ARTIFICIAL INTELLIGENCE (AI) AND PRECISION MEDICINE: DOES THE HEALTH ECONOMIST NEED TO ADAPT TO THE MACHINE?

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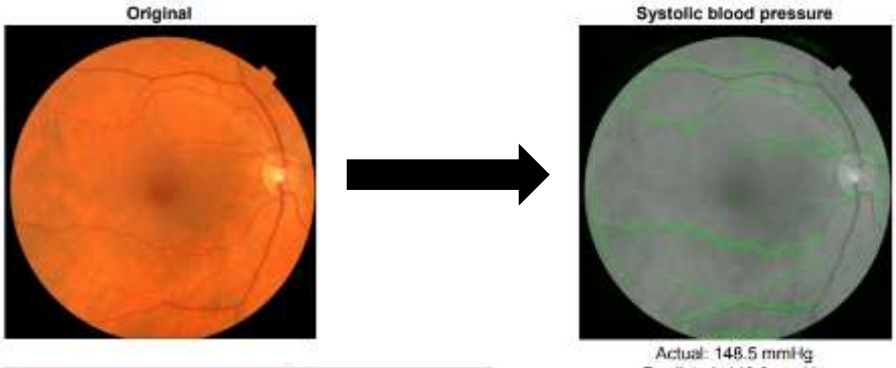
ISPOR 23rd Annual International Meeting
May 21, 2018



ARTICLES
nature biomedical engineering

Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning

Ryan Poplin[1,2], Avinash V. Varadarajan[1,2], Katy Blumer[1], Yun Liu[1], Michael V. McConnell[3,4], Greg S. Corrado[1], Lily Peng[1,2] and Dale R. Webster[1,2]

Traditionally, medical discoveries are made by observing associations, making hypotheses from them and then designing and running experiments to test the hypothesis. However, with medical images, observing and quantifying associations can often be difficult because of the wide variety of features, patterns, colours, values and shapes that are present in real data. Here, we show that deep learning can extract new knowledge from retinal fundus images. Using deep-learning models trained on data from 284,335 patients and validated on two independent datasets of 12,026 and 999 patients, we predicted cardiovascular risk factors not previously thought to be present or quantifiable in retinal images, such as age (mean absolute error within 3.26 years), gender (area under the receiver operating characteristic curve (AUC) = 0.97), smoking status (AUC = 0.71), systolic blood pressure (mean absolute error within 11.23 mmHg) and major adverse cardiac events (AUC = 0.70). We also show that the trained deep-learning models used anatomical features, such as the optic disc or blood vessels, to generate each prediction.

NATURE BIOMEDICAL ENGINEERING | VOL 2 | MARCH 2018 | 158–164 | www.nature.com/natbiomedeng

CONCLUSION
Artificial intelligence predicts cardiovascular risk factors based on retinal images.

AGENDA

- How AI relates to Precision Medicine
- Introduction to AI
- AI-backed precision medicine
  - An illustration: skin cancer detection
  - A definition
  - Advantages and challenges
  - Market access considerations
- Real-life examples
  - Cardiac arrhythmias detection
  - Lung cancer detection
  - Diabetic retinopathy detection
- Impact on health economics
- Conclusion

Feb 3rd 2018

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HOW AI RELATES TO PRECISION MEDICINE

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PRECISION MEDICINE

- **Definition** – an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment and lifestyle (NIH)
- **Personalized medicine** – an older term that can be misinterpreted to imply treatments and preventions are uniquely developed for each individual (NRC) Still continues to be used interchangeably by some people

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AI-enabled Precision Medicine

- AI is an important enabler of PM
- Primarily for big data analytics
  - Analyze large medical data sets
  - Draw conclusions
  - Find new correlation based on existing precedences
  - SUPPORT the doctor's job in decision-making

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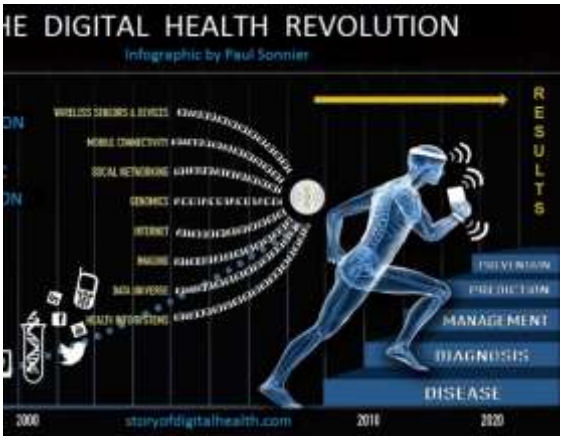
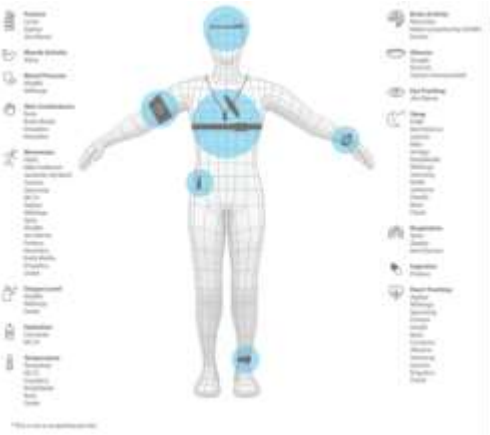


Relationship of AI to Precision Medicine

- Make patients the point of care
- Create vast amounts of data that require advanced analytics
- Establish the foundation of precision medicine
- AI is key technology that can bring these opportunities to everyday practice



Challenges

- Need to create ethical standards
- Incremental development to evaluate all implications
- Medical professionals need to learn how AI works in practice
- Patients need to become accustomed
- Decision-makers need to assess effectiveness

What is required

- Patient-centric approach
- Appropriate regulatory framework
- Appropriate ethical framework to proactively address ethical challenges
- Consumer education

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A QUICK INTRODUCTION TO AI

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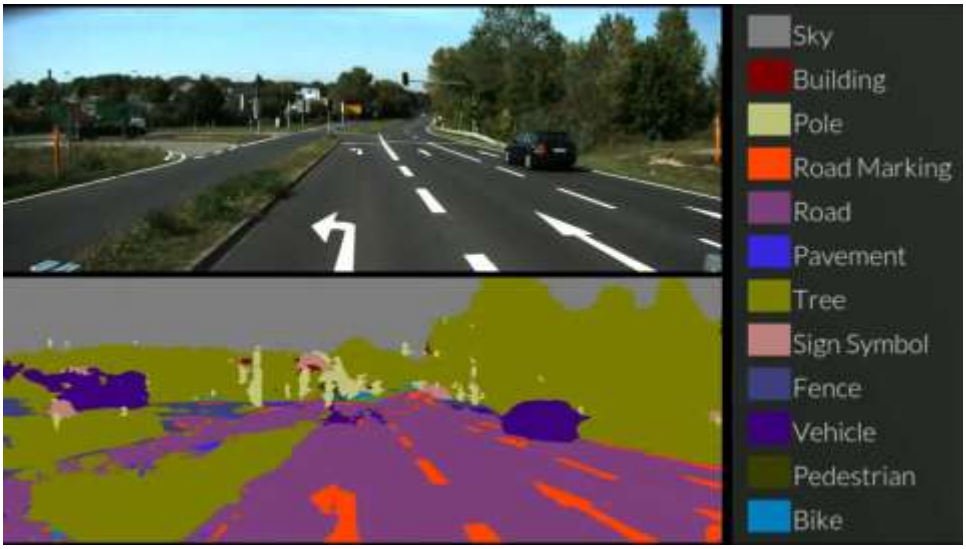

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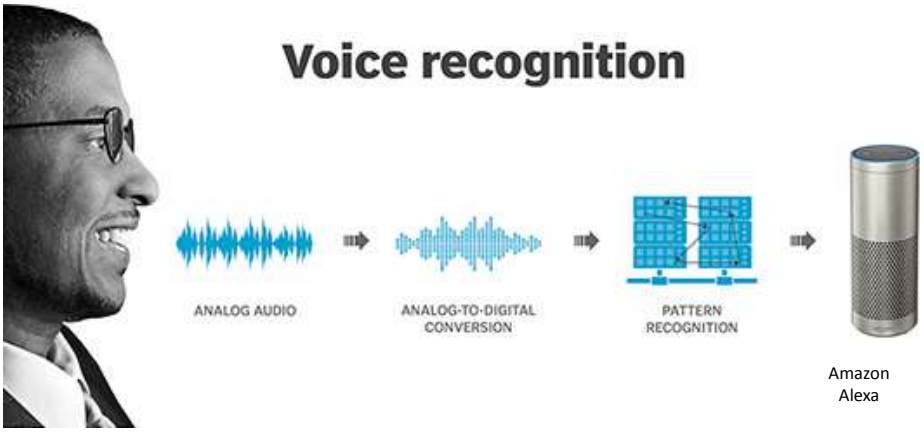

Amazon Alexa

www.searchcrm.techtarget.com/definition/voice-recognition

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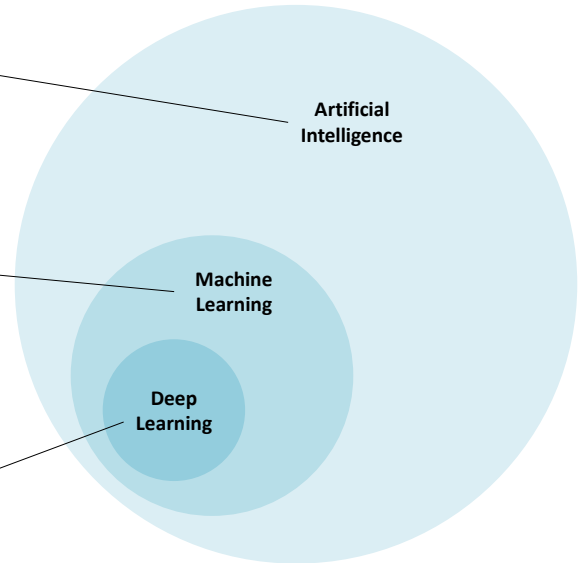
Gatys LA and al., A Neural Algorithm of Artistic Style, 2015

MACHINES CARRY OUT TASKS IN A "SMART" WAY

TRAINING TEST

NEURAL NETWORK



This last category will be covered today!

$$Y = f(X)$$

CARDIOVASCULAR RISK

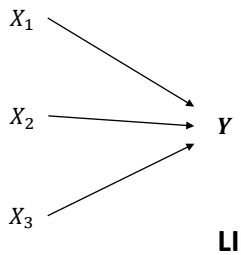
Risk Factor	Parameter Estimate	P-Value	Hazard Ratio (HR) (95% CI for HR)
Age, years	0.11691	0.0001	1.124 (1.111-1.138)
Male Sex	0.40359	0.0002	1.497 (1.215-1.845)
Systolic Blood Pressure	0.01645	0.0001	1.017 (1.012-1.021)
Current Smoker	0.76798	0.0001	2.155 (1.758-2.643)
Total Serum Cholesterol	-0.00209	0.0863	0.998 (0.995-2.643)
Diabetes	-0.02366	0.1585	0.816 (0.615-1.083)

A smoker has twice the chance of developing a CV event as compared to a non-smoker

(the other parameters being the same)

Source: Framingham CVD risk estimate, Lisa Sullivan, Boston University School of Public Health, 2016

LINEAR REGRESSION

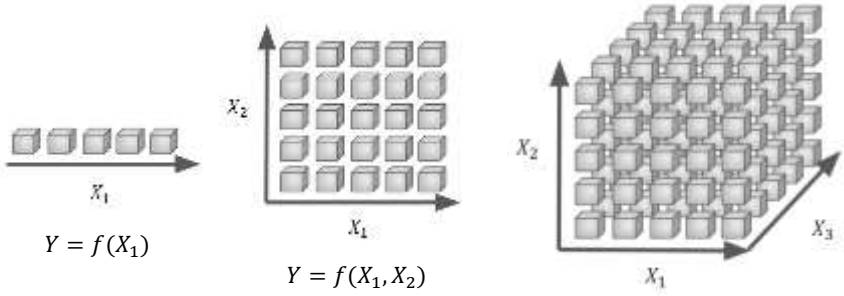


LINEAR RELATIONS between **X**

$$Y = w_0 + w_1 \cdot X_1 + w_2 \cdot X_2 + w_3 \cdot X_3$$

Interpretability	Predictive power
HIGH "We, poor humans, need to see"	Low Because most real-life optimization problems are non linear

The curse of high dimensionality



$Y = f(X_1)$

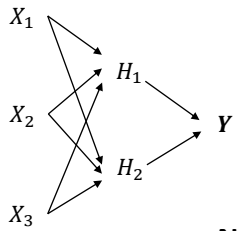
$Y = f(X_1, X_2)$

$Y = f(X_1, X_2, X_3)$

$$Y = f(X_1, X_2, X_3, \dots, X_{1,000,000,000})$$

Is linear regression sufficient here?

DEEP LEARNING



NON LINEAR RELATIONS between **X**

$$Y = \frac{1}{1 + e^{-(w_0 + w_1 \cdot \frac{1}{1+e^{-(w_0' + w_1' \cdot X_1 + w_2' \cdot X_2 + w_3' \cdot X_3)}} + w_2 \cdot \frac{1}{1+e^{-(w_0'' + w_1'' \cdot X_1 + w_2'' \cdot X_2 + w_3'' \cdot X_3)}})}}$$

Interpretability	Predictive power
Low	**HIGH**

This extra performance comes at the cost of interpretability!

AI-BACKED PRECISION MEDICINE

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SKIN CANCER DETECTION

SKIN CANCER (in US)
- 5.4 million new cases / year

MELANOMAS (in US)
- Fewer than 5% of all skin cancers
- 75% of all skin-cancer-related deaths (10,000 deaths annually)
- 5-year survival rate
  - 99% if detected in its earliest stages
  - 14% if detected in its latest stages

→ Early detection is critical

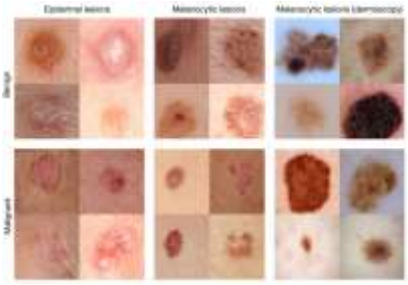
Source: Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017 Feb 2;542(7639):115-118.

130,000 labelled clinical images

LABELS

0. Cutaneous lymphoma and lymphoid infiltrates
1. Benign dermal tumors, cysts, sinuses
2. Malignant dermal tumor
3. Benign epidermal tumors, hamartomas, milia, and growths
4. Malignant and premalignant epidermal tumors
5. Genodermatoses and supernumerary growths
6. Inflammatory conditions
7. Benign melanocytic lesions
8. Malignant Melanoma

CLINICAL IMAGES



$$Y = f(X)$$

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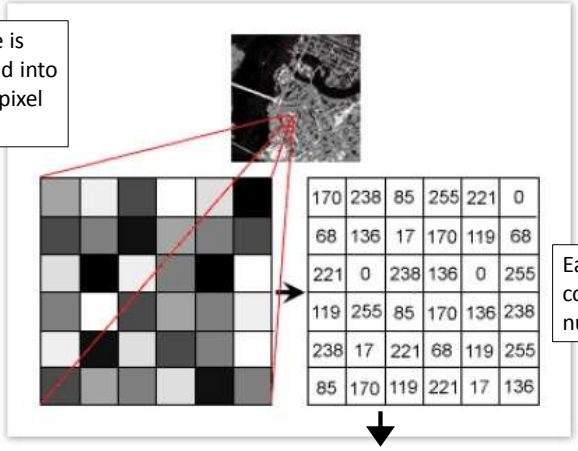
A simple image processing technique

Each image is transformed into a series of pixel squares.



170	238	85	255	221	0
68	136	17	170	119	68
221	0	238	136	0	255
119	255	85	170	136	238
238	17	221	68	119	255
85	170	119	221	17	136

Each pixel is converted to a number.

Each pixel is a predictor.

$X_1 = 170$
$X_2 = 238$
$X_3 = \cdots$

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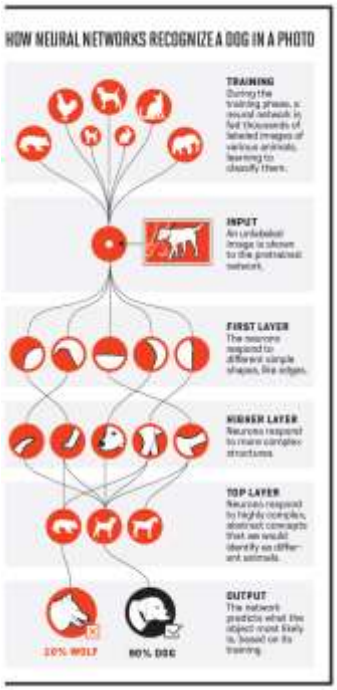
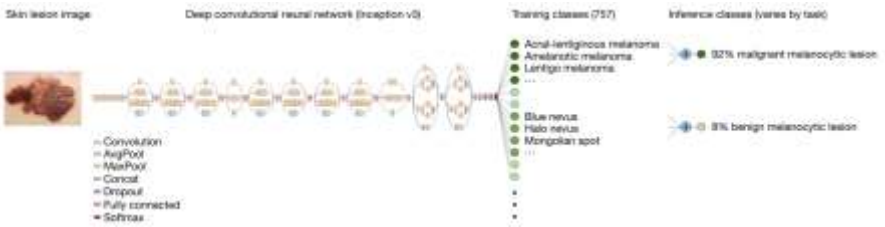
GoogleNet Inception v3 CNN

Pre-defined algorithm is **pre-trained** on non-health-specific images!

1.28 million images (1,000 object categories) from the 2014 ImageNet Large Scale Visual Recognition Challenge



Training and test



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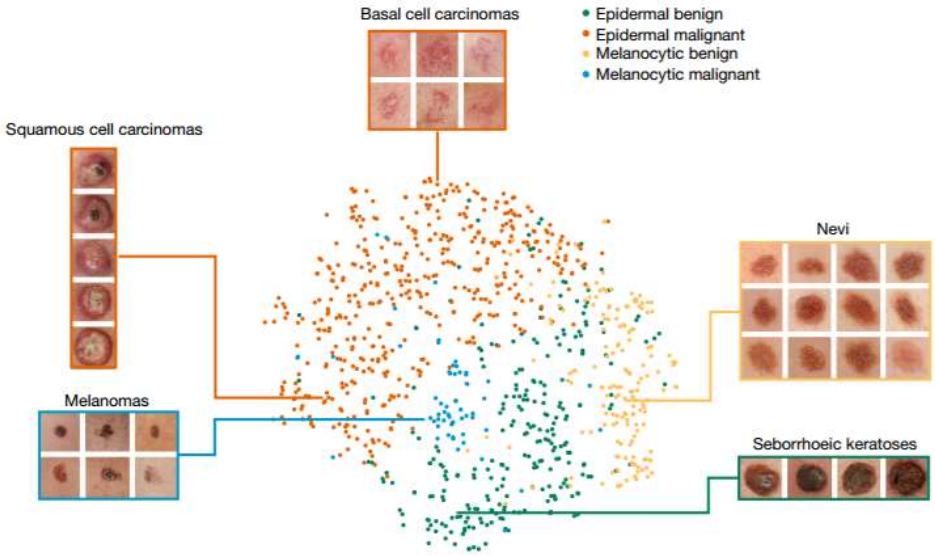

OBSERVATIONS (from the last layer)
- We see clusters of points of the same clinical classes
- Benign classes are separated from their malignant counterparts

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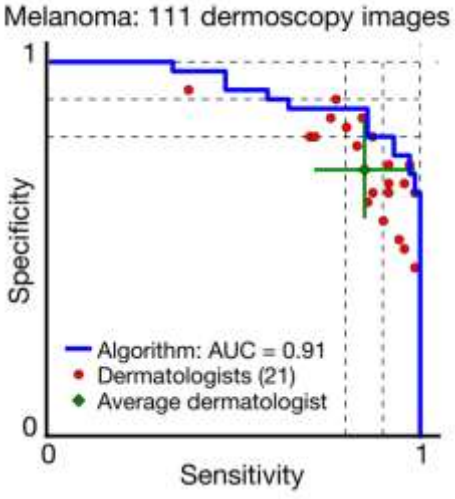
PERFORMANCE



$$\text{sensitivity} = \frac{\text{true positive}}{\text{positive}}$$

$$\text{specificity} = \frac{\text{true negative}}{\text{negative}}$$

CONCLUSION
The machine is on par with the performance of the dermatologists and outperforms the average.

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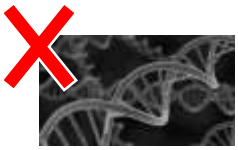
AI-BACKED PRECISION MEDICINE

Definition

This is NOT …

Social networks



Omic data

Connected devices

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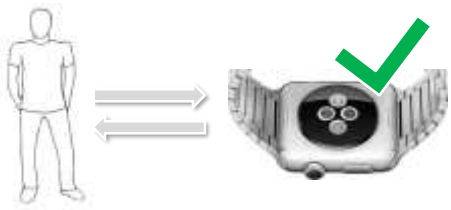
AI-BACKED PRECISION MEDICINE

Definition

PRECISION MEDICINE
Medical decisions are tailored to patient characteristics.

ARTIFICIAL INTELLIGENCE
Device that mimics human learning and reasoning.

Machine that can advice a patient with health behaviors … without human supervision!



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AI-BACKED PRECISION MEDICINE

	ADVANTAGES	DRAWBACKS
Manufacturer	- Shorter time, less expensive and less risky development (From 10 years – pill – to a few days – app – to reach the market) - High-performance tool (Sensitivity and specificity)	- Performance are data-dependent (Asthma understood by AI as a protective factor for pneumonia whereas the original study advised asthma patients to be treated in ICU) - Lower interpretability (« Black box » model) - Stronger competition (40,000 health-related apps are today available)
Payer	- Higher detection of false positive (Those often result in unnecessary invasive biopsies) and false negative (More lives are saved) - Easier to set up performance-based risk sharing agreement (Cheaper post-launch studies)	- Tests might be expensive - Tests might be over-/under-prescribed
Physician **Ophthalmology** **Otolaryngology (ENT)** **Radiology**	- Augmented clinical decision-making for specialists - Limited time dedicated by the specialist	- "Deskilling" = human expertise likely to disappear (14% decrease in diagnostic sensitivity when human readers are facing computer-aided detection) - "Demise of context" = lack of ability to assess patients holistically (Only visual and dermoscopic inspection of a skin lesion)
Patient	- Reaching underserved communities (6.3 billion smartphones will exist by 2021) - Health-promoting behaviors	- Data privacy (Sensitive patient information and data security breaches) - Responsibility (in case of false positive diagnosis …)

Cabitza F, Rasoini R, Gensini GF. Unintended Consequences of Machine Learning in Medicine. *JAMA*.2017;318(6):517–518. doi:10.1001/jama.2017.7797

Regulatory overview

TRADITIONAL DRUG DEVELOPMENT
Takes years
Applies on static products
Aims at being transparent

→ FDA/EMA walk the line between protecting the patient and avoiding over-regulation! →

AI-based HEALTH DEVICES
Need months
Always learning "on the fly"
"Black box" models

FDA AGENDA
2017 : Selection of 9 pilot partners for AI-related assessment (Apple, Google Verily, Fitbit, Johnson & Johnson, Roche, Samsung, Tidepool, Pear Therapeutics, Phosphorus)
2018 : FDA approves first AI software that can identify disease (no specialists needed).

MAIN NEW REGULATORY APPROACH
- Excellence rather than compliance (= companies with proven track-report enjoy fast-track approval)
- Breakthrough Device designation (= intensive interaction between manufacturer and FDA to optimize the device development)

https://www.wired.com/2017/05/medicine-going-digital-fda-racing-catch/
U.S. Food and Drug Administration. (2015). What is a medical device? U.S. Food and Drug Administration. 28 December [online]. Available at https://www.fda.gov/AboutFDA/Transparency/Basics/ucm211822.htm [Accessed 09 October 2017].

H2020 program – 7.5b€ to position EU as a top healthcare actor in the world

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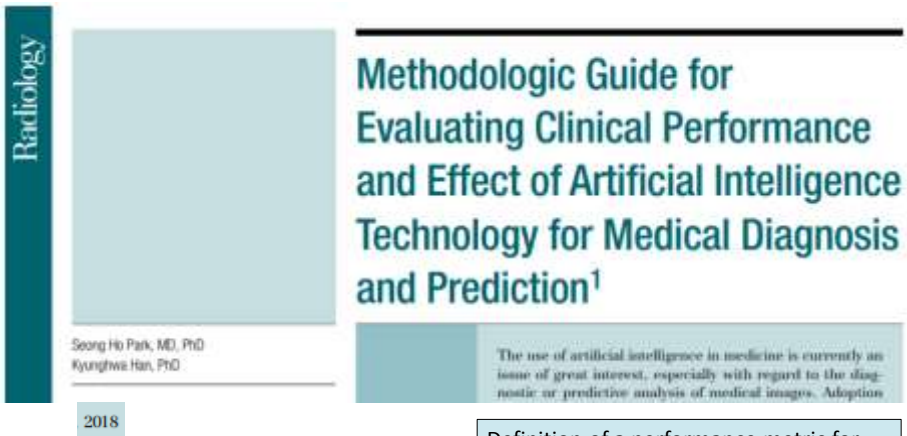
Clinical guidelines



Definition of a performance metric for AI-based medical diagnotic tool
- Sensitivity
- Specificity

Payer overview

Today, AI generates traction among payer bodies in Europe

New guidelines are being set up

→ Illustration: NIA and Alivecor

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REAL-LIFE EXAMPLES

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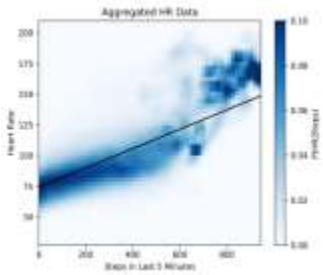
Alivecor and atrial fibrillations

ATRIAL FIBRILATIONS
- Irregular heart rhythm that is often abnormally fast
- 5-fold increase in the risk of stroke and 50% more at risk of death

AI SOLUTION
- Heart rate/activity discordance identifies times when a user should take an ECG.



There is a complex "**non-linear**" relation between heart rate and activity

Heart rate was outside the range which AliveCor predicted for the level of activity at that time.

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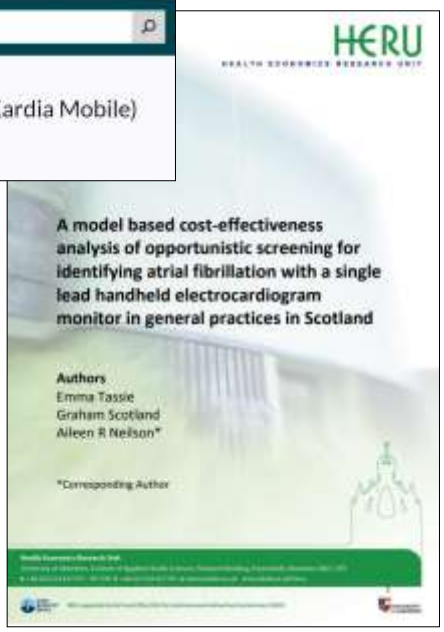
NICE National Institute for Health and Care Excellence

AliveCor Heart Monitor and AliveECG app (Kardia Mobile) for detecting atrial fibrillation


HERU

A model based cost-effectiveness analysis of opportunistic screening for identifying atrial fibrillation with a single lead handheld electrocardiogram monitor in general practices in Scotland

Authors
Emma Tassie
Graham Scotland
Aileen R Nelson*

*Corresponding Author

We looked at the UK system …

NICE Headlights

ALIVECOR
- Sensitivity = 98.5%
- Specificity = 91.4%

VS.

HUMAN PHARMACIST
- Sensitivity = 77%
- Specificity = 87%

COST CONSEQUENCES
- Fewer GP appointments
- More 12-lead ECGs checks
- More stroke prevention medications (e.g. warfarin)
- Less stroke-related event (e.g. hospitalizations)

From NICE: Lowres N and al., Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. Thromb Haemost. 2014 Jun

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Scottish Highlights

Simulation of the cumulative costs and life years of a cohort over a 30 year horizon

Strategy	Cost, £	Incremental cost, £	QALYs	Incremental QALYs	ICER
AliveCor	1,922.93	-	9.5496	-	-
Usual Care	2,005.98	83.05	9.5336	-0.0160	Dominated

AliveCor arm costs less than the comparator arm

AliveCor arm brings more QALYs than the comparator arm

Main assumptions
- High-risk population
- Patients in the comparator arm did not receive screening
- Screening with AliveCor costs £22.02 per patient screened.

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Pricing in the US

- Mostly NOT currently reimbursed by private insurers or Medicare
  - Eligible for payment with a Flexible Spending Account, Health Savings Account or Health Reimbursement Arrangement
  - Physicians who purchase device for use in office or bedside can submit for reimbursement with CPT code for 1-3 lead rhythm ECG with interpretation and reports
- Mostly sold directly to consumers (DTC)
  - One-time charge of $99 for basic service
  - Premium service for $10 a month (or $100 a year)
    - Includes features such medication tracking, unlimited storage, history of heart health data and the ability for customers to email EKGs to themselves and their doctors.

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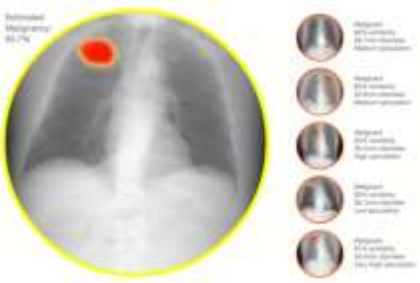
Enlitic and lung cancers

LUNG CANCERS
- 80% of patients in late-stages die
- If caught early, survival is nearly 10 times more likely
- Hardest cancer to detect in medical images

AI SOLUTION
- AI detects lung cancer nodules in chest CT images 50% more accurately than an expert panel of thoracic radiologists
- AI speed is 50,000 times faster than a human radiologist



ENLITIC
- Founded in 2014, $15 millions in funding
- Current positioning: AI technology "enables" radiologists (and do not replace them).
- Business model: take a cut of the profits realized by the clients that adopt the solution

Avoided biopsies and cancer-related events

$9 billions being spent in on radiologists
- Average radiologist's salary is $286,000 a year
- 1 radiologist per 10,000 people → 31,800 radiologists in the US

https://www.enlitic.com/press-release-10272015.html

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IDx-DR and diabetic retinopathy

DIABETIC RETINOPATHY
- If uncaught early, diabetic retinopathy can lead to vision loss.
- 50 percent of diabetic patients do not see their eye doctor on a yearly basis

AI SOLUTION
- FDA wanted sensitivity > 85% and specificity > 82.5%.
- IDx-DR passed the bar, with rates of 87.4% and 89.5 % percent, respectively.

"(…) IDx-DR makes a clinical decision, without someone like me being involved — it's fully autonomous."

Michael Abràmoff, opthalmologist and CEO

FDA News Release

FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems

For Immediate Release

Unlike other AI-based tools, IDx-DR is designed to make a directive, not a recommendation.

https://medcitynews.com/2018/02/ai-screening-tool-diabetic-retinopathy-makes-decision-not-recommendation/ https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm604357.htm

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IMPACT ON HEALTH ECONOMICS

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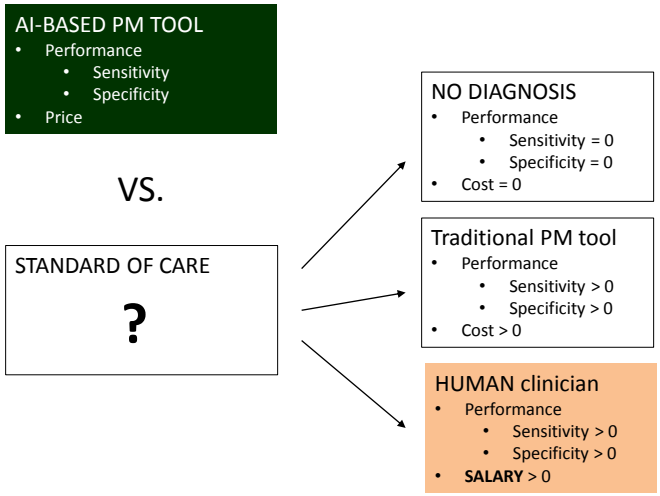
Redefining the standard of care



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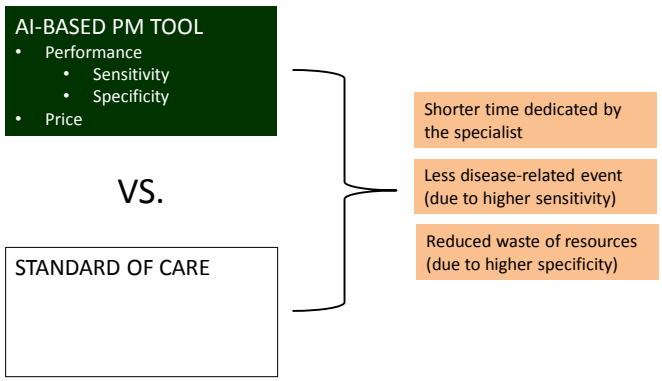
New claims of interest



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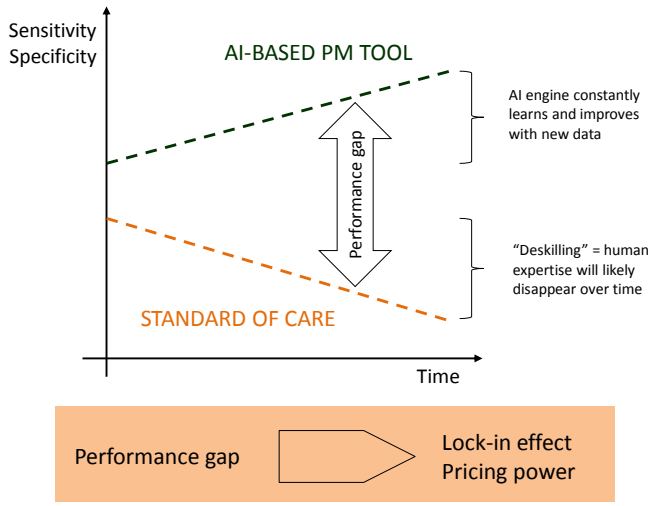
Increasing relative performance of AI-based PM tools over time



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CONCLUSION

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CONCLUSION

NEW TECHNOLOGY
- Lower interpretability
- Higher performance
  - Sensitivity
  - Specificity

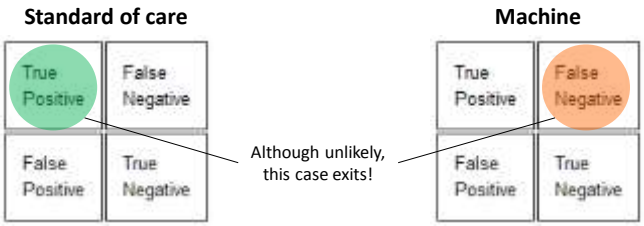
IMPACT ON MARKET ACCESS
- Regulatory
  - New skills needed
  - New way of thinking
- Payers
  - [On the short run] Cost burden will decrease
    - Less specialists
    - Shorter time dedicated by the specialist
    - Less disease-related event
    - Reduced waste of resources
  - [On the long run] Cost burden might increase
    - Lock-in effect
    - Pricing power

Q&A

Responsability

In case the machine goes wrong, who is responsible?

What about the case where the standard-of-care algorithm would have saved the patient?



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Data security

When you undergo diagnostic tests to determine the best way to treat your skin cancer, are you concerned your sensitive information will be collected by a machine?

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Being a health economist

In your opinion, if IA-based precision medicine tools enter the playground tomorrow, how would health economics be impacted?