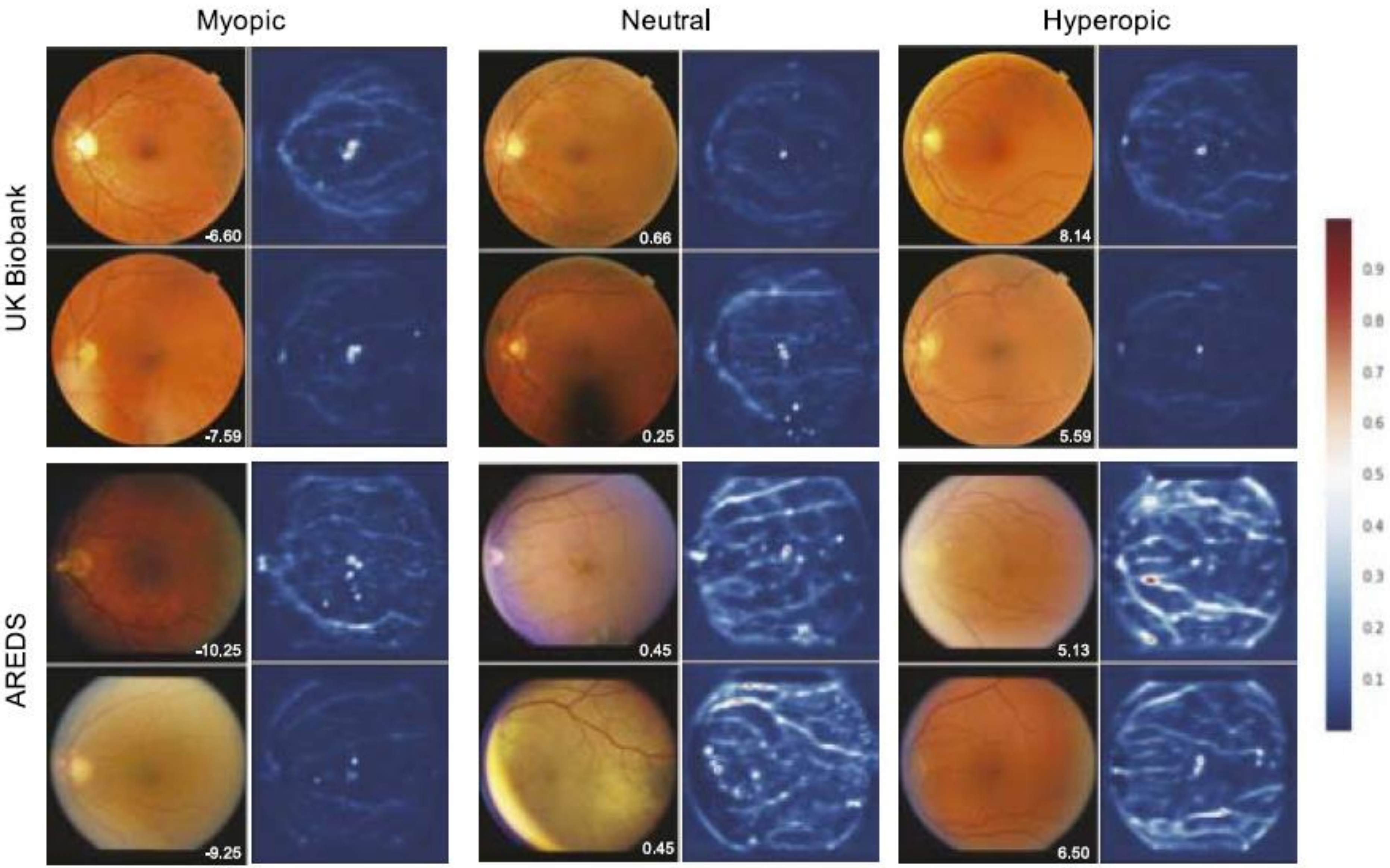
Vardarajan AV, Poplin R, Blumer K, Angermueller C, Ledsam J, Chopra R, Keane PA, Corrado GS, Peng L, Webster DR. Deep learning for predicting refractive error from retinal fundus images. Invest Ophthalmol Vis Sci. 2018 Jun; 59(7): 2861-2868.

Predicting Refractive Error from Fundus Images



Model performance in predicting SE on the two clinical validation sets. (A) Histogram of prediction error (Predicted Actual) UK Biobank data set (blue) and AREDS data set (red). (B) Scatter plot of predicted and actual values for each instance in the validation sets. Black diagonal indicates perfect prediction, where y ¼ x.

Vardarajan AV, Poplin R, Blumer K, Angermueller C, Ledsam J, Chopra R, Keane PA, Corrado GS, Peng L, Webster DR. Deep learning for predicting refractive error from retinal fundus images. Invest Ophthalmol Vis Sci. 2018 Jun; 59(7): 2861-2868.



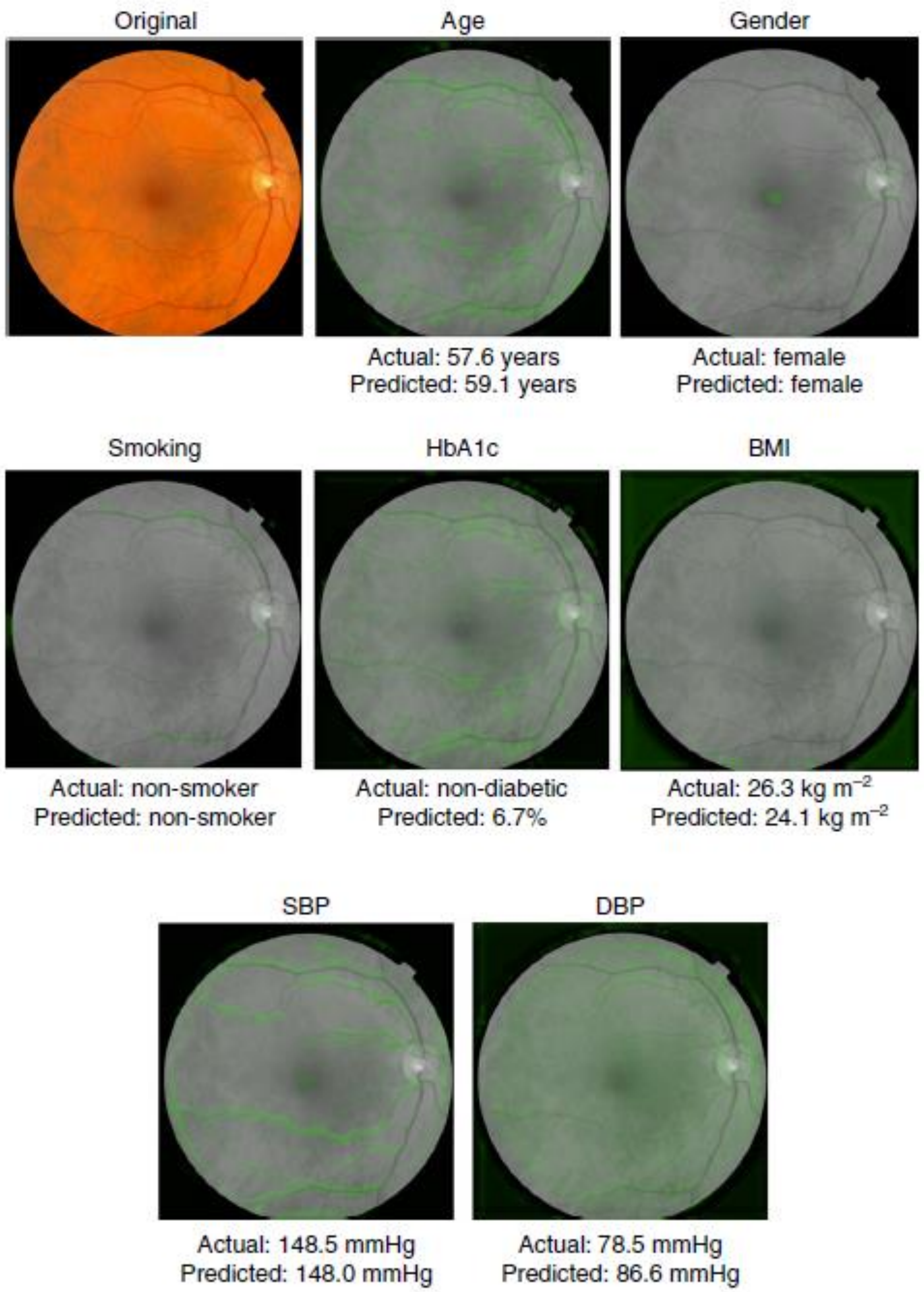
Example attention maps for three left myopic (SE worse than 6.0), neutral (SE between 1.0 and 1.0), and hyperopic (SE worse than 5.0) fundus images from UK Biobank (two top rows) and AREDS (two bottom rows). Diagnosed SE is printed in the bottom right corner of fundus images. Scale bar on right denotes attention pixel values, which are between 0 and 1 (exclusive), with the sum of all values equal to 1.

Vardarajan AV, Poplin R, Blumer K, Angermueller C, Ledsam J, Chopra R, Keane PA, Corrado GS, Peng L, Webster DR. Deep learning for predicting refractive error from retinal fundus images. Invest Ophthalmol Vis Sci. 2018 Jun; 59(7): 2861-2868.

Predicting Cardiovascular Risk Factors from Retinal Fundus Images

- Extracting knowledge from retinal fundus images
- Data obtained from 284,335 patients
  - Validated on two independent datasets of 12,026 and 999 patients
  - New cardiovascular risk factors predicted
    - Age (MAE within 3.26 years)
    - Gender (Area under receive operating characteristic curve, AUC = 0.97)
    - Smoking status (AUC = 0.71)
    - Systolic blood pressure (MAE within 11.23 mmHg)
    - Major adverse cardiac events (AUC = 0.70)
  - Trained deep-learning models used anatomical features to generate each prediction
    - Optic disk
    - Blood vessels

Poplin R, Varadarajan AV, Blumer K, Liu Y, McConnell MV, Corrado GS, Peng L, Webster DR. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng. 2018 Feb. 2;158-164.



Attention maps for a single retinal fundus image. The top left image is a sample retinal image in color from the UK Biobank dataset. The remaining images show the same retinal image, but in black and white. The soft attention heat map (Methods) for each prediction is overlaid in green, indicating the areas of the heat map that the neural-network model is using to make the prediction for the image. For a quantitative analysis of what was highlighted, HbA1c values are not available for UK Biobank patients, so the self-reported diabetes status is shown instead.

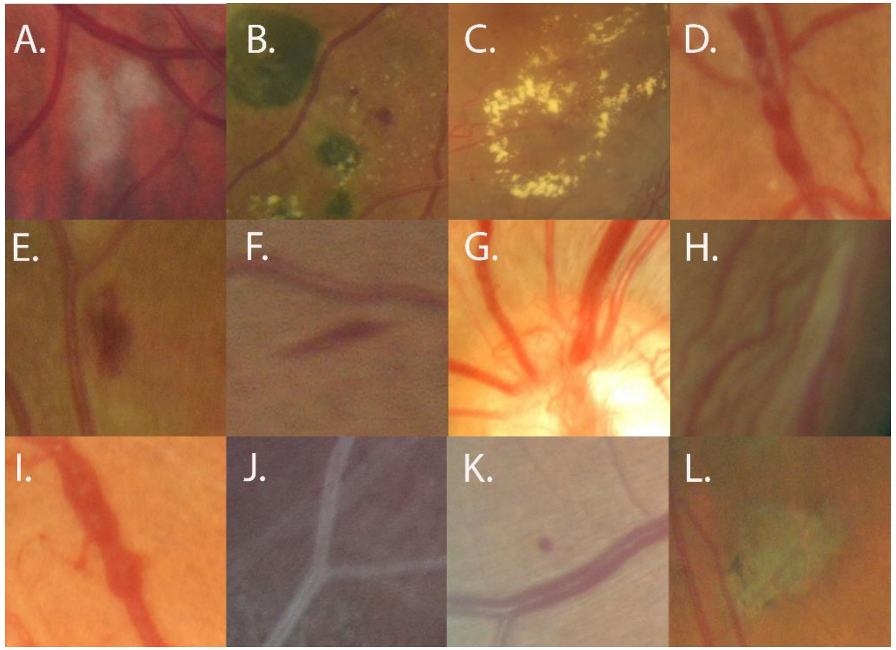
Poplin R, Varadarajan AV, Blumer K, Liu Y, McConnell MV, Corrado GS, Peng L, Webster DR. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng. 2018 Feb. 2;158-164.

AI Applications

- Corneal Topography
- Dry Eye Diagnosis
- Smart Intraocular Lenses
- Glaucoma Diagnosis
- **Fundus Photography:**
  - Refractive Error Prediction
  - **Identification of retinal lesions**
  - Diabetic Retinopathy
- OCT:
  - AMD Progression Prediction
  - Diagnosis and Referral

Retinal Lesion Detection with Deep Learning

- 243 retinal images verified and important subsections labelled to generate 1324 **image patches** containing hemorrhages, microaneurysms, exudates, retinal neovascularization or normal-appearing structures
- Images patches used to train one standard CNN to predict the presence of the above 5 cases
- Sliding window method used to generate probability maps across the entire image



Examples of manually cropped **image patches** containing lesions of interest. (**A**) Cotton wool spot, (**B**) laser scars and exudate, (**C**) circinate ring, (**D**) venous beading and intraretinal vascular abnormality, (**E**) intraretinal hemorrhage, (**F**) intraretinal hemorrhage, (**G**) neovascularization of the disc, (**H**) fibrotic band, (**I**) venous beading, (**J**) sclerotic ghost vessel, (**K**) microaneurysm, and (**L**) laser scar.

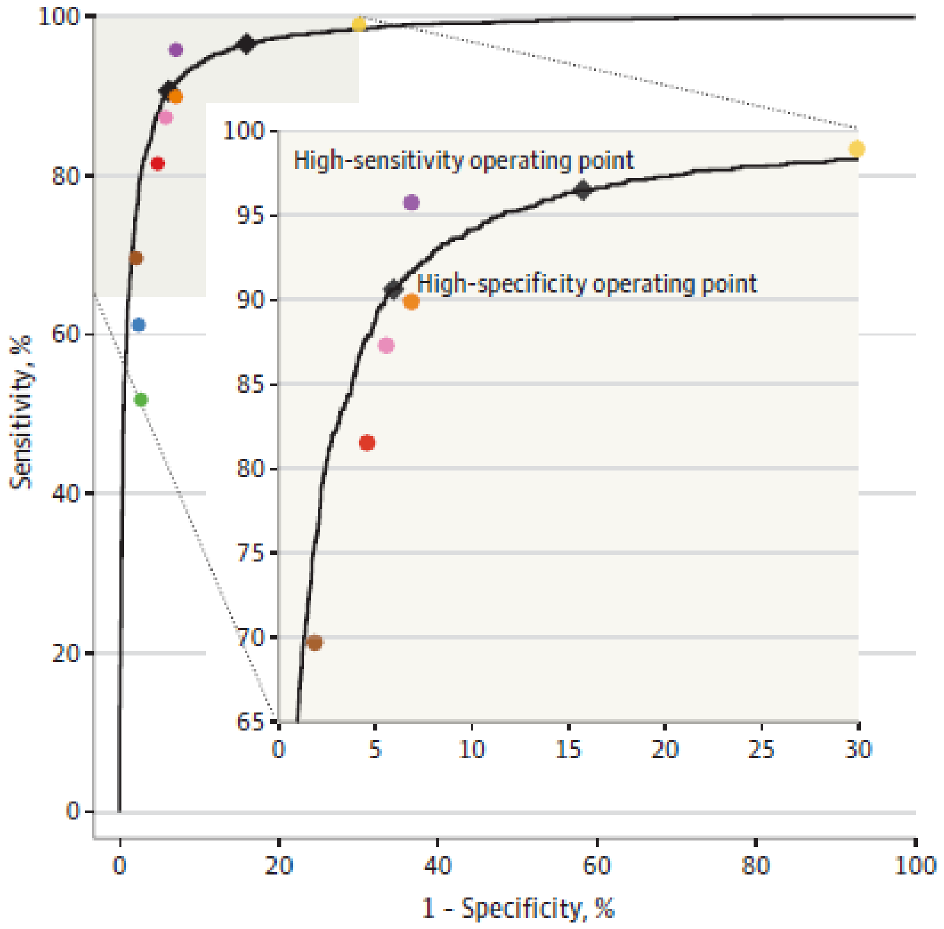
Lam C, Yu C, Huang L, Rubin D. Retinal lesion detection with deep learning using image patches. Invest Ophthalmol Vis Sci. 2018 Jan 1; 59(1):590-596.

AI Applications

- Corneal Topography
- Dry Eye Diagnosis
- Smart Intraocular Lenses
- Glaucoma Diagnosis
- **Fundus Photography:**
  - Refractive Error Prediction
  - Identification of retinal lesions
  - **Diabetic Retinopathy**
- OCT:
  - AMD Progression Prediction
  - Diagnosis and Referral

Diabetic Retinopathy

Performance of the algorithm (black curve) vs. 8 ophthalmologists (colored circles) for all-cause referable diabetic retinopathy, defined as moderate or worse diabetic retinopathy, diabetic macular edema, or ungradable image.
For the **high-sensitivity operating point, specificity** was **84.0% (**95%CI, 83.1%-85.0%) and **sensitivity** was **96.7%**
(95%CI,
95.7%-97.5%).
For the **high-specificity operating point**, **specificity** was **93.8%** (95%CI, 93.2%-94.4%) and **sensitivity** was **90.7%**
(95%CI, 89.2%-92.1%).
There were 8 ophthalmologists who graded EyePACS-1.
The area under the receiver operating characteristic curve was 97.4%(95%CI, 97.1%-97.8%).



Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, Venugopalan S, Widner K, Madams T, Cuadros J, Kim R, Raman R, Nelson PC, Mega JL, Webster DR. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA. 2016 Dec 13; 316(22); 2366-2368.

AI Applications in Ophthalmology

- Corneal Topography
- Dry Eye Diagnosis
- Smart Intraocular Lenses
- Glaucoma Diagnosis
- Fundus Photography:
  - Refractive Error Prediction
  - Identification of retinal lesions
  - Diabetic Retinopathy
- **OCT:**
  - **AMD Progression Prediction**
  - Diagnosis and Referral

Prediction of Individual Disease Conversion in Early AMD

- **Results:**
  - 159 of 495 eyes (32%) progressed to advanced AMD within 2 years
    - 114 eyes progressed to CNV
    - 45 eyes progressed to GA
  - Predictive model differentiated between advancing vs. non-advancing eyes with
    - CNV: 0.68
    - GA: 0.80
  - Most critical quantitative features for progression
    - **Retinal thickness**
    - **Hyperreflective foci**
    - **Drusen area**
  - Predictive hallmarks
    - CNV: Mostly drusen-centric
    - GA: Associated with neurosensory retina and age

Schmidt-Erfurth U, Waldstein SM, Klimscha S, Sadeghipour A, Hu X, Gerendas BS, Osborne A, Bogunovic H. Prediction of individual disease conversion in early AMD using artificial intelligence. Invest Ophthalmol Vis Sci. 2018 Jul 2;59(8):3199-3208.

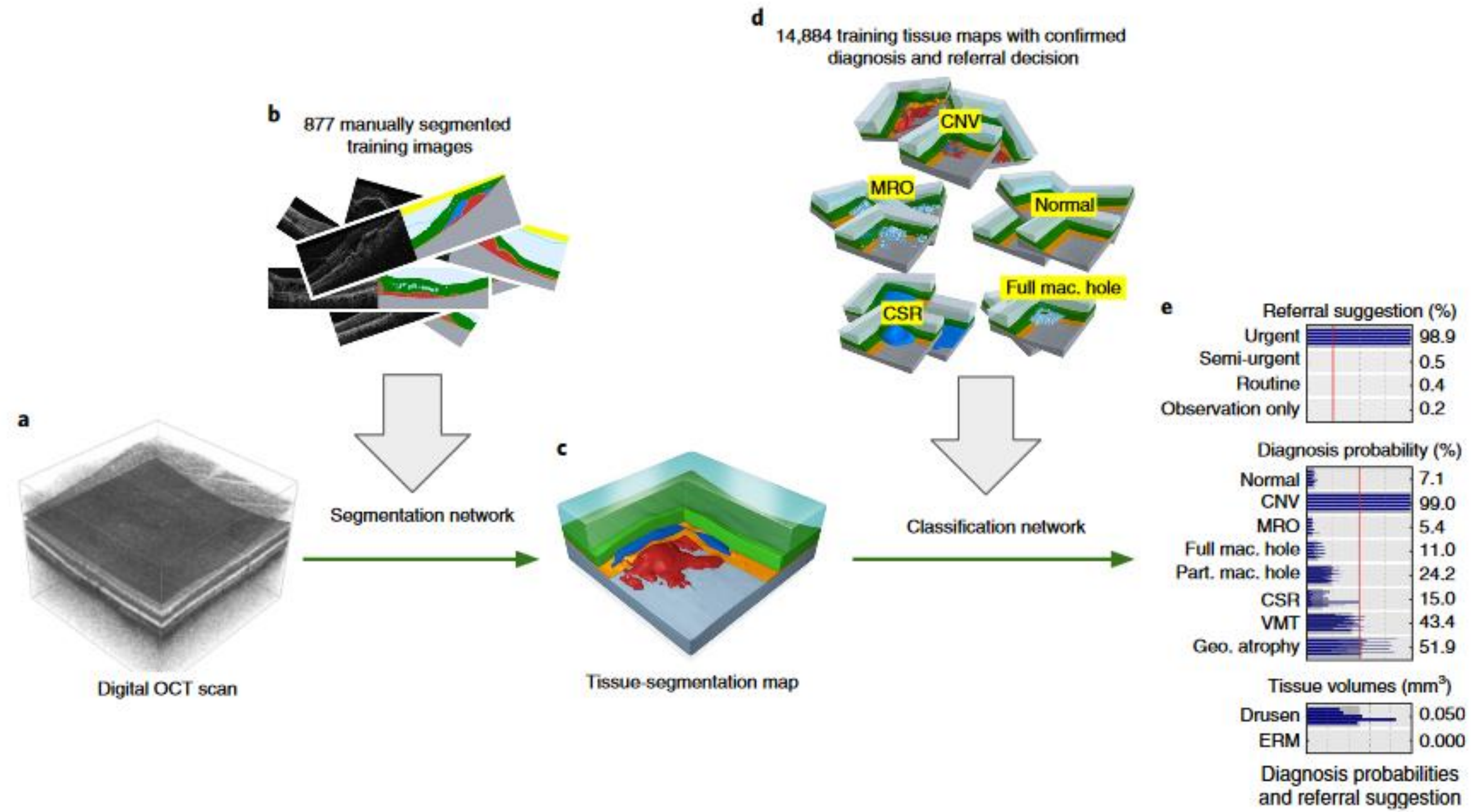
AI Applications

- Corneal Topography
- Dry Eye Diagnosis
- Smart Intraocular Lenses
- Glaucoma Diagnosis
- Fundus Photography:
  - Refractive Error Prediction
  - Identification of retinal lesions
  - Diabetic Retinopathy
- **OCT:**
  - AMD Progression Prediction
  - **Diagnosis and Referral**

Diagnosis and Referral in Retinal Disease

- Challenges in automated diagnosis of medical image
  - Technical variations in the imaging process (different devices, noise, ageing of the components and so on)
  - Patient-to-patient variability in pathological manifestations of disease
- Existing deep learning approaches
  - Use single end-to-end black-box network to deal with the all the combinations of the variations
  - This would typically require millions of labeled scans
- **New deep learning approach**
  - Decoupling the 2 problems: **technical** variation & **pathological** variations
  - Independent problem solving

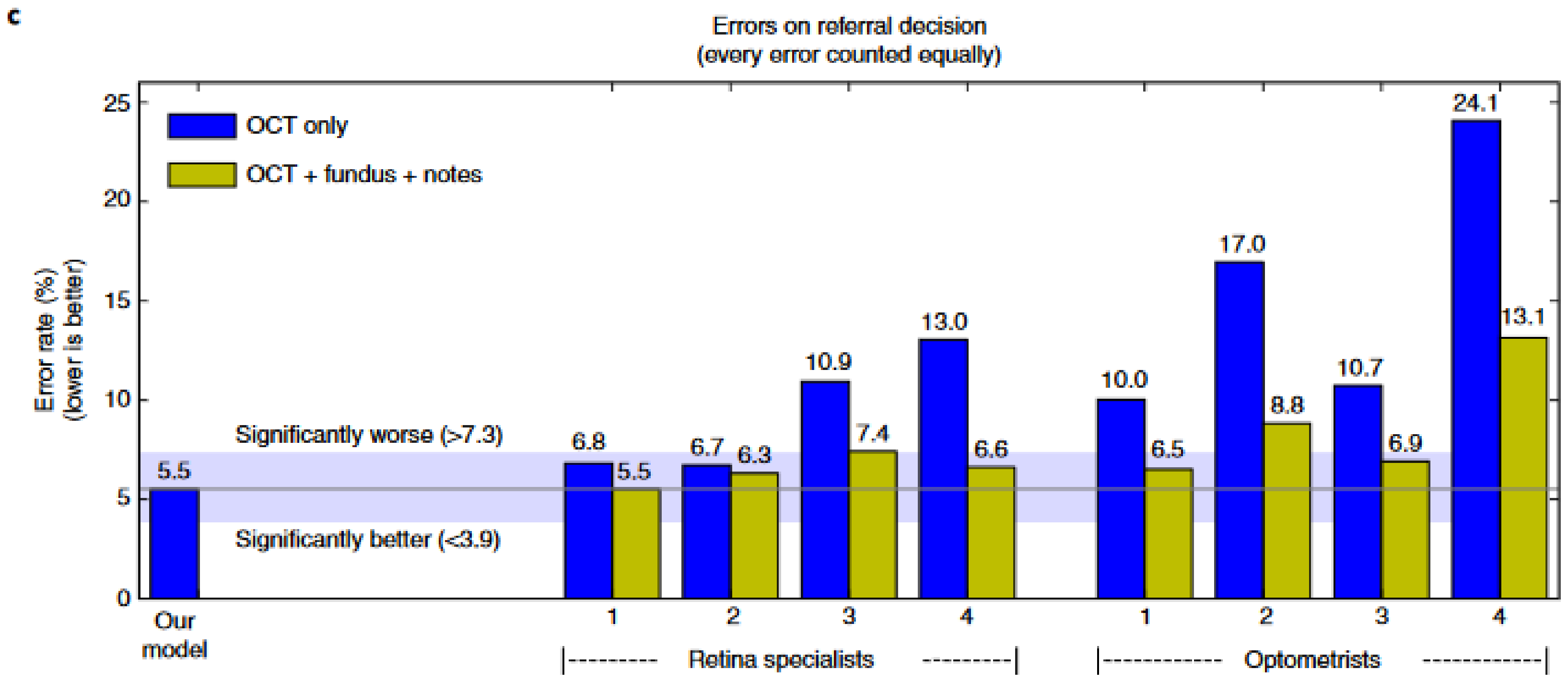
De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nature Medicine. 2017 Dec. https://doi.org/10.1038/s41591-018-0107-6.



Sparse annotation enabled the coverage of large variety of scans and pathologies with the same workload as ~ 21 dense manual segmentations

De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nature Medicine. 2017 Dec. https://doi.org/10.1038/s41591-018-0107-6.

Diagnosis and Referral in Retinal Disease



Results on the patient referral decision. (C) Total error rate (1 − accuracy) on referral decision. Values outside the light-blue area (3.9–7.3%) are significantly different (95% confidence interval, using a two-sided exact binomial test) to the framework performance (5.5%). AUC, area under curve.

De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nature Medicine. 2017 Dec. https://doi.org/10.1038/s41591-018-0107-6.

Current Applications of AI in Retinal Disorders

- Age-related macular degeneration (AMD)
  - Currently affecting 170 million people world-wide
  - Estimated that 288 million people will have AMD by 2040

(Pennington and DeAngelis, 2016)

- Diabetic retinopathy
  - World-wide epidemic; 1/3 of estimated 285 million diabetic patients have DR signs; 1/3 of them have vision threatening DR
  - Estimated the number of DR patients to triple by 2050

(Lee et al., 2015)

- Reticular pseudodrusen
- Retinopathy of prematurity (ROP)

Pennington KL, DeAngelis MM. Epidemiology of age-related macular degereation (AMD): associations with cardiovascular disease phenotypes and lipid factors. Eye Vis (Lond). 2016; 3; p.34

Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis (Lond). 2015, p.17

SUMMARY:

AI has great applications in Ophthalmology;

But Limitations Exist:

- Quality and diversity of the training sets
  - The systems are only as good as they are taught, so important to give robust reference standards to the algorithms.
- Problems with image quality
  - Good quality images are important to avoid confusion. Example – algorithms at present often get confused by patient who as a central retinal vein occlusion instead of DR.
- A CNN-based system is likely to make error:
  - An experiment: Making changes to a small number of pixels in fundus photos of eyes with DR caused image-based black box CNN systems to evaluate these altered images as disease-free, while an ophthalmologist would still consider them to have DR

Summary: Convergence

- Over 100 years ago, the Flexner report established the **biomedical model** of education, training and research as an enduring basis for medical education.
- Now, in an era of AI and increasing technological pervasiveness, the biomedical science-centric model should be enhanced to better **incorporate the growing convergence** of medicine with engineering, computational science, physical sciences, and artificial intelligence.
- The technological innovations that will result from this **trans-disciplinary convergence** in Ophthalmology will enable increasingly effective and affordable eye care for communities living in diverse urban, rural and suburban settings worldwide.

CONCLUSIONS:

Implications for the future of eye care:

- Education of Ophthalmology Fellows, Residents and Students:
  - *The Knowledge base is only a **foundation** to facilitate interpretation of data*
  - *The importance of the **humanistic** elements of medicine:*
    Professionalism, Communication, Empathy, Compassion, Respect…
- Regulatory:
  - *First systems in DR have been approved (CE and FDA)*
  - *How will future evolving/**learning systems** be approved?*
- The black box dilemma
  - *A CNN-based system analyzes new images/data based on its **self-generated rules**, so how can the **ophthalmologist be truly confident** that the outcome is correct?*
- Fear of the unknown:
  - *We must insure that AI will be a **helpful tool, rather than a competitor**, for early referrals and easy diagnoses.*

Now is not the end. It is not even the beginning of the end.

But it is, perhaps, the end of the beginning.

THANK YOU

Dimitri Azar, MD, MBA