AI applications in modern oncology: What reliable support for clinical decisions?

AI in Medical Oncology

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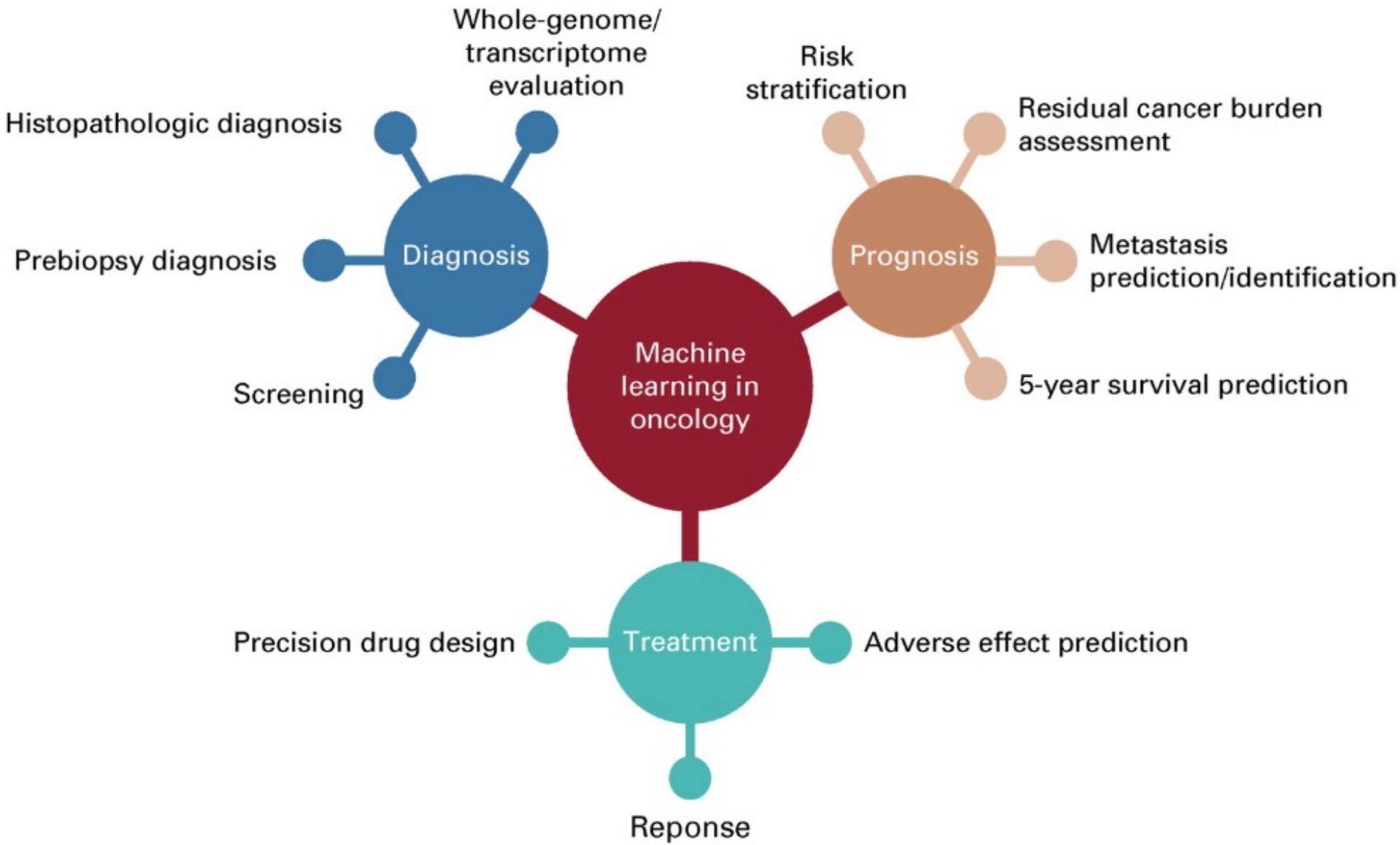
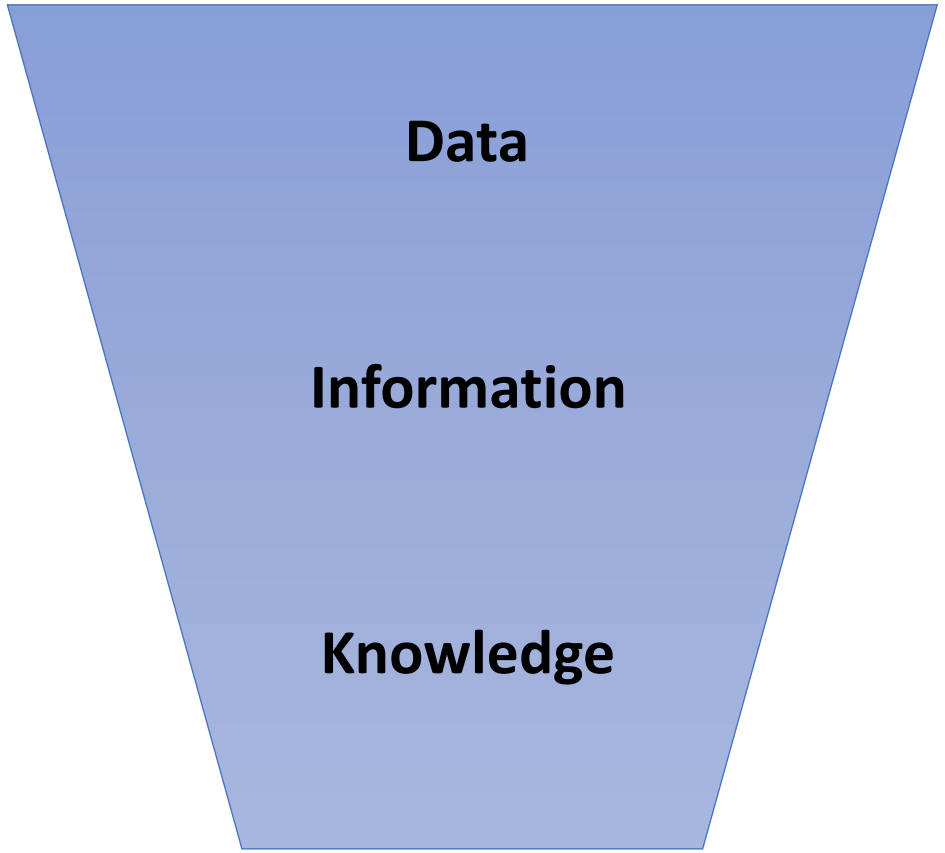


Nagy M et al. JCO Clin Cancer Inform 2020

Use cases

- Basic science: drug discovery
- TR (multiomic)
- Advanced CDSS
- Chat bots
- Augmented reality
- Hospital scheduling

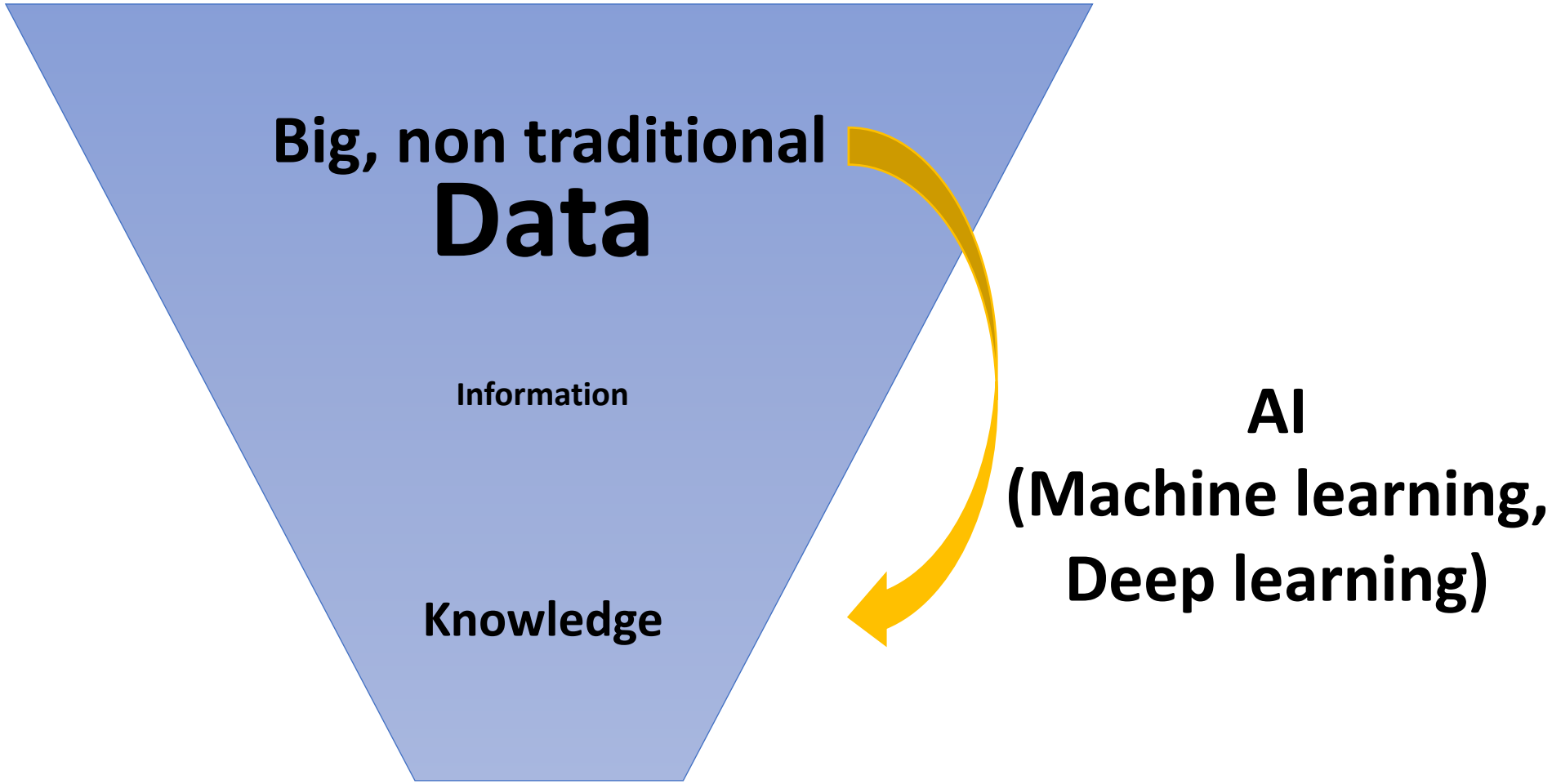
Data – Information – Knowledge



- **Data**
  - ✓ Raw observation, objective facts
- **Information**
  - ✓ Data in meaningful context
- **Knowledge**
  - ✓ Understanding about the world
    - Explicit, codifiable (e.g. Wikipedia, guidelines)
    - Tacit, not codifiable (e.g. expertise)
  - ✓ Process knowledge (e.g. riding a bike)
  - ✓ Useful for explaining, predicting, guiding future action

Adapted from *Sim I. Two Ways of Knowing: Big Data and Evidence-Based Medicine. Ann Intern Med. 2016*

Big Data – Analytics Approach



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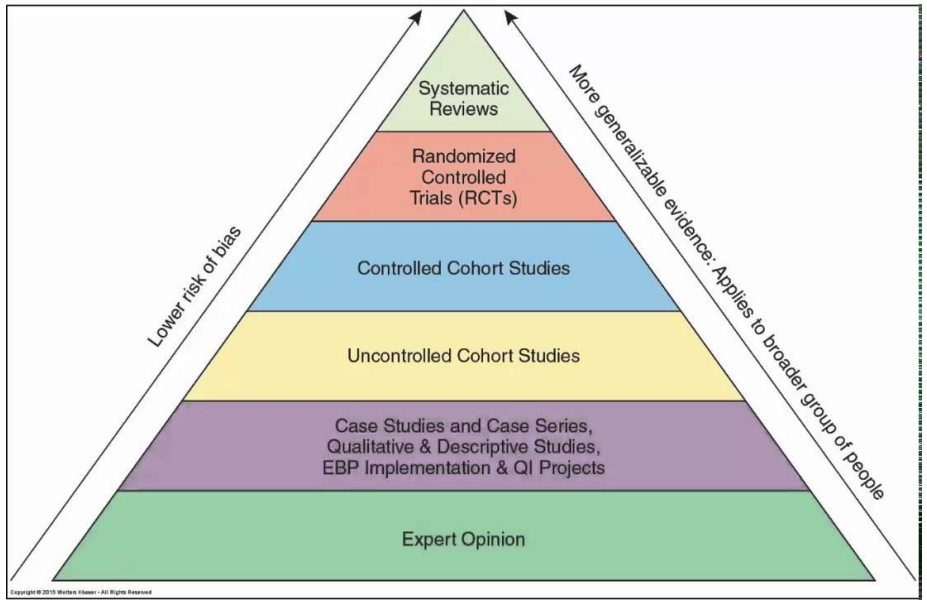
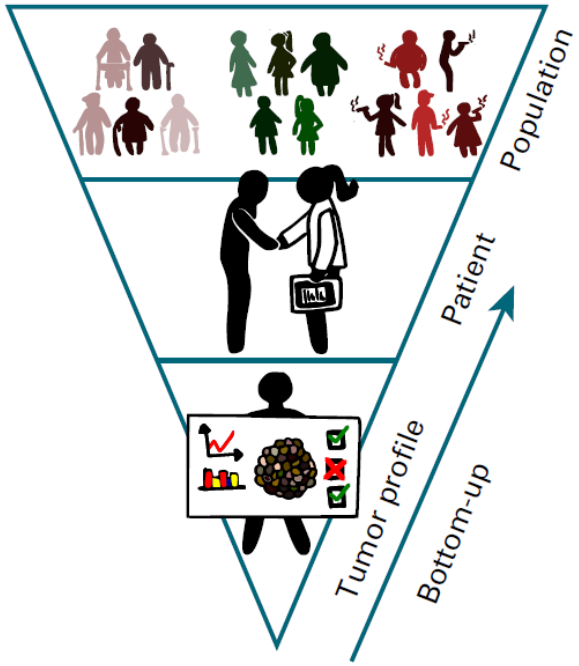
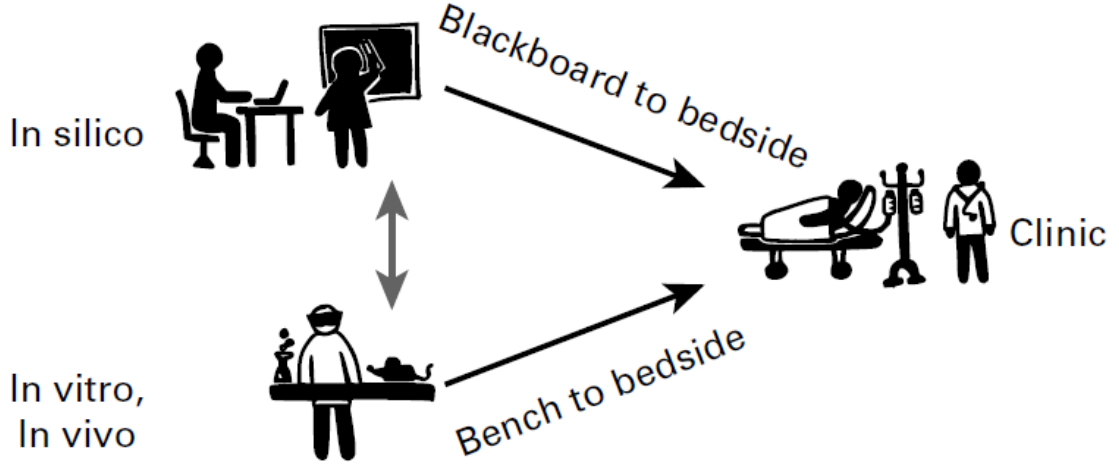






Adapted from *Hamis S, et al. Clin Cancer Inform 2019*

AI in cancer genomic

- From simple observation to genomic infomed clinical models
- Ever expanding list of new prognostic and predictive factors
- Each additional predictor elevates complexity beyond comprehension with the classical approach, but increases the potentials of the associated model algorithms
- Examples:

  cancer screening projects on ctDNA

  multiomics combined with clinically annotated data: drug susceptibility genes, variant detection, new biological insights

Welcome to OncoKB

MSK's Precision Oncology Knowledge Base

An FDA-Recognized Human Genetic Variant Database*

682	5670	125	103
Genes	Alterations	Cancer Types	Drugs

Search Gene / Alteration / Drug

Therapeutic Levels | Diagnostic Levels | Prognostic Levels | FDA Levels

Level 1
FDA-approved drugs
43 Genes

Level 2
Standard care
17 Genes

Level 3
Clinical evidence
24 Genes

Level 4
Biological evidence
23 Genes

Level R1/R2
Resistance
11 Genes

OncoKB

- Expert-guided precision oncology knowledge base
- Annotates the biologic and oncogenic effects and prognostic and predictive significance of somatic molecular alterations
- Potential treatment implications are stratified by the level of evidence that a specific molecular alteration is predictive of drug response
- Offers oncologists detailed, evidence-based information about individual somatic mutations and structural alterations present in patient tumors with the goal of supporting optimal treatment decisions

Chakravarty D et al. JCO Precision Oncology 2017

Biomarker

Reference	Definition
FDA	A key medical product development tool capable of facilitating development of medical products and spurring innovation
BEST Resource (Biomarkers, EndpointS, and other Tools)	A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions
EMA	A biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals

Biomarker characteristics

- When used in the right context, potential to help expedite patient access to safe and effective treatments by reducing the time and cost of clinical trials while maintaining patient protections

https://www.fda.gov/science-research/about-science-research-fda/biomarkers-fda

Companion diagnostic – Definitions

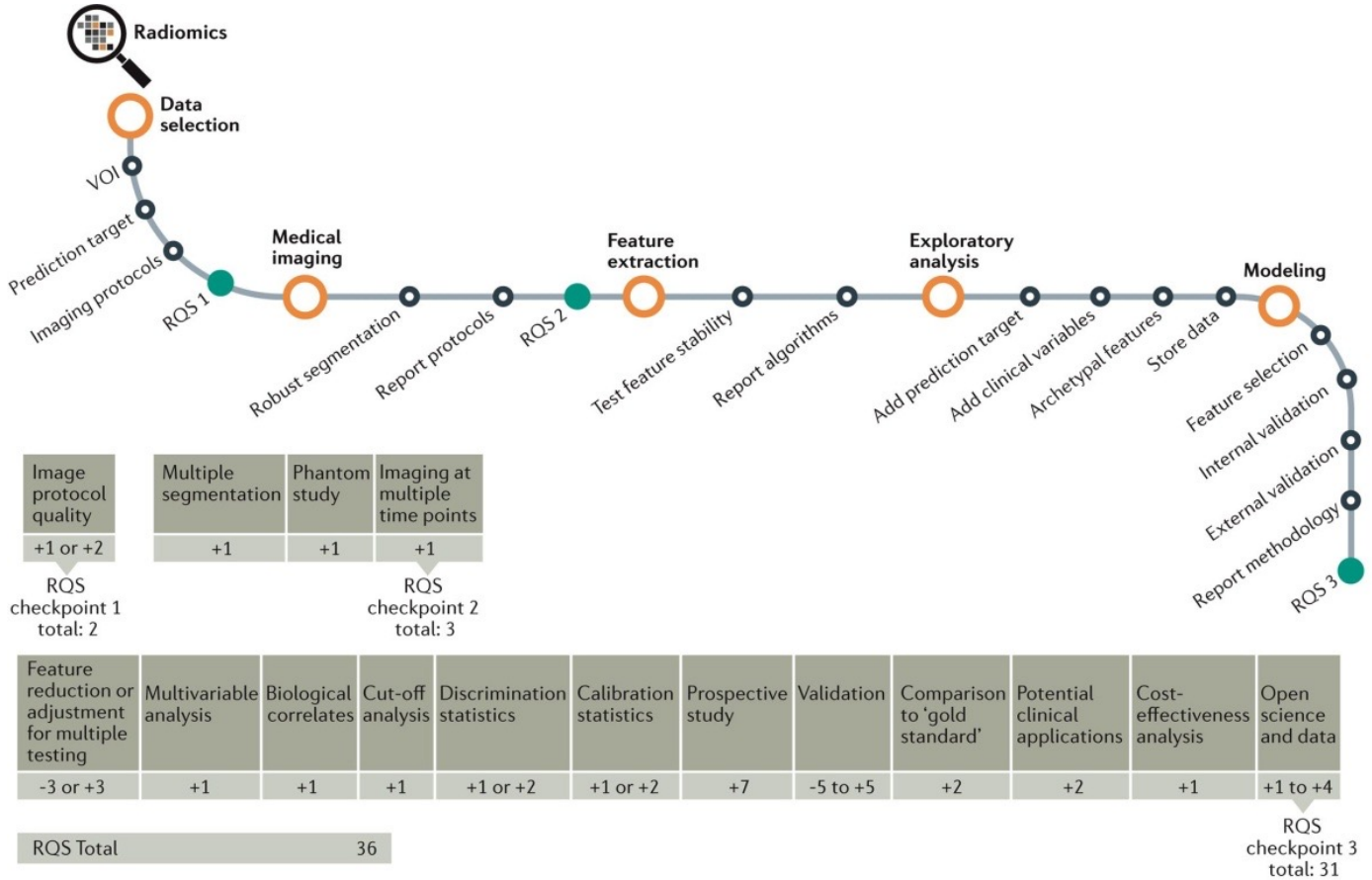
- FDA:
  - Former definition (until 2021): A medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product
  - Current definition (2022): A *companion diagnostic device* can be *in vitro* diagnostic (IVD) device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product

- EMA: An **in-vitro** diagnostic test that supports the safe and effective use of a specific medicinal product, by identifying patients that are suitable or unsuitable for treatment

Biomarker development procedure

- Scientific perspective
- Regulatory perspective
  - FDA
  - EMA

The case of radiomics: a codified workflow



RQS = Radiomics Quality Score

Lambin P. Nat Rev Clin Oncol 2017

Investigator’s & clinician’s perspective

- Biomarkers and companion diagnostics must undergo specific regulations
- Should AI-derived (e.g., multiomics) markers follow the same rules?
- If not, how to incorporate these markers in clinical practice?

Biomarker development procedure

- Scientific perspective
- Regulatory perspective
  - FDA
  - EMA

Biomarker Qualification Program *

SPOTLIGHT Events & Announcements

To locate a project or a qualified biomarker go to CDER & CBER's DDT Qualification Project Search database

Web content is updated for consistency with 21st Century Cures Act!

Get Started with your submission:

Resources for Biomarker Requestors

Content current as of:
07/07/2021

Regulated Product(s)
Drugs

Topic(s)
Research
Drug Development Tools

Law(s) & Regulation(s)
21st Century Cures Act of 2016

** CDER = Center for Drug Evaluation and Research*

Biomarkers for FDA-regulated products

Biologics

- Guidance for Industry: E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions
- Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions
- Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices

Drugs

- Biomarker Qualification Program
- Table of Pharmacogenomic Biomarkers in Drug Labeling
- Guidance for Industry: E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions
- Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools
- Guidance for Industry: Use of Histology in Biomarker Qualification Studies
- Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices

Medical Devices

- Laboratory Developed Tests
- Companion Diagnostics
- List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)
- Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions
- Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices

Tobacco

- Biomarkers of Tobacco Exposure: A Public Workshop
- Biomarkers of Potential Harm: A Public Workshop

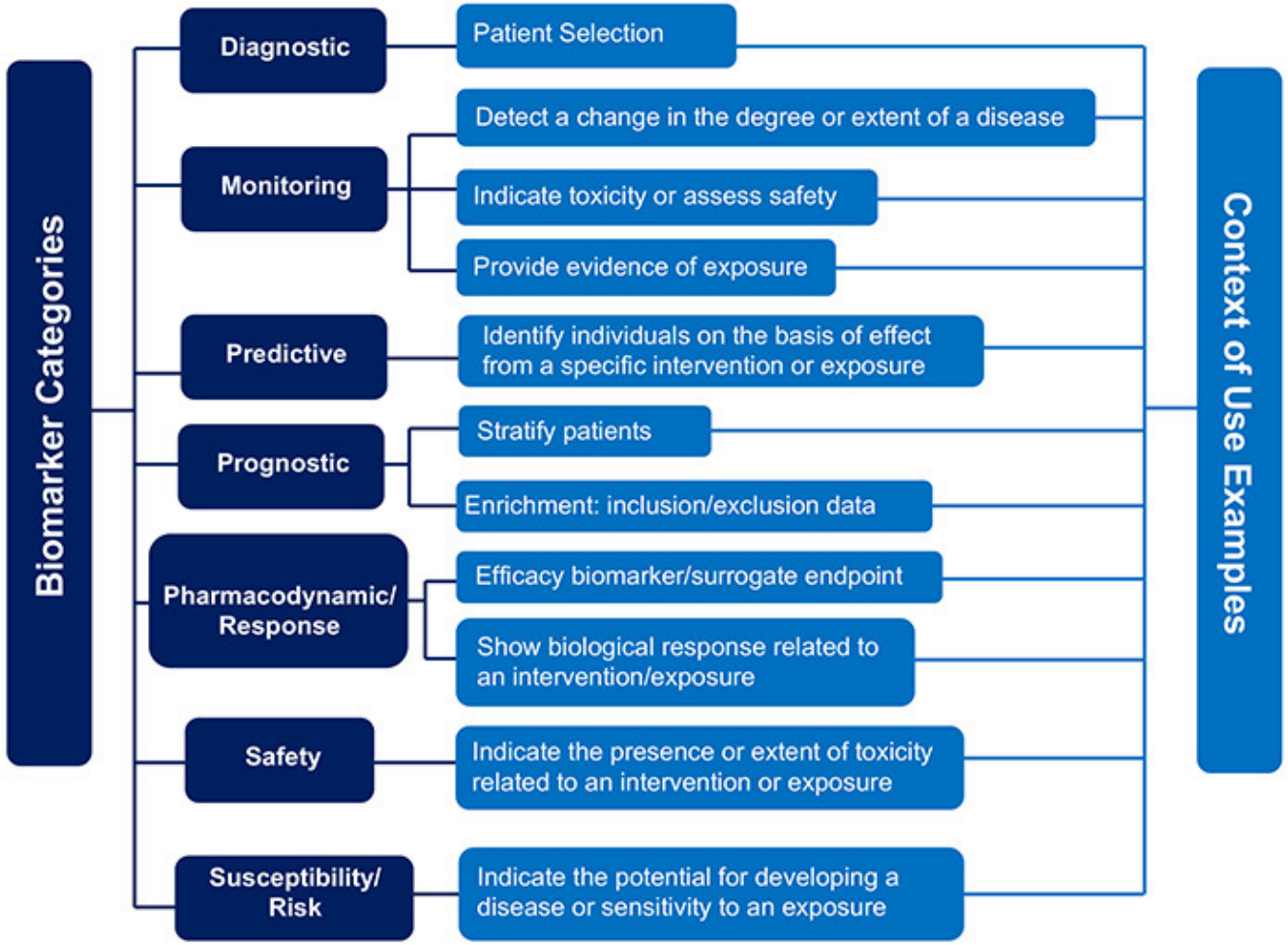
Companion diagnostic device

- To identify patients who are most likely to benefit from a particular therapeutic product
- To identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product
- To monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness

Context of Use (COU)

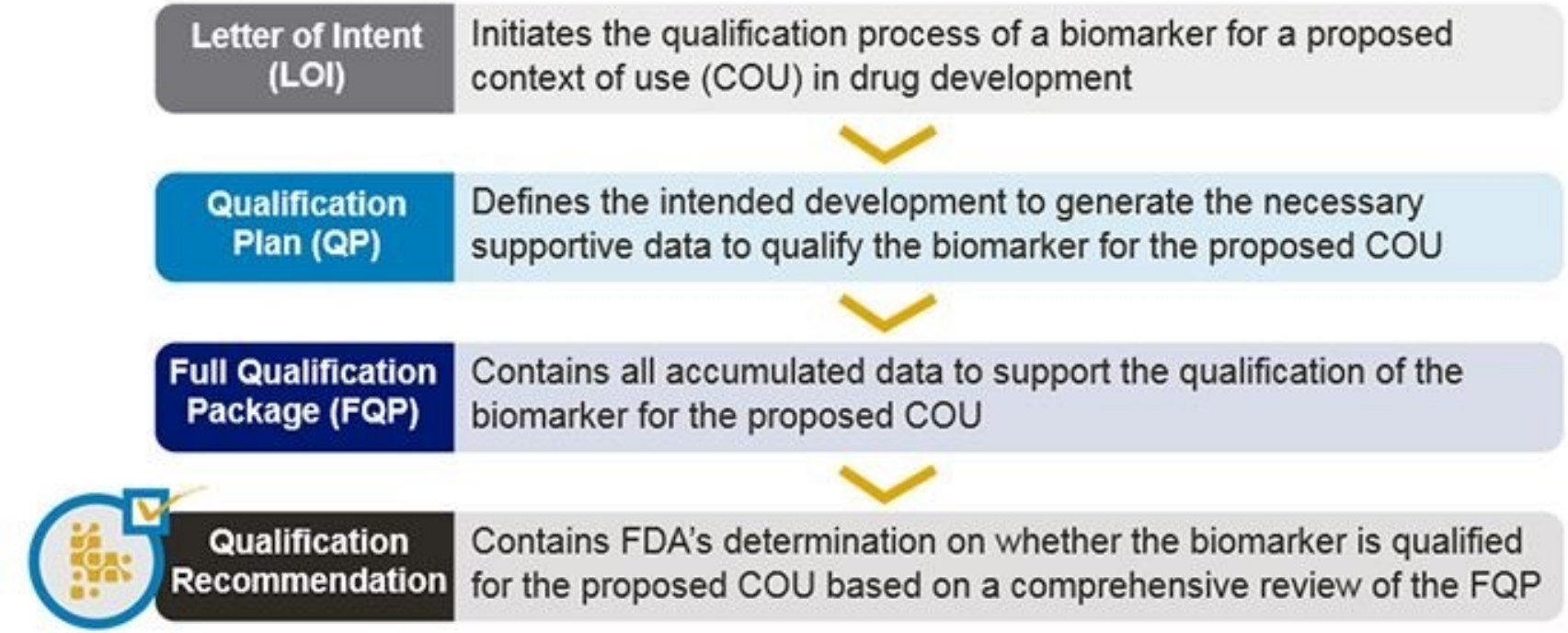
Definition

COU = a concise description of the biomarker's specified use in in drug development



https://www.fda.gov/drugs/cder-biomarker-qualification-program/context-use

Qualification process



FDA approved companion diagnostic devices

- October 2022: 149 Cleared or Approved Companion Diagnostic Devices (vs. 46 in 2021)

- All molecular assays (e.g. BRCA analysis, PD-L1 IHC, HER2 etc.)

FDA U.S. FOOD & DRUG ADMINISTRATION

Search Menu

Home / Medical Devices / Digital Health Center of Excellence / Software as a Medical Device (SaMD) / Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices

Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices

October 5, 2022 update: 178 Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices were added to the list below. With this update, the FDA has also added the ability to download the list as an Excel file.

7th October 2022:
521 AI/ML Enabled Medical Devices

Field	N	%
Radiology	392	75%
Cardiovascular	57	11%
Hematology	15	3%
Neurology	14	3%
Ophthalmic	7	1%
Clinical Chemistry	6	1%
General And Plastic Surgery	5	1%
Microbiology	5	1%
Anesthesiology	4	<1%
Gastroenterology-Urology	4	<1%
Pathology	4	<1%
General Hospital	3	<1%
Gastroenterology & Urology	2	<1%
Dental	1	<1%
Obstetrics And Gynecology	1	<1%
Orthopedic	1	<1%

https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices

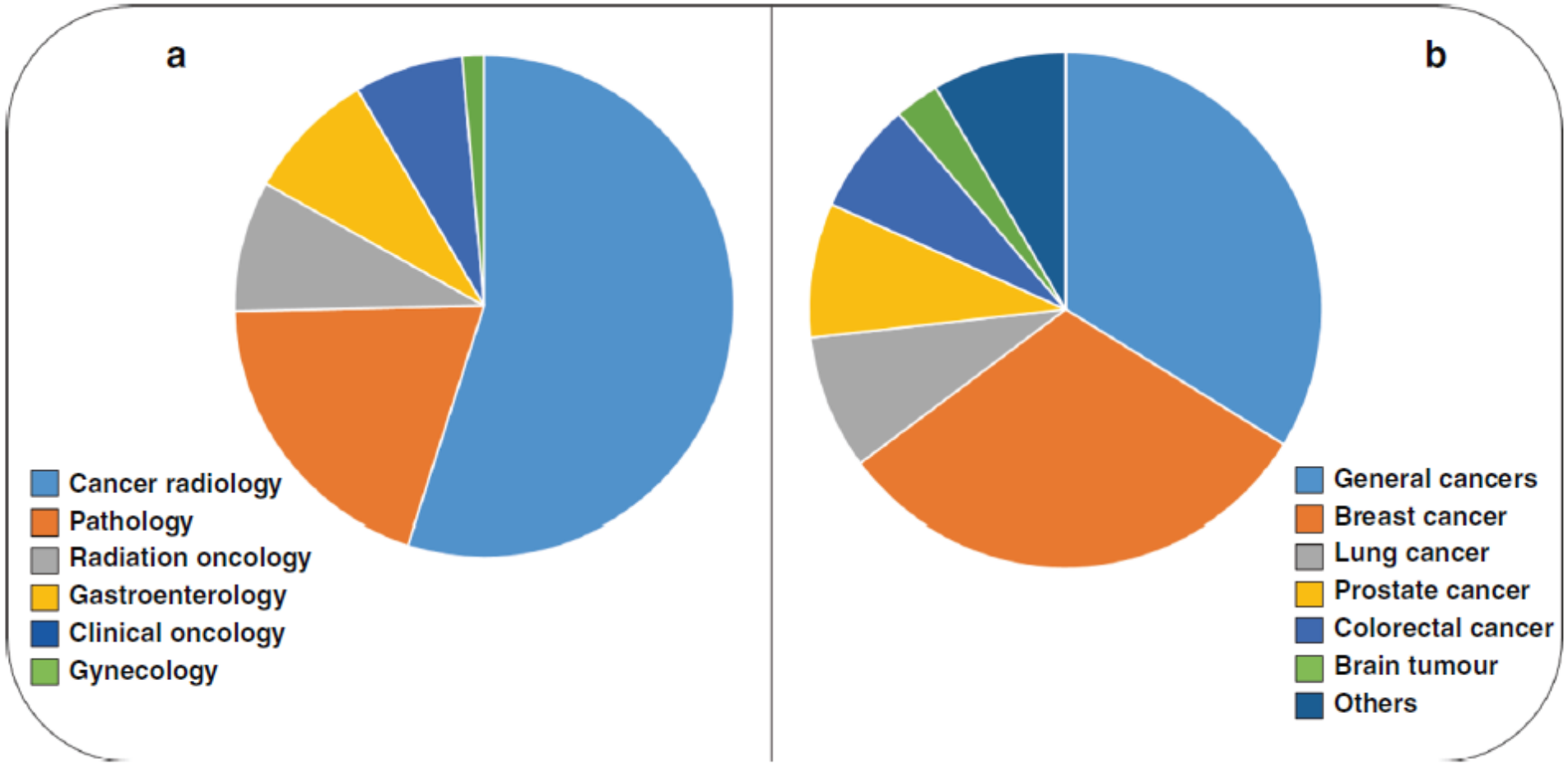


Fig. 1 Current status of Artificial intelligence in oncology and related fields. Summarising representations of the artificial intelligence-based devices, FDA-approved, expressed by oncology-related specialties (**a**: cancer radiology 54.9%, pathology 19.7%, radiation oncology 8.5%, gastroenterology 8.5%, clinical oncology 7.0% and gynaecology 1.4%) and by tumour types (**b**: general cancers 33.8%, breast cancer 31.0%, lung cancer 8.5%, prostate cancer 8.5%, colorectal cancer 7.0% and brain tumours 2.8%, others: 6 tumour types, 1.4% each).

Biomarker development procedure

- Scientific perspective
- Regulatory perspective
  - FDA
  - EMA

Biomarker qualification

- Certification of the acceptability of a biomarker for a specific use in pharmaceutical research and development

- The Agency gives opinions on biomarker qualifications

Companion diagnostic (in vitro) qualification

- Before it can issue a CE certificate, the notified body must seek a scientific opinion from EMA on the suitability of the companion diagnostic to the medicinal product concerned if:
  - the medicinal product falls exclusively within the scope of the centralised procedure for the authorisation of medicines, or
  - the medicinal product is already authorised through the centralised procedure, or
  - a marketing authorisation application for the medicinal product has been submitted through the centralised procedure.

- For other substances, the notified body can seek the opinion from a national competent authority or EMA.

EU regulation

- Medical Device
  - EU Regulation 2017/745
- In-Vitro Diagnostic Devices
  - EU Regulation 2017/746

Limitations to development and adoption of a AI driven models

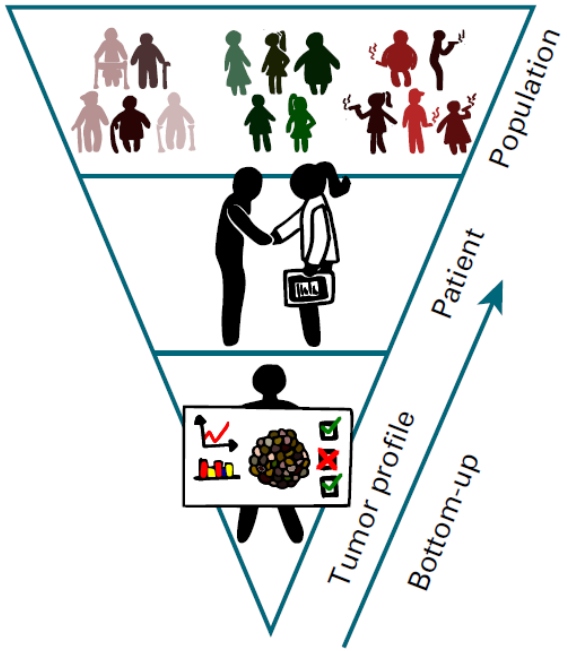
- Lack of standardisation: common oncology data elements work in progress, IT resources needed, interoperability
- Black box/trust
- Reverse engineering: weight of single variables
- Robust AI core services facilitate working with AI derived models without having bioinformatic experience
- Few studies about clinical implementation

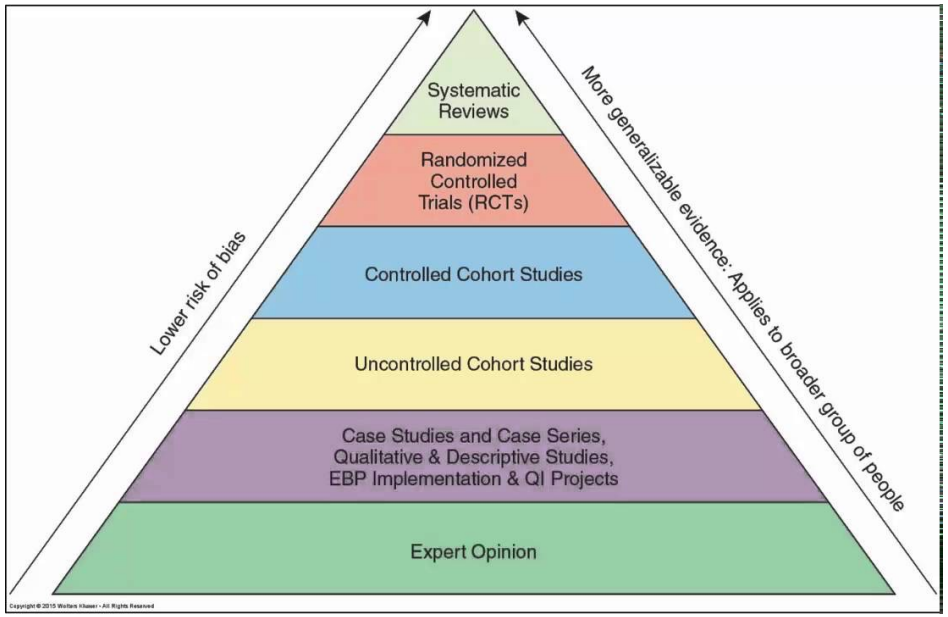
Clinical Trials Transformation Initiative (CTTI) Recommendations: Advancing the Use of Mobile Technologies for Data Capture & Improved Clinical Trials

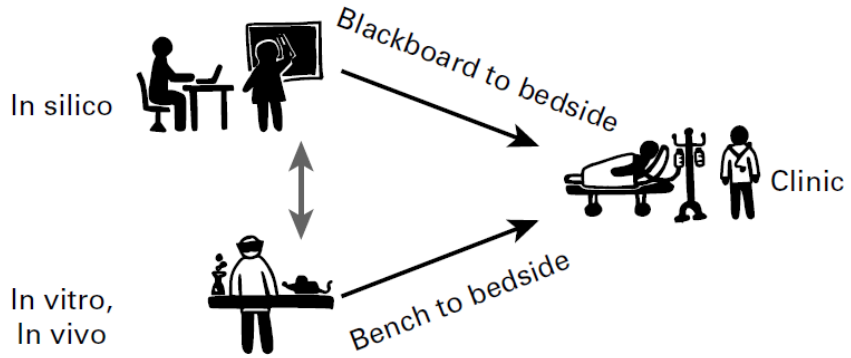
Standard Protocol Items: Recommendations for Interventional Trials – Artificial Intelligence

Biases, legal, ethical issues

- Representativeness of the population under scrutiny (including vulnerable)
- Models to test the presence of biases
- Standardisation of reporting
- Data drift over time (model monitoring, live models)
- FDA and EMA rules/draft guidance for AI algorithms and advanced CDSS
- Legal responsibility: delegations/errors







Adapted from *Hamis S, et al. Clin Cancer Inform 2019*

Thanks for your attention

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