MAI4CAREU | Master programmes in Artificial Intelligence 4 Careers in Europe

University of Cyprus

MAI643 Artificial Intelligence in Medicine

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January – May 2023

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Connecting Europe Facility

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No 2020-EU-IA-0087, co-financed by the EU CEF Telecom
under GA nr. INEA/CEF/ICT/A2020/2267423

Introduction to AIM and tracing its history

(largely adapted from V.L. Patel and T.A. Cohen's chapter in T.A. Cohen, V.L. Patel and E.H. Shortliffe (editors), Intelligent Systems in Medicine and Health: The Role of AI, Springer, 2022.)

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UNIT 1

Introduction to AIM and tracing its history

CONTENTS

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INTENDED LEARNING OUTCOMES

Upon completion of this unit on Introduction to AIM, students will be able to:

- Appreciate the importance of AI in medical informatics
- Overview the various topics that will be addressed in the course
- Emphasize on the importance of AI in different types of medical applications
- Provide examples of the use of ML and deep learning in medicine
- Overview the different medical task where AI is applied
- Identify and discuss the challenges of AIM considering the evolution of AIM through the years

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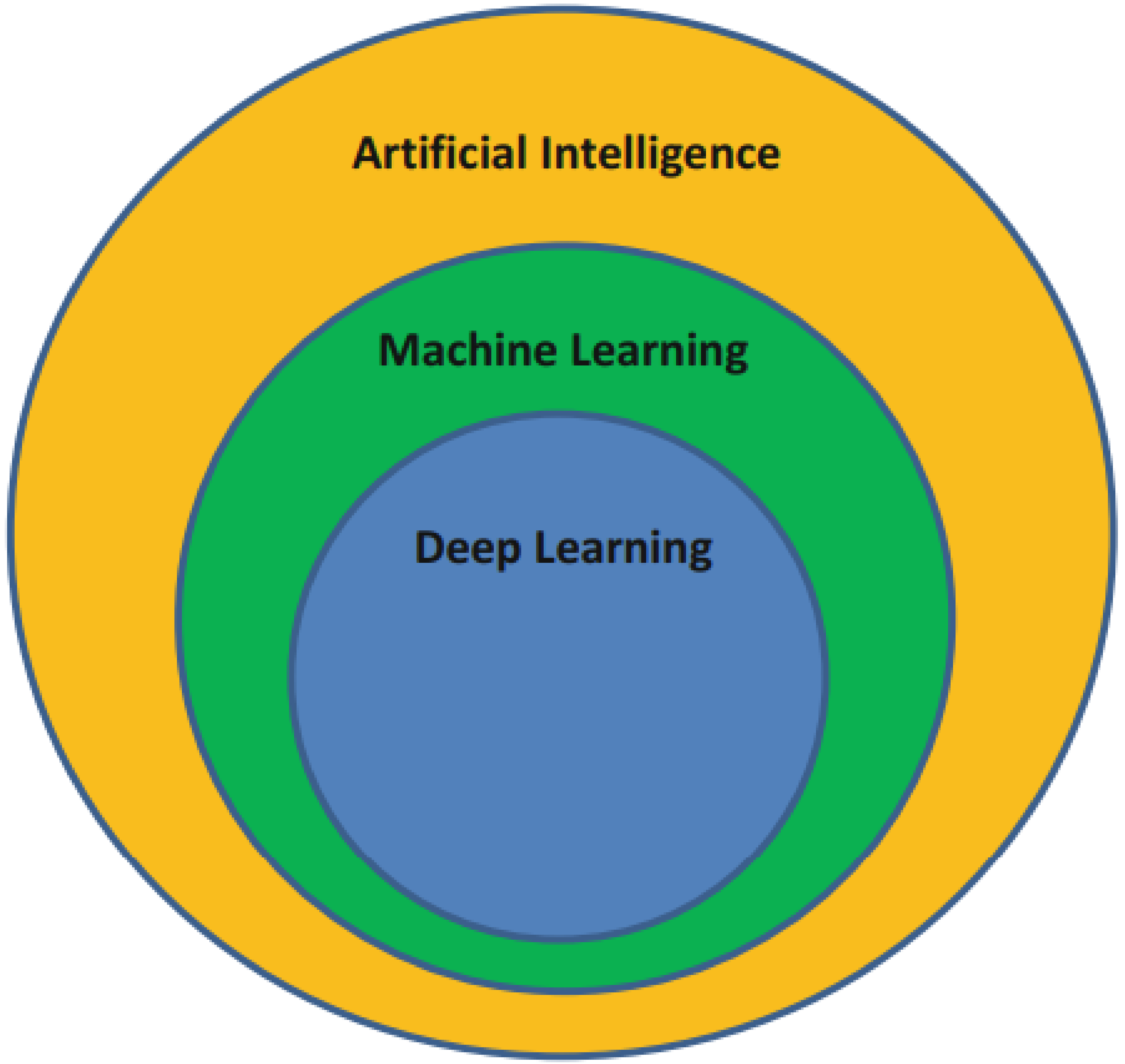
Artificial Intelligence (AI)

- AI is an emerging field
- Widely applied for decision making which normally requires human-level expertise.
- Machine learning (ML) is a subfield of AI that helps a system to learn from the environment automatically without any human intervention.
- Deep learning (DL) is a subclass of ML
  - ➢ A multi-layer network that provides the ability to understand the data from a lower-level all the way up to the upper-level.



AI in Medicine (AIM)

- AIM concerns the application of AI methods in healthcare.
- AIM being the automated accomplishment of tasks that would be challenging for a highly trained human.
- AI along with ML and DL methods has led to a huge impact in the medical domain.
- AI uses the different types of data (temporal data, genomic data, imaging data, signal data..) to extract the potential features/attributes that can be assisted for disease screening/diagnosis and prediction.
- AI in disease management helps people to have healthier and longer lives.

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Healthcare System

Not long ago, the health care system was perceived as being slow to understand information technology and slow to exploit it for its unique practical and strategic functionalities.

Now:

- mass storage of data (both locally and in the “cloud” – rise of Big Data)
- new methods for human-computer interaction
- electronic health records (EHR)
- personalization in patient treatment and monitoring
- mobile health application
- telemedicine
- medical decision-support systems

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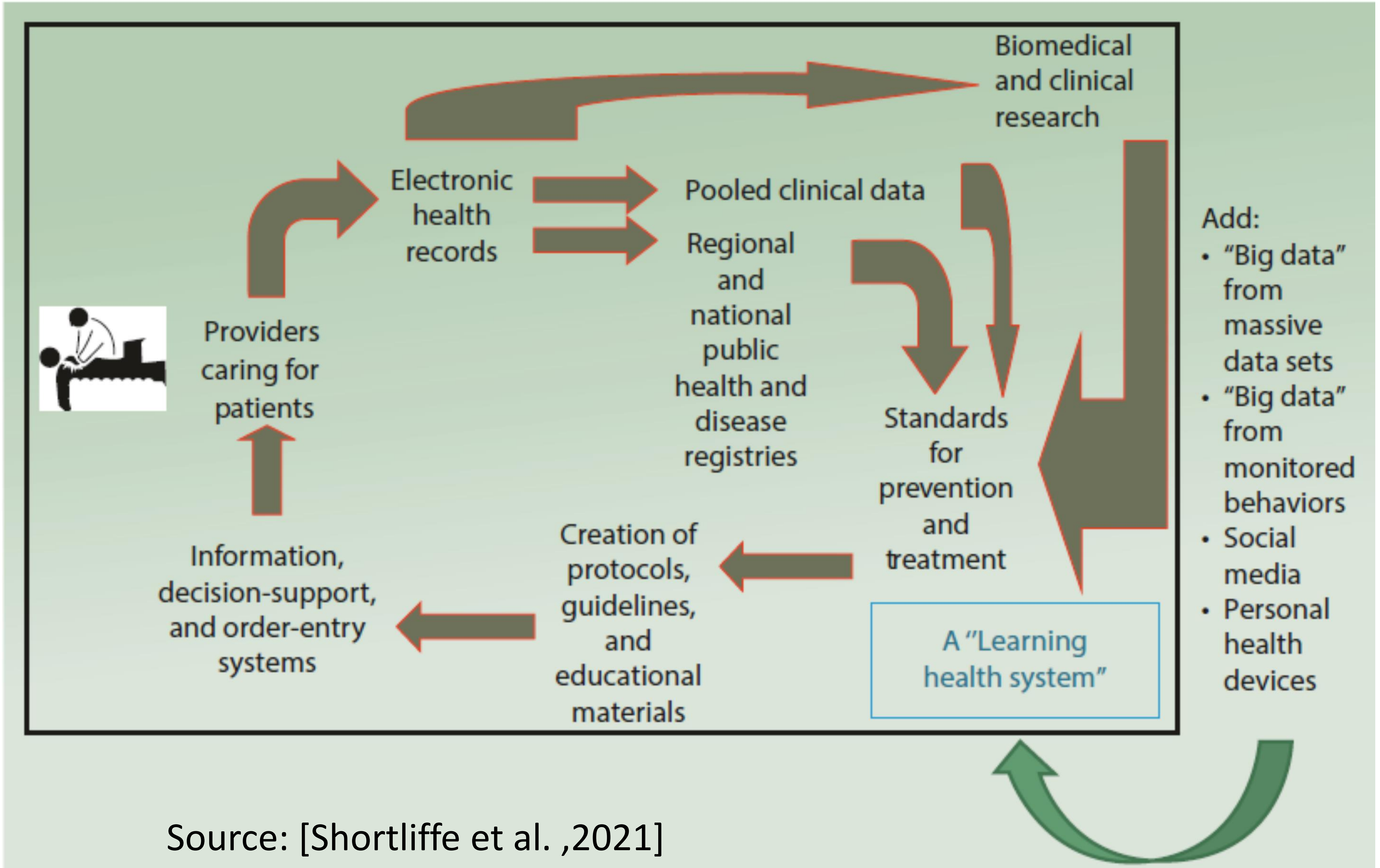
Unit 1



Source: [Shortliffe et al. ,2021]

Patients vs Clinicians (Communication)

- Medical knowledge is **incomplete** and there are no good treatment options, and sometimes **no good diagnostic criteria**, for some conditions. E.g., Parkinson's disease can be managed, but is still not curable after decades of research.
- Information about an individual patient is almost **always incomplete and mostly uncertain** E.g., false positive and false negative test results are expected for almost every diagnostic test.
- Patients' medical problems exist within a larger **emotional, social, economic, and cultural context**. E.g., the most effective treatment options may be unaffordable or unacceptable to an individual.

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Patients vs Clinicians

- Clinicians are expected **to learn from their own, and others', experience** (both positive and negative). E.g., continuing to recommend a failed treatment is reason for the patients not to trust them.
- Clinicians at the level of recognized specialists **are expected to deal with unique cases** for which there are neither case studies nor established diagnostic or treatment wisdom. E.g., primary care providers refer recalcitrant cases to specialists for just these reasons.
- **Communication between patients and clinicians is imperfect**. E.g., language is full of ambiguity, and we all have biases in what we want to hear or fear most.

→ **The problem of providing health care is overwhelming -> significance of using AI**

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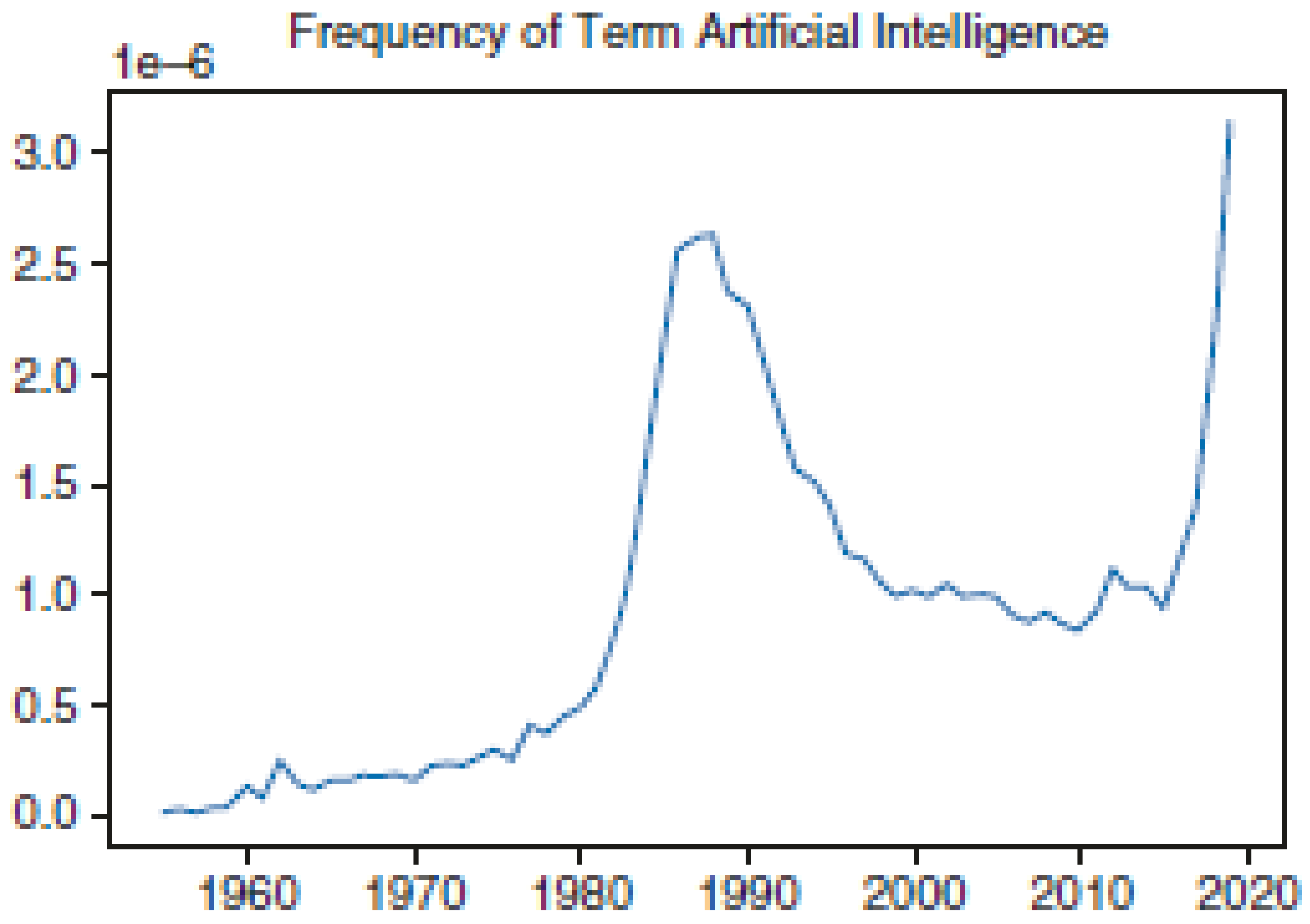
The Rise of AIM

- In the mid-1980s, there was a first peak where the term AI appears in books
  - Followed by a period of rapid progress in the development of knowledge-based expert systems.
- Diagnostic reasoning in medicine was one of the first focus area of such systems providing proof that medical decision making has had an influence on AI research for decades.
- The last 20 years, due to the growth of neural networks and deep learning, there was also a rapid growth in AIM applications.

→ **High-profile medical demonstrations of diagnostic accuracy i.e. in medical images**



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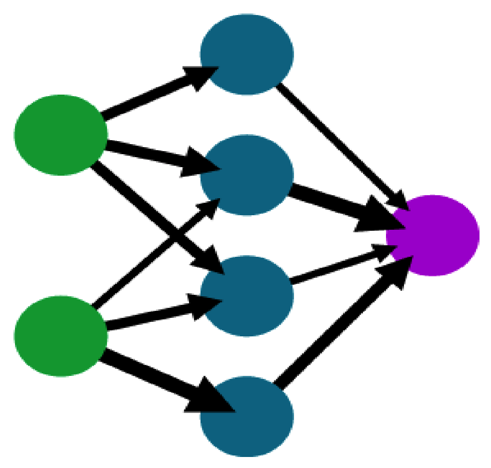
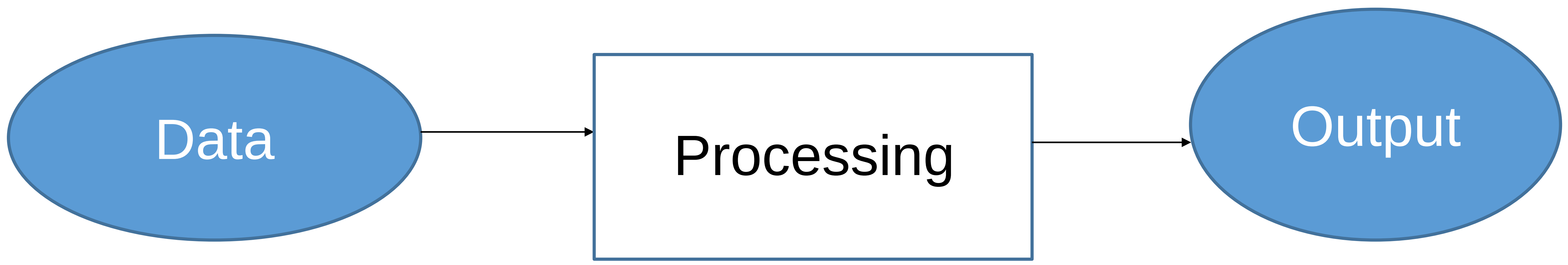
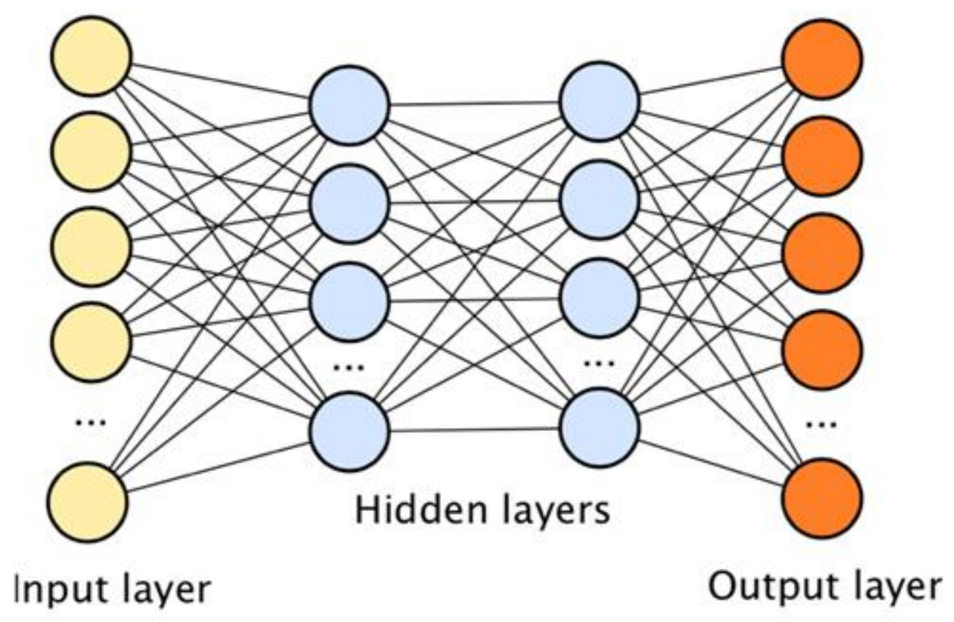
Evolution of ML







1950s–1970s
Neural networks

The first machines with a cognition

1980s–2010s
Machine Learning

Today

Deep Learning

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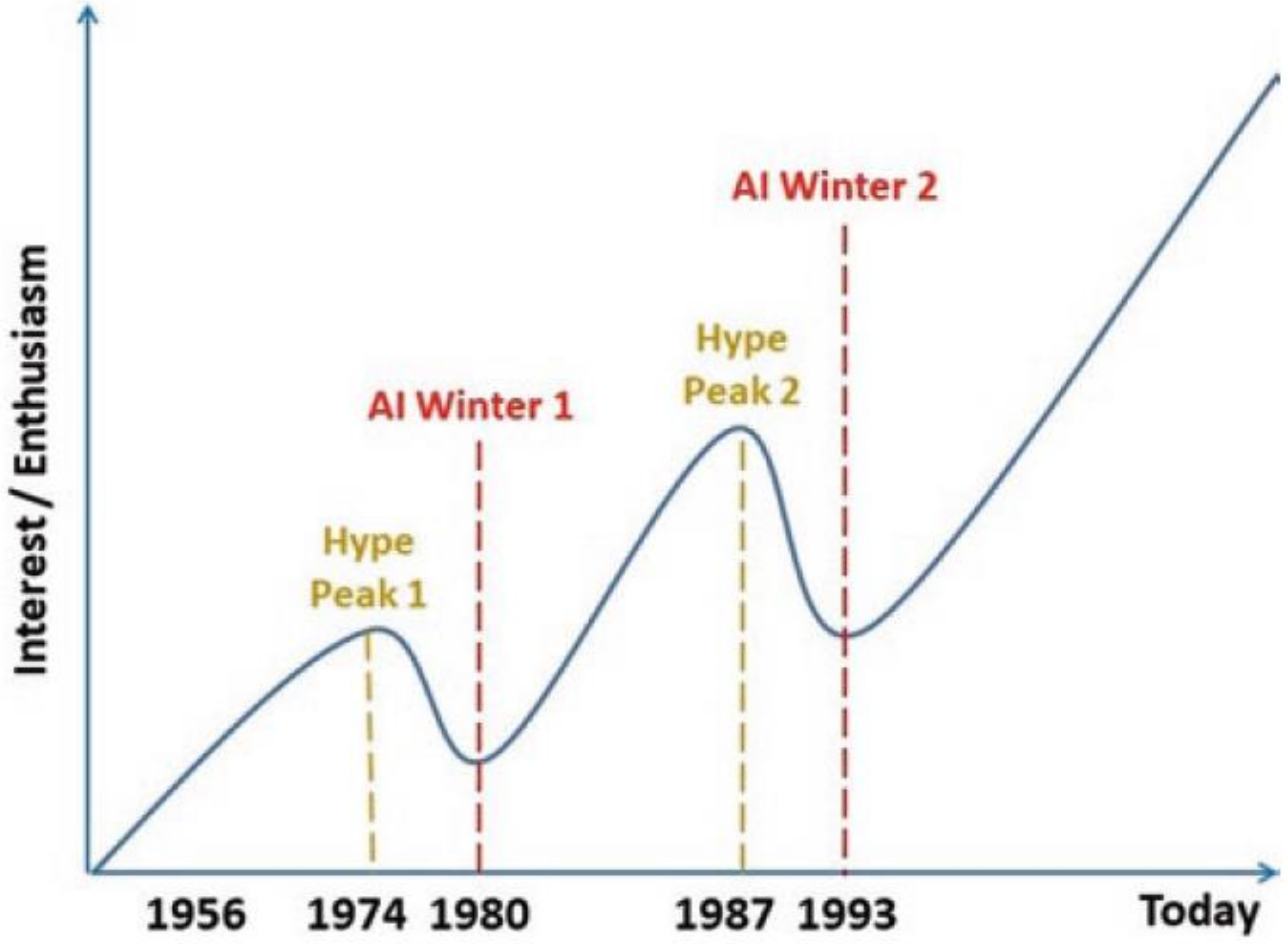
Evolution of AI in Medicine



Source: Shortliffe et al. 2022

Graphic shows the two periods often called AI Winter, one at the end of the 1970s (which had little impact on AIM) and the second in the late 1980s and early 1990s (which did affect AIM work for several years)

Evolution of AI in Medicine

- **1965:** A chatbot program "Doctor" or "Eliza" which attempted to provide psychiatric assessments.
  - Focus on maintaining the conversation intelligently rather than actually reaching a psychiatric diagnosis
  - Became a popular easy-to-use toy at AI centres
- Few years later, a psychiatrist develop a conversational AI program, known as "Parry" that would simulate the behavior of a patient with paranoid schizophrenia.
  - In **1972**, Eliza and Parry had a conversation (**here**)

Evolution of AI in Medicine

- **Dendral project:** Started in the early 1950 (U. Stanford) but finalized in early 1970 where has also been applied in other domains.
  - Generate the entire exhaustive set of potential structures for any organic compound (mass spectroscopy).
  - Focus on knowledge representation and production rules
  - **Meta-Dendral** by Bruce Buchanan – infer rules from lots of examples of mass spectra and the corresponding compounds of known structure.
- **Starting in 1970**, Bayesian probability theory and other statistical methods have been used to medical diagnosis and patient management.
  - Integration of human-knowledge with statistical methods

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Influential AI Medical Applications (early 1970)

- DENDRAL (1970)
- INTERNIST-I (1974)
  - Rule-based expert system designed at the University of Pittsburgh
  - Diagnosis of complex problems in general internal medicine
- MYCIN (1976)
  - Rule-based expert system designed to diagnose and recommend treatment for certain blood infections
  - IF-THEN rules
  - Outperform even human experts in some cases

Influential AI Medical Applications (early 1970)

- CASNET (Causal ASsociational NETwork) (1978)
  - Diagnosis and treatment of glaucoma-related diseases

- First approaches for decision support models for medical diagnosis and patient management

- **More details will be given in Week 2**

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Knowledge-based and Machine Learning-based AIM

- **By the end of 1970**, the AIM field focus on knowledge representation notion as the most important part of an AIM system
- **By the early 1980s** there was a rapid growth of medical expert systems – knowledge-based systems where knowledge is provided by medical practitioners
- In the **1990**, there was the largest growth in AIM due to the rapid growth of machine learning methods

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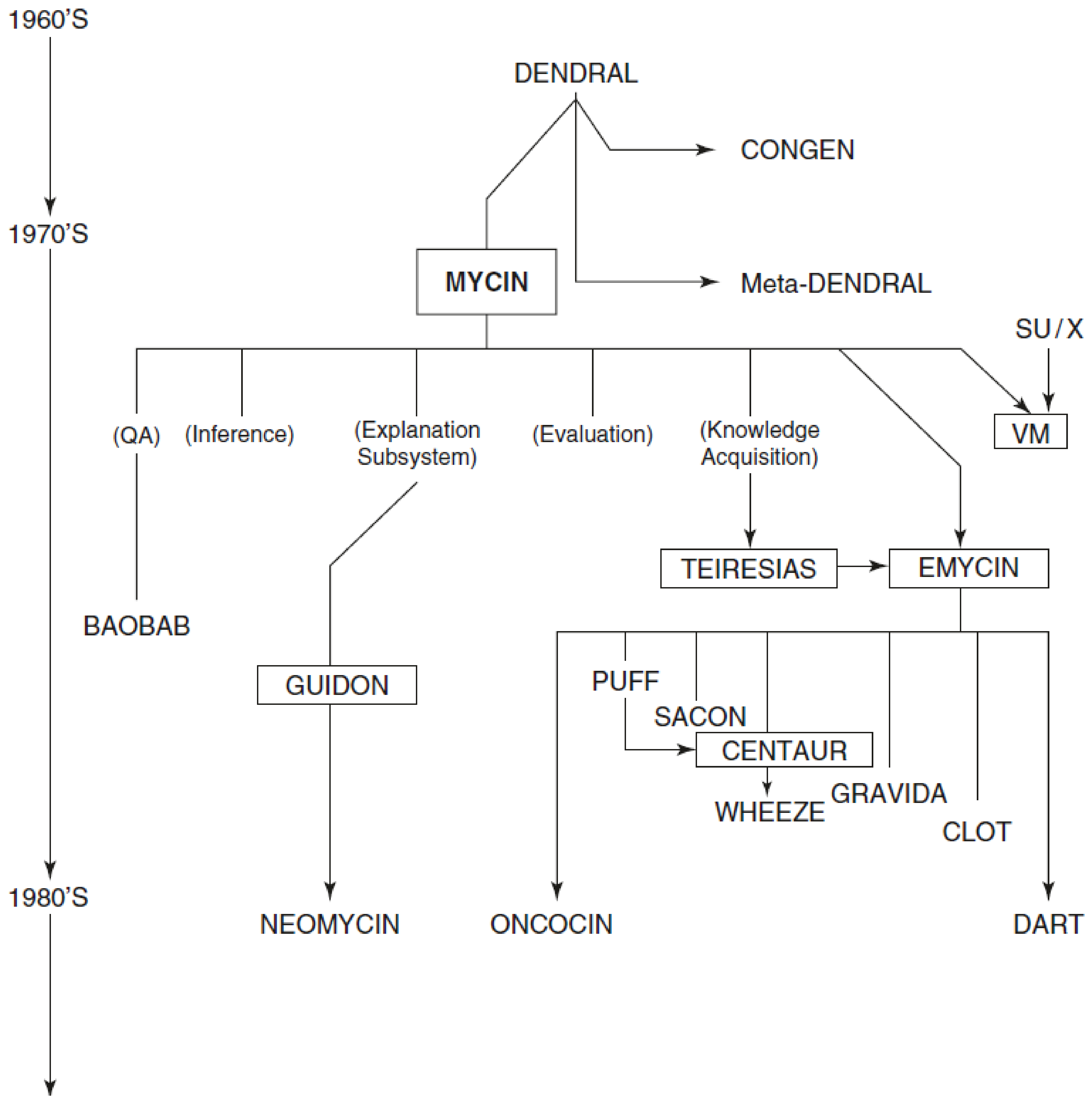
AIM in 2000- Now

- **The early 2000s: Human Genome Project**
  - Rise interest in bioinformatics (translational bioinformatics)
- **2010:** ImageNet – large image database
- **By 2012**: increase in medical imaging informatics, text and speech processing of clinical notes, due to the powerful hardware with huge computational capabilities i.e. cloud computing storage and the appearance of deep learning and the large amount of data stored in electronic health records
- In **the last few years**: concerns arise around explainability and transparency of AIM systems focusing on preventing bias and ensuring fairness in medical decision making.



Source: Shortliffe, 2022 - Just as MYCIN drew inspiration from the earlier DENDRAL work, several other Stanford research projects built on the methods and concepts that MYCIN had introduced. This diagram shows many of these projects and their ancestry. Those projects depicted in rectangles were themselves the basis for computer science doctoral dissertations (VM: LM Fagan; TEIRESIAS: R Davis; EMYCIN: W van Melle; GUIDON: WJ Clancey; CENTAUR: J Aikins)

AIM Application Areas

- **Clinical informatics:** including medicine, nursing, dentistry, and veterinary care.
- **Public health informatics:** similar methods are generalized for application to populations of patients rather than to single individuals.
  - i.e. applications/treatments that occurred in response to the COVID-19
- **Imaging informatics:** radiology and other image management and image analysis domains such as pathology, dermatology, and molecular visualization.
- **Bioinformatics:** informatics methods applying at the molecular and cellular levels.

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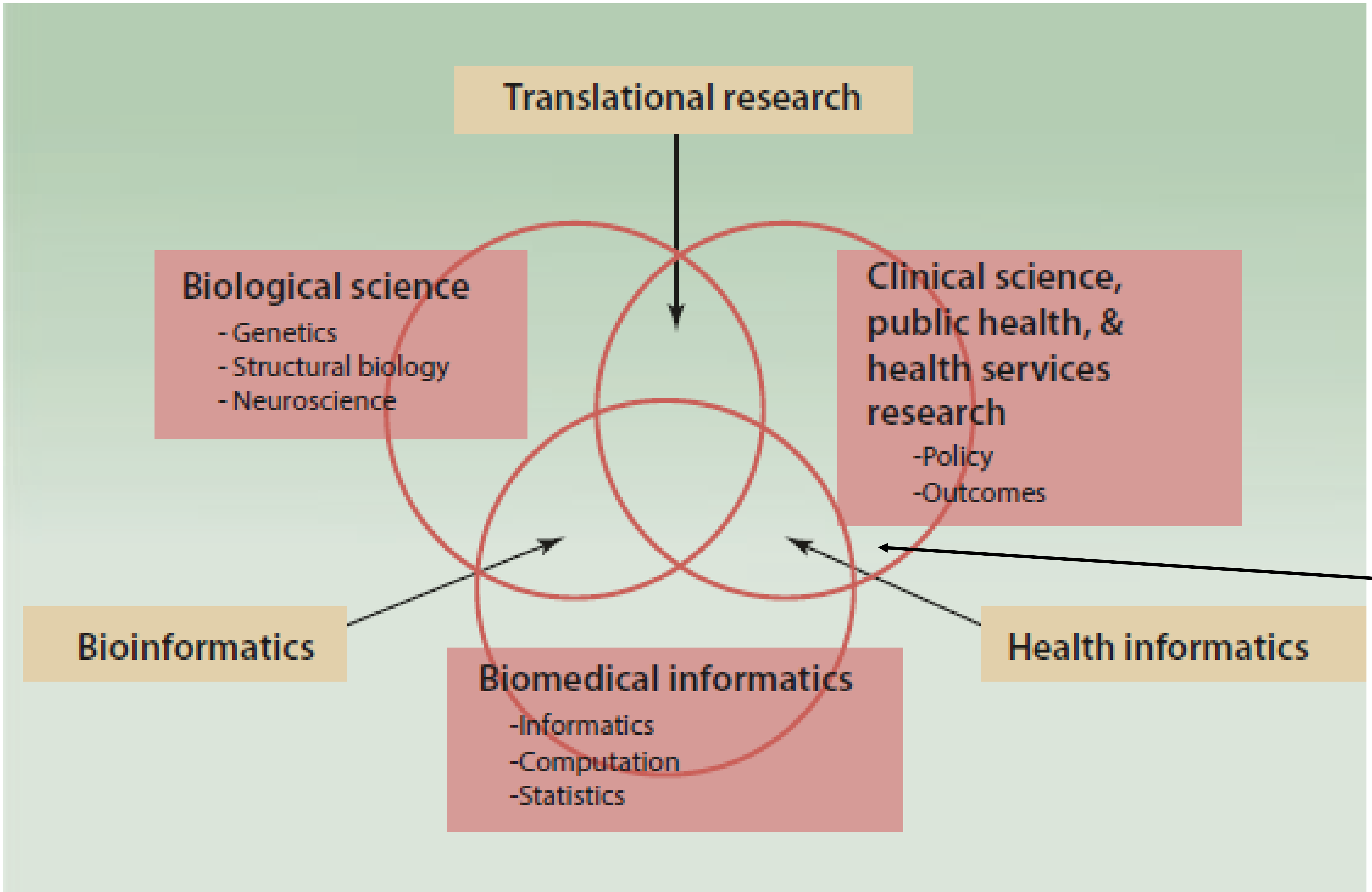
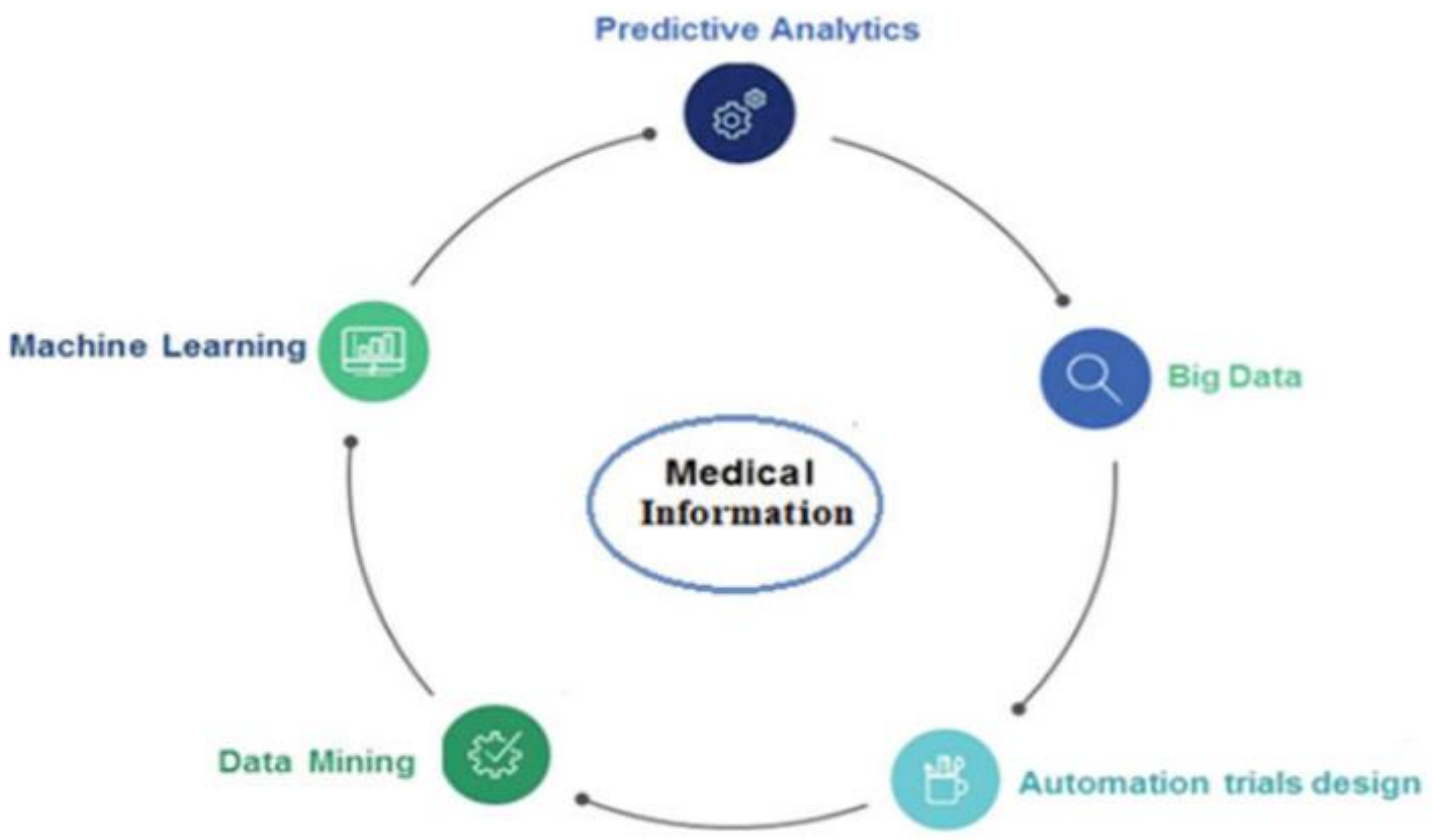
Unit 1



[**Source:** Shortliffe et al. 2021 - Adapted with permission from a diagram developed by the Department of Biomedical Informatics at the Vanderbilt Medical Center, Nashville, TN]

Cognitive Informatics

Role of Machine Learning in Medical Practice



Source: Linh N.T.D. & Lu Z., 2021.

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Role of Machine Learning in Medical Practice

- A diverse collection of data such as **basic demographics, identified disorders**, and a wealth of clinical knowledge such as findings from laboratory tests are included in medical records.
- For patients with chronic conditions, a long and comprehensive history of data on a variety of health metrics may be available.
- Patient records information may be mixed with outside data.
- Models can be developed and trained to predict several outcomes of interest with this rich data about a patient as well as their environment.
  - ➢ **Predictive models:** predict disease progression, which can be used for disease management and planning.
  - ➢ Predictive models may also alert clinicians about patients who may need treatments.

Types of ML Methods in AIM

- Unsupervised learning – clustering methods (especially for analyzing signal data).
- Supervised learning methods – for classifying a disease.
- Real-time analytics – processing of longitudinal data.
- Deep learning – especially for clinical image data analysis and big data.
- Natural language processing techniques for extracting information and knowledge from text data i.e. clinical notes.

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Knowledge-based vs ML - AIM Systems

- Knowledge regarding the medical domain is derived from clinical experts
- Encoded knowledge (including probabilistic estimates or uncertainty) is formalized using **knowledge representation** approaches
- ML models learn from the training data but also consider the encoded knowledge

→ **increases interpretability**

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Neural Networks and AIM

- Due to their ability of dealing with **big data** and their increasing computational power, they have been used a lot in AIM applications.
- Do not explicitly model human knowledge → **difficult to explain themselves**.
- NN models can learn to make impressively **accurate predictions**, especially when large data sets are available for training**, but systems leveraging explicitly modeled human knowledge are much better positioned to explain themselves**.
- **Explanation** has long been recognized as a desirable property of AI systems for automated diagnosis, and as a prerequisite for their acceptance by clinicians [**more on this on Week 12**]

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Unit 1

Box 1.1 An explanation provided by the MYCIN system in response to a user entering "WHY": From Shortliffe et al. 1974 [7]

- **WHY
- [1.0] It is important to find out whether there is therapeutically significant disease associated with this occurrence of ORGANISM-1.
- It has already been established that:
- [1.1] the site of the culture is not one of those which are normally sterile, and
- [1.2] the method of collection is sterile
- Therefore, if:
- [1.3] the organism has been observed in significant numbers
- Then: there is strongly suggestive evidence (.9) that there is therapeutically significant disease associated with this occurrence of the organism
- [Also: there is strongly suggestive evidence (.8) that the organism is not a contaminant]

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Deep Learning and AIM

- Deep learning models - the lower layers of a network can learn to represent incoming data
  - to extract useful representations for one task can often be learned from training on another related one.
- **Transfer learning:** the ability to apply information learned from one task or data set to another
  - A standard approach to classifying medical images.
  - i.e. adding a classification layer to a deep neural network that has been pretrained on the task of recognizing non-medical images in ImageNet
- Ability to train on **EHR data** to predict in-hospital mortality, unplanned re-admission, prolonged length of stay, and final discharge diagnosis.

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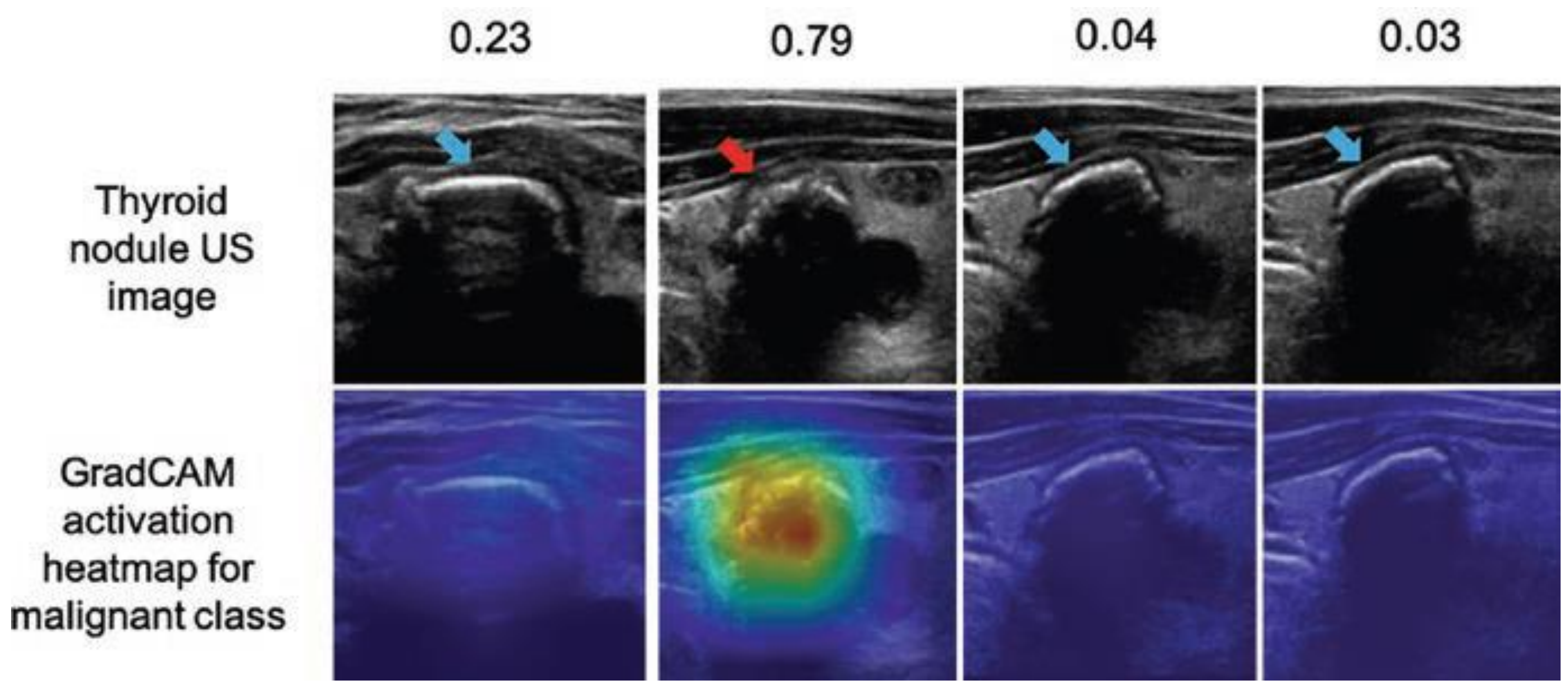
Deep neural network: Detection of thyroid cancer



From Shortliffe, 2022: Recognition of a subtle diagnostic cue by a deep neural network trained to detect thyroid cancer in different ultrasound images of the same nodule. Each image (top row) is annotated with the probability of malignancy according to the model, and is paired with a visualization of the pixels attended to by the deep learning model when making a prediction for whether an image is in the “malignant class”.

Benefits of AI in Medical-Decision Making

- Increased quality of health care and enhanced health outcomes
- Improved efficiency, cost-benefit and patient satisfaction
- Patient specific or generalised
- Based on expert knowledge (expert systems)
- Provide support to physicians since there are limited resources

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Benefits of AI in Medical Practice

- The ability to recognise diagnostically important features from different types of data
- Capable of answering clinical questions accurately based on **written clinical notes** and the computational processing for decision support.
- High accuracy in predicting a disease or the severity of the disease due in part to the **large volume of digitized medical data** and the widespread use of **digital platforms for image storage** and retrieval.
- A strong indicator of the commercial potential of AI-based systems in medicine is the emergence of **regulatory frameworks** for their application in practice, with several AI systems already **approved for medical use in the United States and Europe**.

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Limitations of AI in Medical Practice

- ML models must be embedded in systems that are both **usable** and **acceptable to clinicians**.
- The design of AI systems should be **motivated by the needs of clinicians**, which are best understood in the context of the processes and **environmental constraints** in which they work.
- **Accuracy** comes at the cost of **interpretability**

	Demonstration		Impact
1	Need	5	Management
2	Expert-level performance	6	Patient outcome
3	Usability	7	Cost-effectiveness
4	Acceptance by clinicians		

Overview: seven considerations for system evaluation
[Shortliffe and Davis 1975]

Human/AI Collaborative Systems

- The performance of human beings and machines working together can result in **better diagnostic accuracy** than either machines or human beings alone.
- To maximize the effectiveness of the system, considering both the **accuracy of model predictions and the time required for a human to validate them**.
- Human input might resolve uncertainty
- Easier for medical practitioners to trust AIM system
- Patient-centric systems
- **Cognitive informatics (CI)** provides a basis to consider the relationship between AI technologies and human intelligence.

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Applications of AI in Biomedical Informatics

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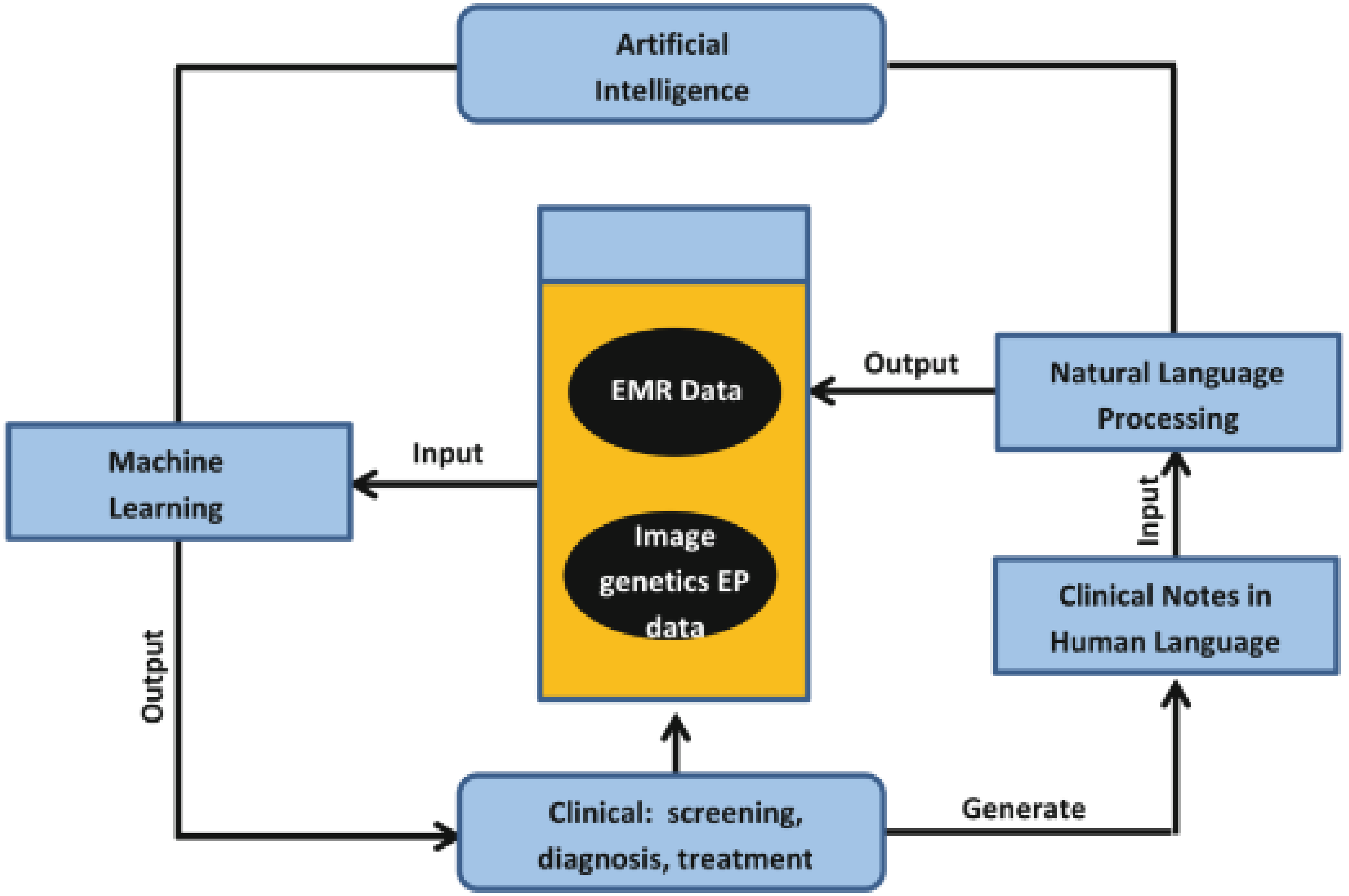
Disease Diagnosis using AI

- May create many fears that AI could lead to the reduction of clinical expertise
- In contrast, these approaches will benefit the clinicians to make better and informed decisions
  - especially when there is an enormous amount of data and different types of data to be analyzed.
- AI can help the clinicians to detect early the disease and make a treatment plan
- Identification of characteristics/trends (images/text data) that improve the accuracy of diagnosis.
- ML can be introduced to help doctors save time by identifying diseases in their initial stages.

Unit 1



Overall process of the application of AI in disease prognosis and diagnosis [From Saxena et al. 2021]

Examples of AI applications for medical diagnosis

- Most public medical domains: **Cancer, diabetes detection, brain tumours**.

A **2016 paper** in the **Journal of the American Medical Association** describes an impressively accurate deep learning system for the diagnosis of diabetes-related eye disease in images of the retina. [Gulshan et al. 2016]

A **2017 paper** in **Nature** describes the application of deep learning to detect skin cancer [Esteva et al., 2017].

  - Identifying two types of neoplastic skin lesions.
  - Over 125,000 images in each study
  - The model pre-trained on over 1.25 million non-medical images labeled with 1000 object categories on over 1.25

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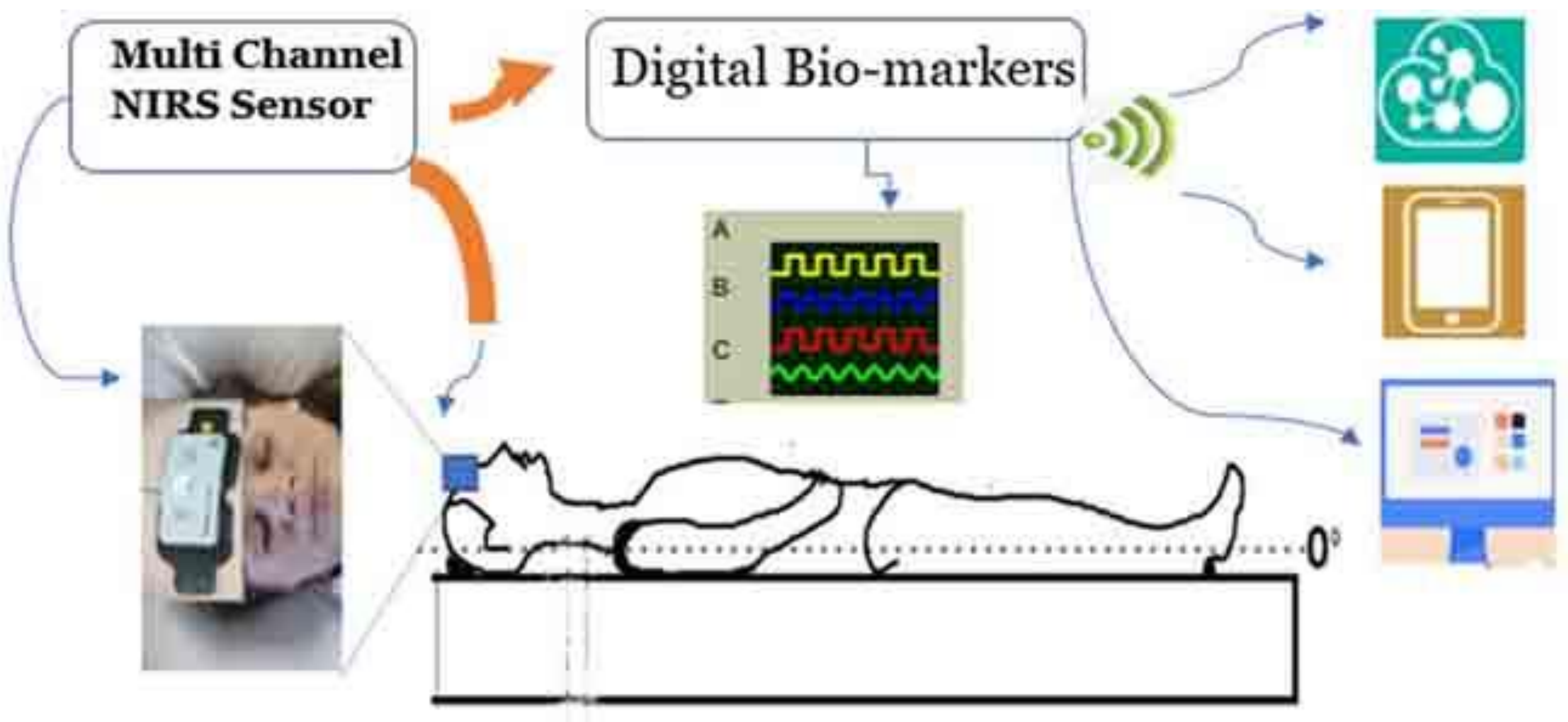
Examples of AI applications for medical diagnosis

- Early diagnosis of cardiovascular disorders using the image data of cardiac patients i.e. CT scan and ECG scan data [Dilsizian and Siegel 2014].
- A device was built that helps in the early diagnosis of stroke using ML algorithms
  - Early diagnosis of stroke in patients [Villar et al., 2015, Ahirwar et al., 2022]



Drug Discovery

- IBM and Google began other health ventures by applying machine learning to find medications.
  - IBM Watson for drug discovery
- Deep learning techniques have been widely used for drug discovery.
- It is possible to process data from millions of test cases within months or hours.
- It helps to determine the drug’s efficiency by data collection.
- Therefore, it is possible to launch a successfully tested vaccine or drug in less than a year with the assistance of ML.

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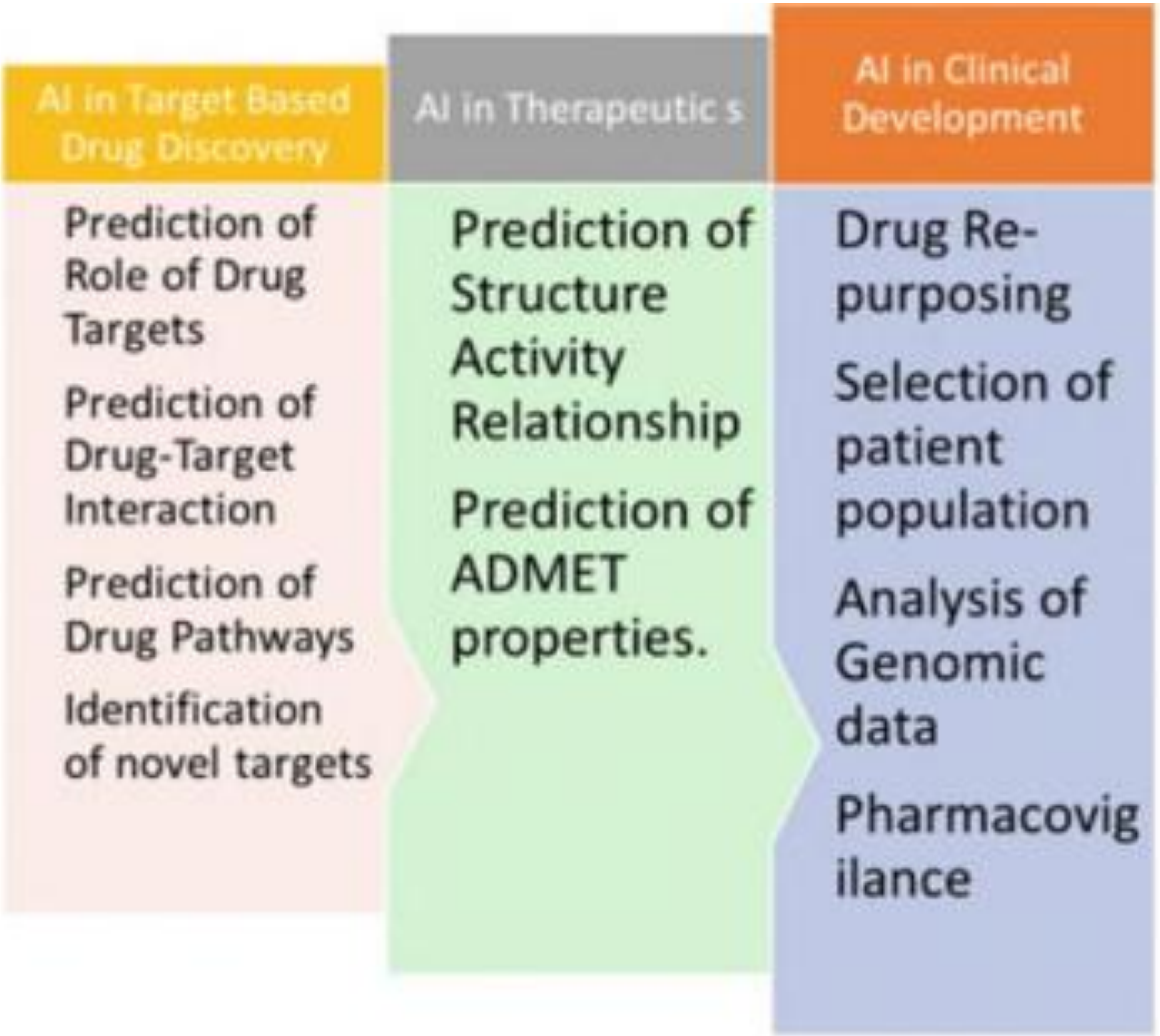
Unit 1



From: Saxena et al. 2021

Examples of AI in Drug Discovery

- Deep learning has been applied to suggest drug compounds and accurately predict the drug properties by analyzing the toxicity of the drugs for risks in its administration [Mohs and Greig 2017]
- AI-based platform developed by IBM Watson for discovering drug to treat amyotropic lateral sclerosis (ALR) [Bakkar et al. 2018].

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Disease Monitoring and Prevention

- ML used for the early identification and monitoring of chronic diseases.
  - Use of wearable devices and online apps for distant monitoring of patients
- AI has been used extensively by the healthcare industries to change patient’s lives and forecast illnesses at an early stage.
- With improvements in medical image processing, it is possible for doctors to recognize microscopic tumours, otherwise be impossible to spot.

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Examples of Applications of AI in Disease Prediction

- Prediction of cardiovascular risk factor status from retinal fundus photographs [Poplin et al. 2018]
- Prediction of 3-D protein structure from an amino acid sequence [Jumper et al., 2021]
- Identify the most potential biomarkers that will help to predict the progression of prostate cancer. [Pawar et al. 2020]
- Fitness trackers, step counters, health apps, sleep sensors, pocket ECG help to collect data and monitor patients.

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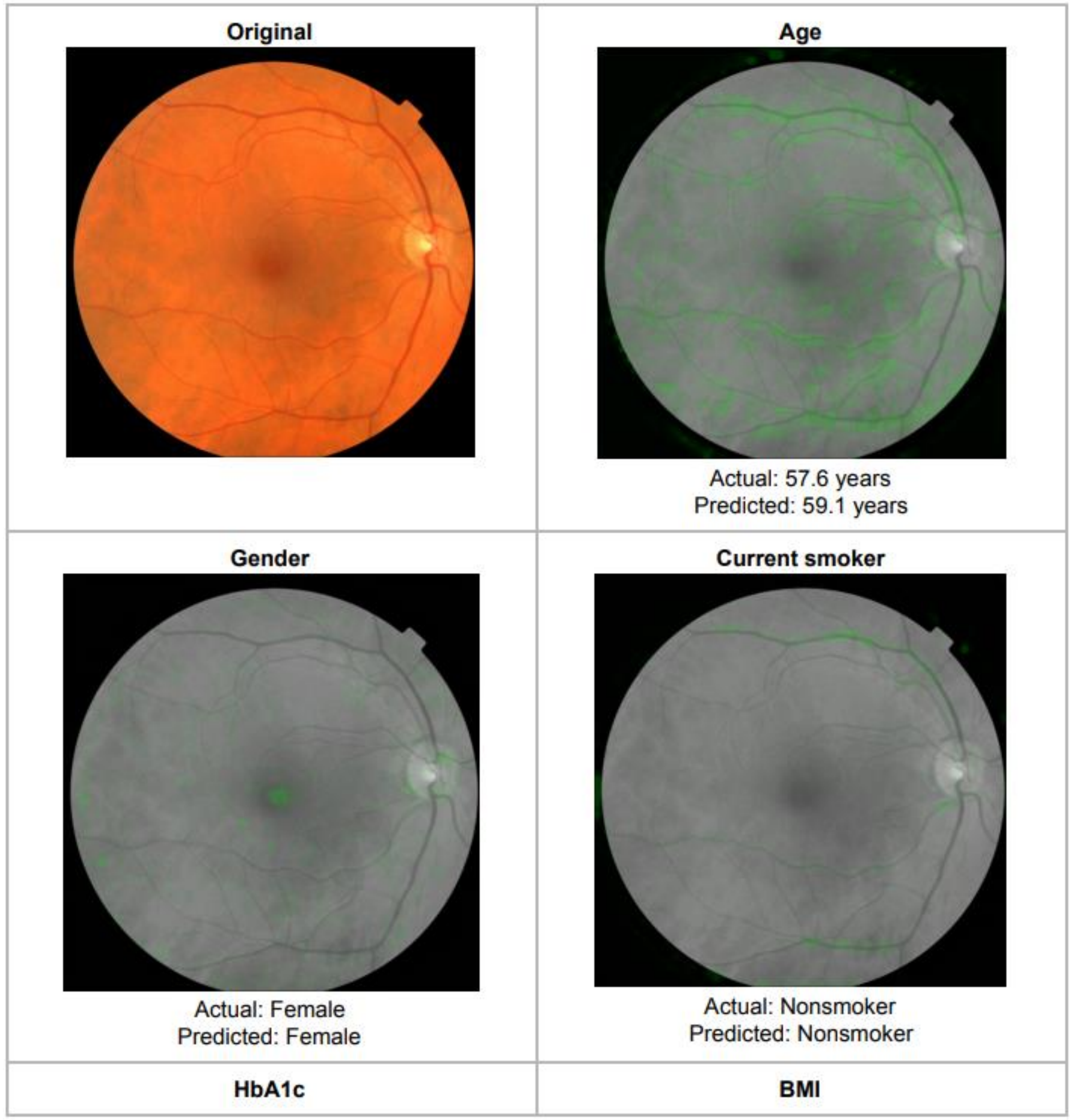
Unit 1

	Development Set		Clinical Validation Set	
Characteristics	**UK Biobank**	**EyePACS**	**UK Biobank**	**EyePACS-2K**
Number of Patients	48,101	236,234	12,026	999
Number of Images	96,082	1,682,938	24,008	1,958
Age: Mean, years (SD)	56.8 (8.2)	53.6 (11.6)	56.9 (8.2)	54.9 (10.9)
Gender (% male)	44.9	39.2	44.9	39.2
Ethnicity	1.2% Black, 3.4% Asian/PI, 90.6% White, 4.1% Other	4.9% Black, 5.5% Asian/PI, 7.7% White, 58.1% Hispanic, 1.2% Native Am, 1.7% Other	1.3% Black, 3.6% Asian/PI, 90.1% White, 4.2% Other	6.4% Black, 5.7% Asian/PI, 11.3% White, 57.2% Hispanic, 0.7% Native Am, 2% Other
BMI: Mean (SD)	27.31 (4.78)	n/a	27.37 (4.79)	n/a
Systolic BP: Mean, mmHg (SD)	136.82 (18.41)	n/a	136.89 (18.3)	n/a
Diastolic BP: Mean, mmHg (SD)	81.78 (10.08)	n/a	81.76 (9.87)	n/a
HbA1c: Mean, % (SD)	n/a	8.23 (2.14)	n/a	8.2 (2.13)
Current Smoker: %	9.53%	n/a	9.87%	n/a

Baseline characteristics of patients in the dataset of UK Biobank

Source: [Poplin et al. 2018]

Unit 1



Sample retinal image from the UK Biobank dataset in color. Remaining images: same retinal image, but in black-and-white. The soft attention heatmap (Methods) for the each prediction is overlaid in green, indicating the areas of the heatmap that the neural network model is using to make the prediction for this image. [Poplin et al. 2018]

Personalized Medicine

- Or ***precision medicine***
- **Translational bioinformatics** is the field studying the analysis of genetic information of individuals for personalized treatment.
- **Genomic analysis** is part of the daily decision-making process for medical treatment.
- It will help to **optimize treatment**, save lives, and decrease costs by **finding connections and recognizing patterns and trends within the data**.
- Data collection using **device/remote monitoring and mobile health** for patient monitoring and personalized treatment.

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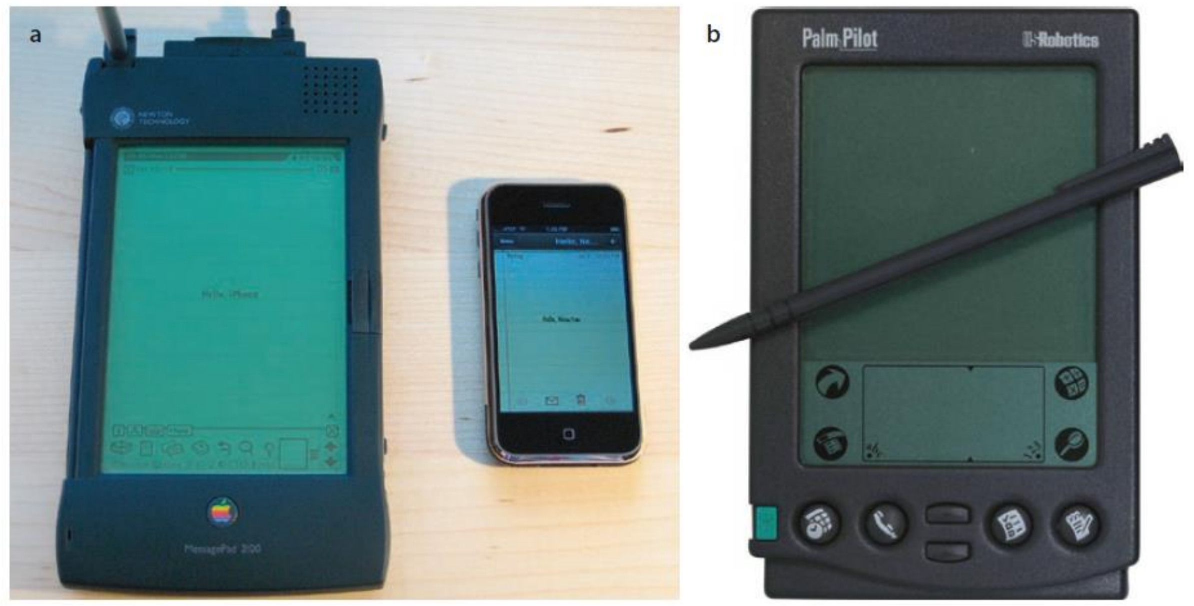
Wearable Devices



a. The Apple Newton MessagePad 2100, running Newton OS, alongside the original iPhone running iOS. By Blake Patterson from Alexandria, VA, USA - Newton and iPhone: ARM and ARM, CC BY 2.0, https://commons. wikimedia.org/w/index.php?curid=7039806.

b. PalmPilot with stylus. By Rama & Musée Bolo - Own work, CC BY-SA 2.0 fr, https://commons. wikimedia.org/w/index .php?curid=36959631

Source: Shortliffe et al., 2021

A person wearing a smartwatch By Crew - https://pixabay.com/en/smartwatch-gadget technologysmart-828786/, https://commons.wikimedia.org/w/index.php?curid=46644979

Medical Image Informatics

- Developing new treatment and medical diagnosis.
- Medical Imaging Techniques:
  - X-ray
  - Computer Tomography (CT)
  - Positron Emission Tomography (PET), and
  - Magnetic Resonance Imaging (MRI)
- Use of machine and deep learning approaches for medical image analysis.
- **More on this on Week 6**

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Challenges of AIM

- Accuracy vs Transparency
- Human-intervention on medical systems
- Privacy issues of sharing personal medical data through multiple devices
  - ➢ Personalized medicine

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SUMMARY

- Artificial intelligence in medicine (AIM) is a field of biomedical informatics
- AIM term appears in 1965
- Through the rise of ML, AIM evolves over time (from knowledge-based systems to data-based systems (neural networks, deep learning)
- ML extract features and patterns from different types of data
- AIM applies for diagnosis of a disease, for prediction and treatment selection, for drug discovery, for personalized medicine
- Challenges of AIM: to find a balance between accuracy and transparency

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Discussion

From Accurate Predictions to Clinically Useful AIM

- How can we achieve this?
- What is the role of Explainable AI?
- How can one compare and contrast knowledge-based systems with machine learning models? What are some of the relative advantages and disadvantages of these approaches?
- Considering the current state of progress, where is research and development most urgently needed in the field and why?
- What is your opinion about patient-centric medical systems?

Articles to read regarding the future of AIM

- Artificial intelligence will improve medical treatments: https://www.economist.com/science-and-technology/2018/06/09/artificial-intelligence-will-improve-medical-treatments
- DeepMind Artificial Intelligence and the future of NHS: https://www.thetimes.co.uk/article/deepmind-artificial-intelligence-and-the-future-of-the-nhs-r8c28v3j6
- How Artificial Intelligence can transform medicine, https://www.nytimes.com/2019/03/11/well/live/how-artificial-intelligence-could-transform-medicine.html

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