CDDF WORKSHOP

27 - 28 September 2021

ONLINE WORKSHOP

Digital Tools and Artificial Intelligence in Oncology Drug Development

APPLYING AI IN CLINICAL DRUG DEVELOPMENT – KEY CHALLENGES

Dónal Landers

digital Experimental Cancer Medicine Team

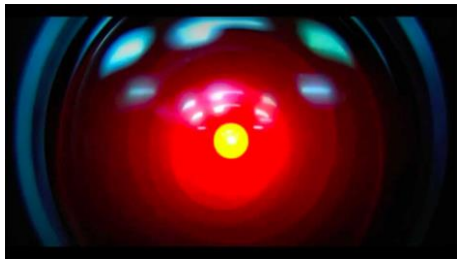
Contents

- What's all the hype about?
- What is AI?
- Challenges and issues in applying AI clinically
- Progress in 'ethical' AI
- An approach – 'Technology' Clinical Trial
- Summary

AI – What's all the hype about?

- 'AI' waves - 1950's, 70s, 90s – so what's changed?
  - ***Access to large data sets – 'Big Data'***
  - ***Increase in compute power – Graphic Processing Units (GPUs)***
- Promise of improved clinical outcomes, reduction in healthcare costs, and a positive impact population health
- Potential immediate areas identified: clinical trial processes (patient trial matching), radiological imaging, radiation oncology, digital pathology and drug discovery (new targets)

HAL 9000 –
'Heuristically programmed Algorithmic' computer
(Space Odyssey 2001)



We're not here yet!
Do we want to be?

- MD Anderson – IBM Watson $62 million
- Moorfields and Google – inappropriate use of patient identifiable data (done under the argument of Direct Care)

AI is here, it's very early days and its long-term implications are uncertain

What is Artificial Intelligence?

- ***What is intelligence?***
  - The ability to learn or understand or to deal with new or trying situations
  - The skilled use of reason
  - The ability to apply knowledge to manipulate one's environment or to think abstractly as measured by objective criteria (such as tests)

- **Definition of 'AI'**
  - ***"Science and engineering of making intelligent machines, especially intelligent computer programs"***
  - ***Intelligence is "the computational part of the ability to achieve goals in the world."*** (Dr. John McCarty, Stanford University)

Acting humanly – Turning Test

Thinking humanly – Cognitive modelling approach, how nervous systems represents, processes, and transforms information

Thinking rationally – The laws of thought approach - logic

Acting Rationally – The rational agent approach

- Rational agent – has clear preferences, models uncertainty and performs an action with the optimal expected outcome for itself from among all feasible actions

AI is not not intelligent…it doesn't represent how humans think

Challenges

What clinical problem/unmet clinical need does the AI address?

How and where to apply AI in clinical drug development?

Who is accountable if AI goes wrong?

Are the AI benefits available to all patients?

Can data only fully inform robust AI development?

How do we trust AI if used in a clinical drug development setting?

How do we prove AI is fit to use on humans?

Does AI benefit the patient, or will it bring them to harm?

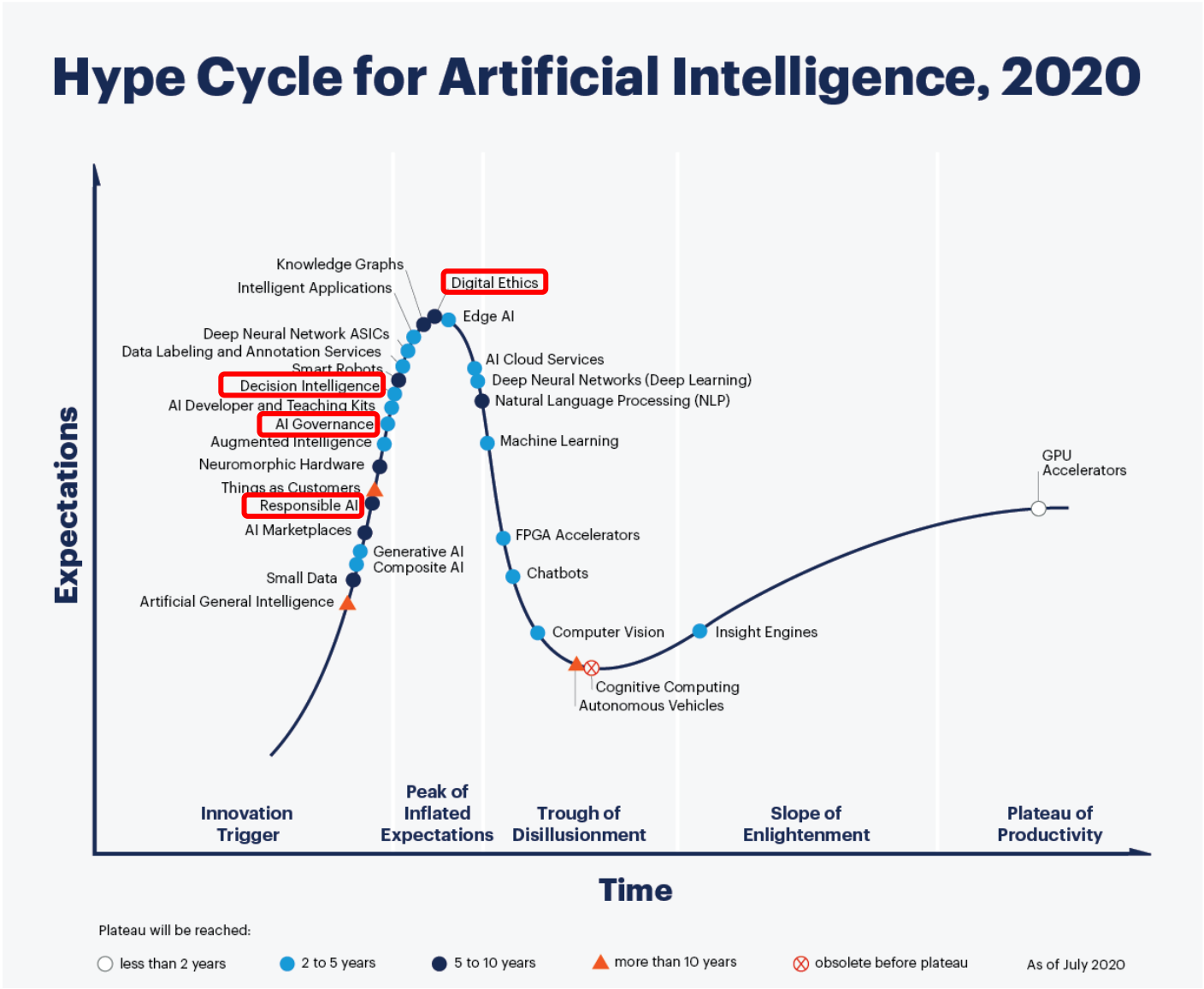
Is AI being used to drive profit?

Who can access patient/clinical data?

Does AI reason or 'think' in the same way as a healthcare professional?

Does AI preferentially benefit a certain group of patients only?

What does the market think?

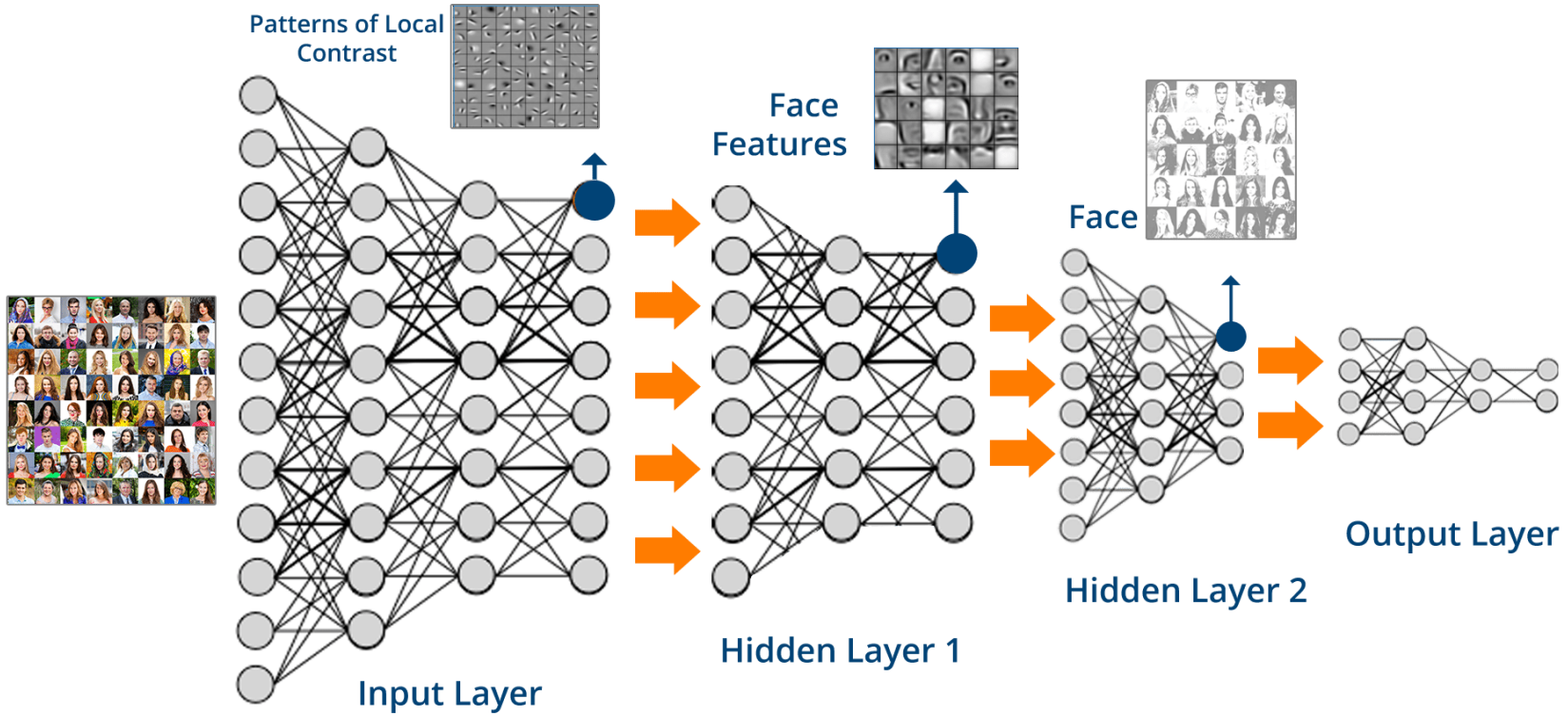


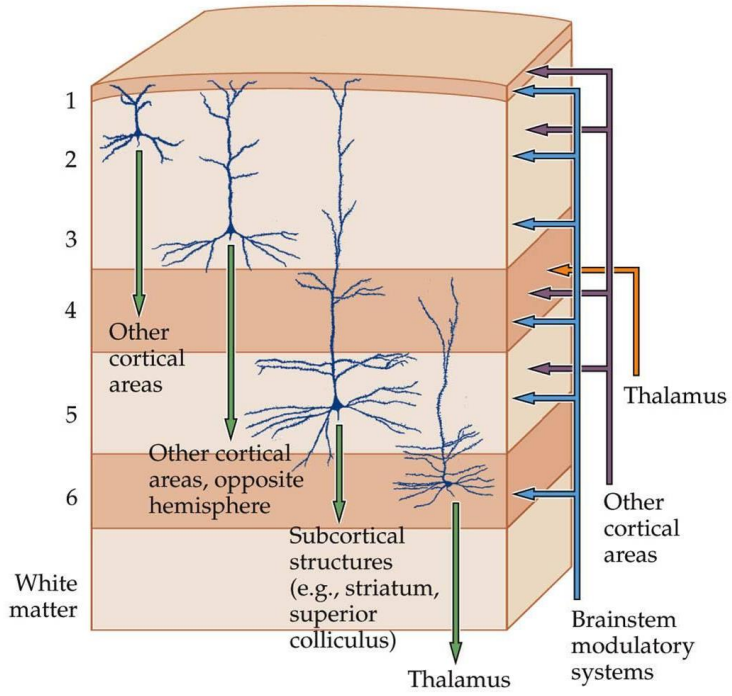
- **Key Points**
  - Ethical AI is not yet fully addressed
  - Responsible AI, Decision Intelligence, AI Governance and Digital Ethics are still several years away
  - Why are these important? – it's about setting realistic expectations

Should I trust AI currently?

https://www.gartner.com/smarterwithgartner/2-megatrends-dominate-the-gartner-hype-cycle-for-artificial-intelligence-2020/

Deep Learning – Convolutional NN Topology example





RETINA/LGN

VISUAL CORTEX (V1-V6)

Example of bias associated with a CNN

The Risk of Racial Bias in Hate Speech Detection

Maarten Sap[◇] **Dallas Card**[♣] **Saadia Gabriel**[◇] **Yejin Choi**[◇♡] **Noah A. Smith**[◇♡]
[◇]Paul G. Allen School of Computer Science & Engineering, University of Washington, Seattle, USA
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- Annotator's insensitivity to differences in dialect can lead to racial bias in automatic hate speech detection models - ***potentially amplifying harm against minority populations***
- Show models trained propagate these biases => AAE tweets and tweets by self-identified African Americans are up to two times more likely to be labelled as offensive compared to others, e.g. white-aligned English
- When *dialect* and *race priming* is introduced, annotators are significantly less likely to label the tweet as offensive

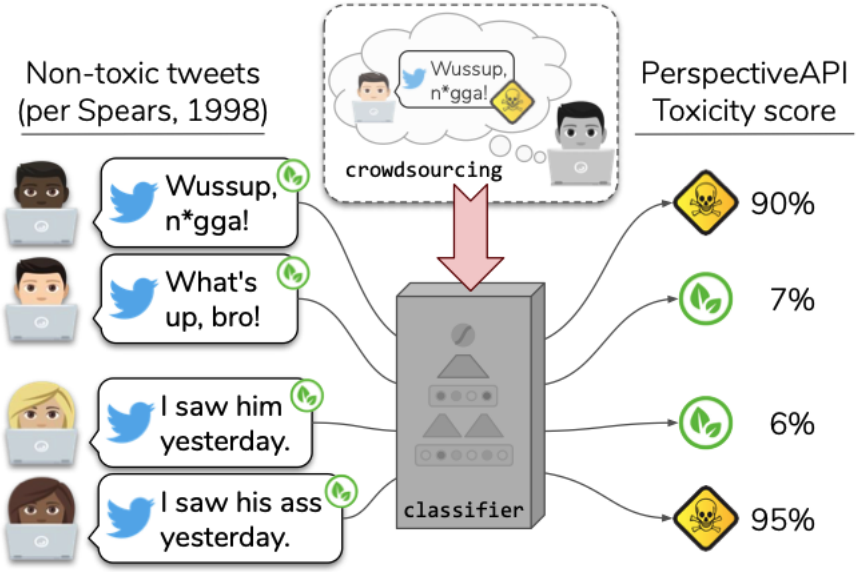
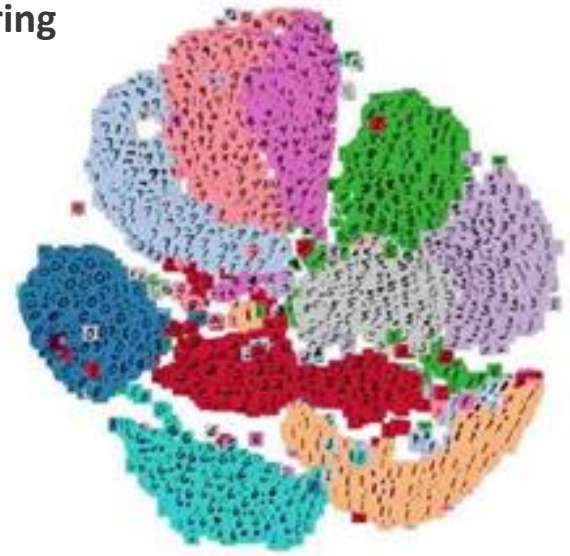


Figure 1: Phrases in African American English (AAE), their non-AAE equivalents (from Spears, 1998), and toxicity scores from PerspectiveAPI.com. Perspective is a tool from Jigsaw/Alphabet that uses a convolutional neural network to detect toxic language, trained on crowdsourced data where annotators were asked to label the toxicity of text without metadata.

Potential for health literacy, gender, age bias etc?

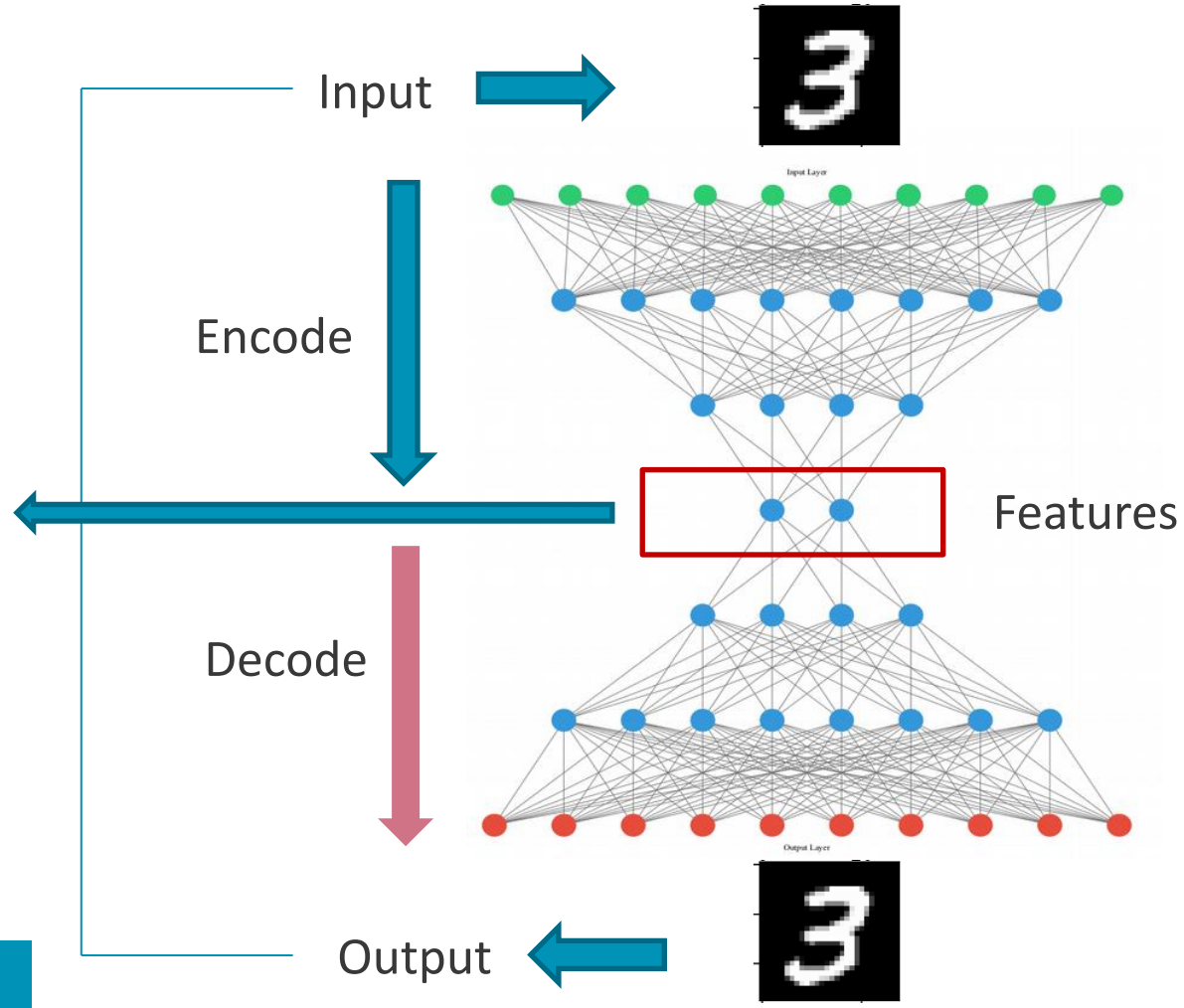
Another example – Autoencoders as an area of research

- Autoencoders perform non-linear dimensionality reduction
- **Unsupervised learning, clustering**



Cancer Core Europe

Research into complex biomarker discovery using AI



More advanced Deep Learning NNs still utilise similar architectures

Should we trust AI/deep learning?

- ***How do we know the algorithm learns and reasons in the same way as a human?***

EXAMPLE

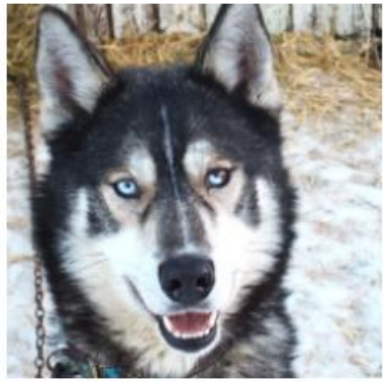
"Why Should I Trust You?" Explaining the Predictions of Any Classifier

Ribeiro, Marco Tulio et al. ""Why Should I Trust You?": Explaining the Predictions of Any Classifier." *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining* (2016): n. pag.

Distinguishing between photos of Wolves and Eskimo Dogs (huskies) using a logistic regression classifier

Wolf pictures had snow in the background

(1) Do they trust this algorithm to work well in the real world, (2) why, and (3) how do they think the algorithm is able to distinguish between these photos of wolves and huskie



(a) Husky classified as wolf

(b) Explanation

Figure 11: Raw data and explanation of a bad model's prediction in the "Husky vs Wolf" task.

	Before	After
Trusted the bad model	10 / 27	3 / 27
Snow as a potential feature	12 / 27	25 / 27

Table 2: "Husky vs Wolf" experiment results.

Just because AI gets the right answer….you still shouldn't blindly trust it

COVID-19 datasets – ‘Frankenstein’ image datasets!

- Systematic review of 2,212 studies, 415 were included after initial screening and 62 studies after quality screening were included
- No papers in the literature review demonstrated:
  1. A sufficiently documented manuscript describing a reproducible method
  2. A method that follows best practice for developing a machine learning model
  3. Sufficient external validation to justify the wider applicability of the method

Why?

Didn’t reach threshold of robustness and reproducibility to support use in clinical practice

- Poor-quality data (non-DICOM), poor application of machine learning methodology and biases (not representative of the target population) in study design

nature machine intelligence
ANALYSIS
https://doi.org/10.1038/s42256-021-00307-0
Check for updates

OPEN

Common pitfalls and recommendations for using machine learning to detect and prognosticate for COVID-19 using chest radiographs and CT scans

Michael Roberts[1,2], Derek Driggs[1], Matthew Thorpe[3], Julian Gilbey[1], Michael Yeung[4], Stephan Ursprung[4,5], Angelica I. Aviles-Rivero[1], Christian Etmann[1], Cathal McCague[4,5], Lucian Beer[4], Jonathan R. Weir-McCall[4,6], Zhongzhao Teng[4], Effrossyni Gkrania-Klotsas[7], AIX-COVNET*, James H. F. Rudd[8,36], Evis Sala[4,5,36] and Carola-Bibiane Schönlieb[1,36]

Frankenstein datasets - datasets assembled from other datasets and redistributed under a new name

Are your datasets used for AI R&D of high enough quality and fidelity for clinical decision making?

Progress in ‘ethical’ AI research and development

nature medicine
CONSENSUS STATEMENT
https://doi.org/10.1038/s41591-020-1037-7
Check for updates

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Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension

Samantha Cruz Rivera[1,2,3], Xiaoxuan Liu[3,4,5,6,7], An-Wen Chan[8], Alastair K. Denniston[1,3,4,5,6,9] ✉, Melanie J. Calvert[1,2,3,6,10,11,12], The SPIRIT-AI and CONSORT-AI Working Group*, SPIRIT-AI and CONSORT-AI Steering Group and SPIRIT-AI and CONSORT-AI Consensus Group

CONSENSUS STATEMENT
https://doi.org/10.1038/s41591-020-1034-x
nature medicine
Check for updates

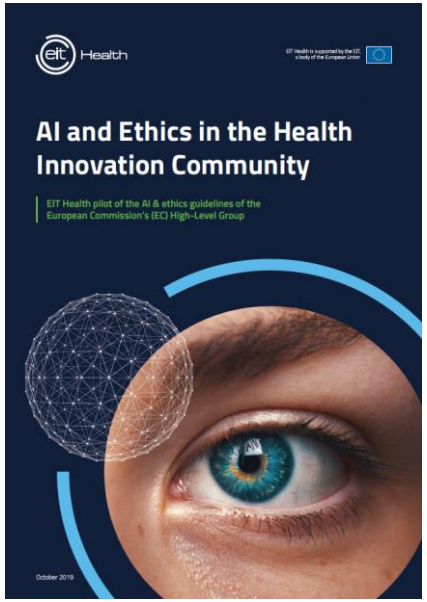
OPEN

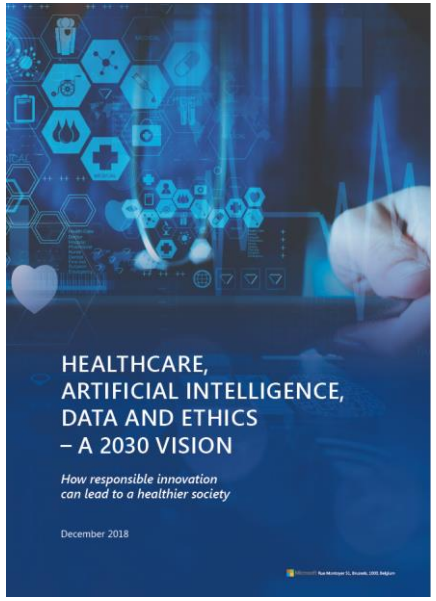
Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension

Xiaoxuan Liu[1,2,3,4,5], Samantha Cruz Rivera[5,6,7], David Moher[8,9], Melanie J. Calvert[4,5,6,7,10,11,12], Alastair K. Denniston[2,3,4,5,6,13] ✉ and The SPIRIT-AI and CONSORT-AI Working Group*

A Typology of AI Ethics Tools, Methods and Research to Translate Principles into Practices

Jessica Morley*[1], Luciano Floridi[1], Libby Kinsey[2], Anat Elhalal[2]
(1) Oxford Internet Institute, University of Oxford, UK
(2) Digital Catapult, UK





Guidelines on ‘ethical’ AI are emerging, and important to read

Medical Ethics and 'ethical' AI

Firstly, what is medical ethics?

- Set of guiding values derived from the common morality (right and wrong human conduct)
- Four clusters of moral principles (framework of norms) using in clinical medicine:

  Respect for autonomy – allowing the patient to fully exercise their rights

  Nonmaleficence – not harm the patient

  Beneficence – deliver benefit to the patient

  Justice – fair distribution of benefits, risks and costs

Ethical AI in Healthcare (WHO 2021)

- Protect autonomy - not to undermine human autonomy
- Promote human well-being, human safety and the public interest - shouldn't harm people
- Ensure transparency, explainability and intelligibility
- Foster responsibility and accountability - regulatory oversight by humans
- Ensure inclusiveness and equity - not discriminatory
- Promote artificial intelligence that is responsive and sustainable - continuous assess AI in the context of healthcare, the environment and workplaces

"Our future is a race between the growing power of technology and the wisdom with which we use it."
Stephen Hawking

Components of ‘ethical’ AI in clinical development

Safe

- Beneficence
- Non-maleficence
- Societal level

Trustworthy

- Explainable
- Interpretable
- Transparent

Protect autonomy

- Consent
- Preserve Dignity

Emerging Principles

Data Privacy

- Security
- Consent to use
- Governing laws

Non-discriminatory

- Justice/Equity
- Non-biased
- Inclusive
- Respectful

Accountability

- Responsibility
- Regulatory
- Ownership

‘Ethical’ AI
Developing a line-of-sight to the clinic

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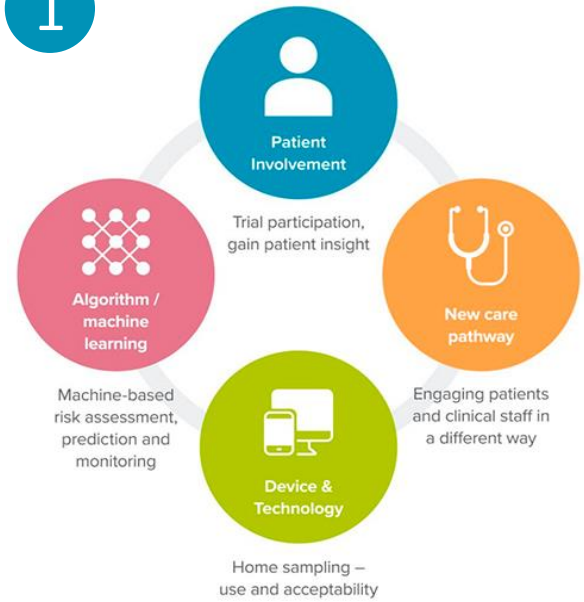
1



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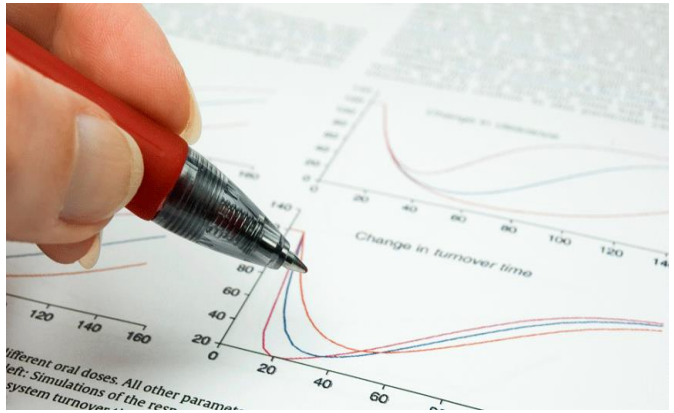


3

‘Technology’ research, innovation and development

- Unmet clinical need/problem
- Hypothesis generation
- Patient engagement/HCPs
- Regulatory/Legal

Conduct **‘Technology’ Clinical Trial** to demonstrate clinical utility and benefit

- Protocol
- Ethics approval
- Publication of study results

Translate to **clinical care pathway** in clinical trial

- Validation pathway
- Scalability
- Data security

Essentially, we apply a similar model to drug development

The Gap – ‘ethical’ AI translation to the clinic

‘Ethical’ AI development – an approach

Identified an unmet clinical need

Have a dataset which can cover the problem space

‘Ethical’ AI Research

Preclinical Translational data science

AI Development Process

Data Assets – high fidelity

Data Integration – clinical++

‘Data’ Lab

AI Methods Research

Clinical algorithms

Validation

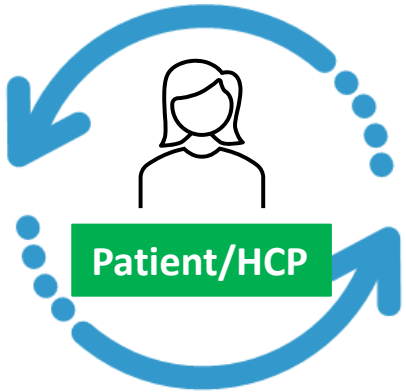
Selected algorithm(s)

Safe, Explainable & Ethical AI

Technology Clinical Trials

Patient Impact

AI as part of a patient centred care pathway



Clinically proven to deliver patient benefit/improve outcomes (RCTs)

The Breast Cancer Recommender DSS tool research project

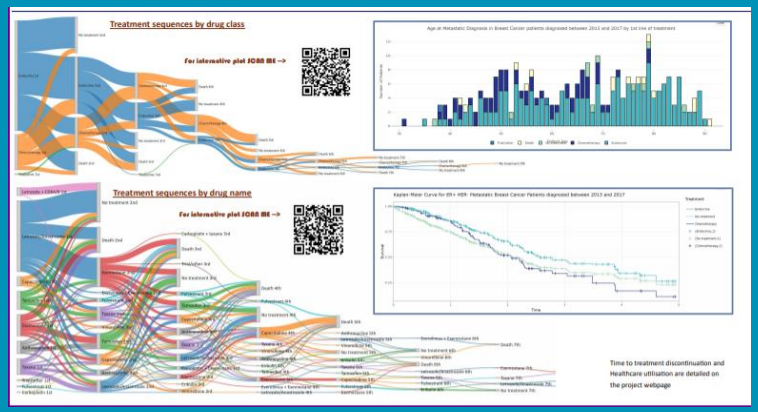
AI research and systems development of a **prototype Clinical Decision Support Tool to** augment clinician decision-making to, improve and increase precision medicine options for breast cancer patients

Clinical Problem:

For Clinical Oncologists,

i) the increasing volume of complex multi 'omic' biomarkers and
ii) a broader range of breast cancer treatment options,

is making it more challenging to determine the best treatment options for an individual patient.



Recommender decision support system & research will :

- Clearly **define the challenging problem** of complex decision making it the Metastatic breast cancer setting
- Capture the **decisioning making process** that Clinicians go through
- Provide a **clear set of DSS requirements** to augment the decision-making capabilities of the breast cancer oncologist and potentially provide more precision medicine options that they can offer to their patients
- Undertake research into the design of an **'ethical' AI model to support** a DSS in Breast cancer, utilising clinical trial data and synthesised data sets.

Summary

Digital Experimental Cancer Medicine Team

- AI has the potential to transform oncology drug development in specific settings, but does raise significant challenges – addressing the **AI 'hype'**, its **trustworthiness** and the **ethical use** of these algorithms clinically
- **AI is not intelligent** – be careful of anthropomorphism
- **Ethical guidelines and principles are emerging**, however implementation of AI in a clinical setting is not formally established
- **High fidelity datasets are essential** and must sufficiently cover the problem domain, but does learning from datasets deliver human reasoning?
- One approach is to formally **evaluate AI in a RCT 'technology' clinical trial** in a similar way to how a new IMP is developed

Ignorance of the implications of AI in clinical drug development is not acceptable…..

While there are tremendous opportunities there are also real inherent dangers if applied in an unethical way…..don't rush blindly into AI!

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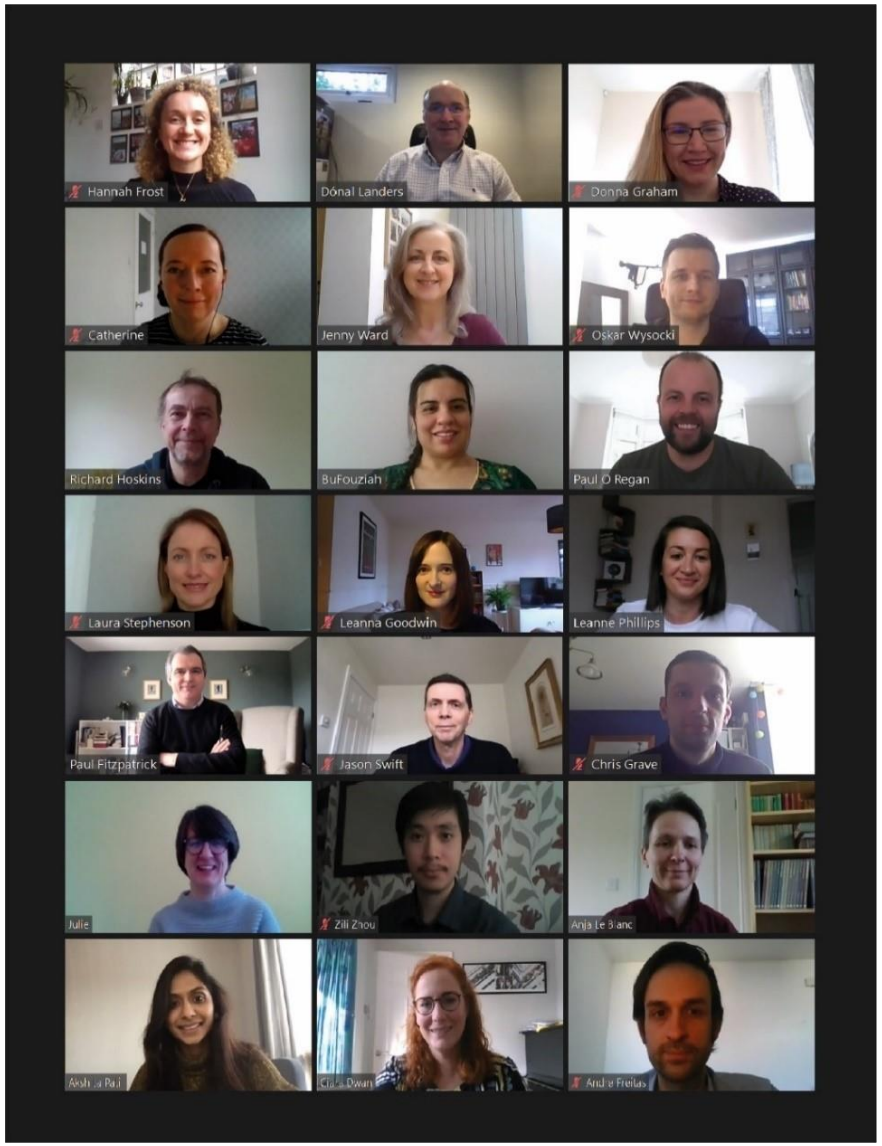

digital ECMT organisational structure 2021

Strategic Director
Dónal Landers

Technology Solutions Paul Fitzpatrick	digital ECMT AI Andre Freitas	Portfolio Administration Laura Stephenson	Technology Clinical Trials Donna Graham	Pharma Innovation Jason Swift
Richard Hoskins Christopher Grave Julie Stevenson Fouziah Butt Anja Le Blanc Catherine McGuire	Oskar Wysocki Paul O'Regan Zili Zhou	Jenny Ward Akshita Patil Ciara Dwan	Hannah Frost Leanna Goodwin Leanne Phillips	Jason Swift (AZ-digital ECMT Collaborations)

Skillsets

Clinical Oncology	**Translational Science**	**Data Science**	**Artificial Intelligence**
Machine Learning	**Early Clinical Development**	**Technology Clinical Trials**	**Software Development**
Project Management	**Enterprise Systems Development**	**Business Analysis**	**Patient Engagement**
Clinical Operations	**Nephrology**	**Mobile Application Development**	**Care Pathway Development**

Thank you

Engaging patients, driving decisions

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CDDF Cancer Drug Development Forum

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