Strategic Panel 2: regulatory science

EDITH-CSA Amsterdam meeting

EDITH is a coordination and support action funded by the Digital Europe program of the European Commission under grant agreement n° 101083771

Aldo Badano

USA-FDA

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Synthetic data, digital twins, and stochastic models for medical device innovation and evaluation

Aldo Badano
Director, DIDSR/OSEL/CDRH/FDA

▸ www.fda.gov/about-fda/cdrh-offices/office-science-and-engineering-laboratories in aldobadano aldobadano

FDA's regulatory science tools

Accelerating Medical Device Innovation with Regulatory Science Tools

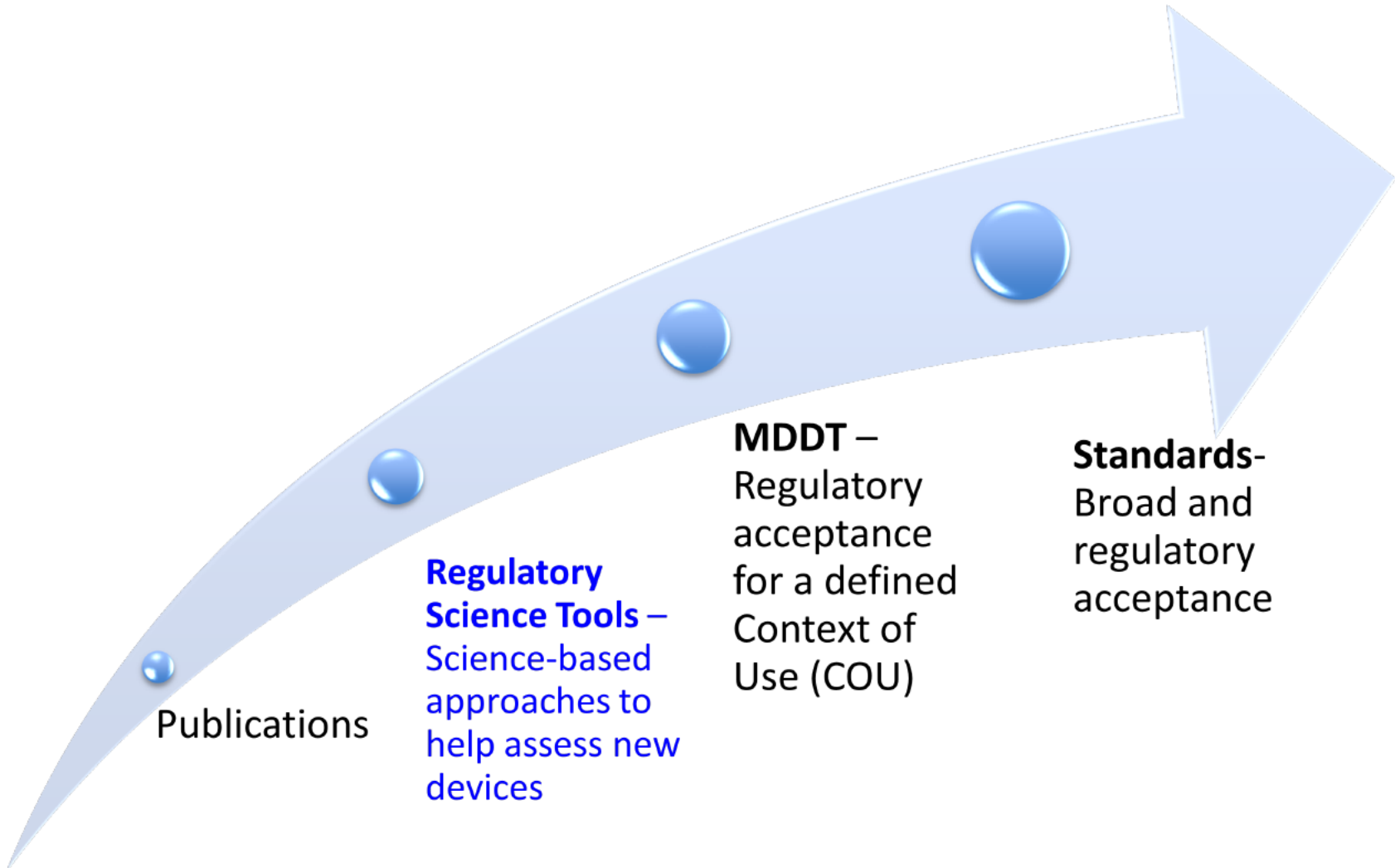
By: Jeff Shuren, M.D., J.D., Director, Center for Devices and Radiological Health (CDRH) and Ed Margerrison, Ph.D., Director, Office of Science and Engineering Laboratories, CDRH

Ed Margerrison, Ph.D.

"The Catalog of Regulatory Science Tools provides a peer-reviewed resource for companies to use where standards and MDDTs do not yet exist. The tools reduce the need for device developers to design ad-hoc test methods and allow them to focus their limited resources on how well their new product works, not how well it may be tested. ."

https://www.fda.gov/news-events/fda-voices/accelerating-medical-device-innovation-regulatory-science-tools

FDA's regulatory science tools



Regulatory Science Tools Catalog

Tools Categories

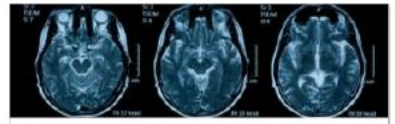
- Lab Method (22)
- Computer Model (20)
- Dataset (5)
- Phantom (2)
  - Physical (1)
- Clinical Outcome Assessment (1)

Program Areas

- Cardiovascular (15)
- Medical Imaging and Diagnostics (12)
- Orthopedic Devices (8)
- Biocompatibility and Toxicology (6)
- Credibility of Computational Models (5)
- Materials and Chemical Characterization (5)
- Neurology (5)
- AI / Machine Learning (2)
- Electromagnetic and Electrical Safety (2)
- Ophthalmology (2)
- Patient Monitoring and Control (2)
- Post Market Signal Response (2)
- Human Device Interaction (1)
- Medical Extended Reality (1)
- Sterility and Infection Control (1)

Search Tool Catalog

Search

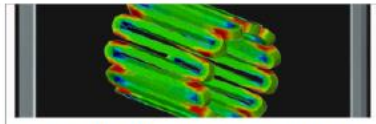


Photoacoustic Imaging Phantoms for Assessing Image Quality and Oximetry Performance

Phantom

This regulatory science tool presents a set of tissue-mimicking phantoms suitable for benchtop performance assessment of photoacoustic imaging (PAI) devices.

Medical Imaging and Diagnostics



Workflow for Assessing the Credibility of Patient-Specific Modeling in Medical Device Software

Computer Model | Lab Method

This regulatory science tool presents a method for assessing credibility of patient-specific computational models implemented in medical device software.

Credibility of Computational Models

TSL/EED/MOS (TEEM) Calculator

Lab Method

This regulatory science tool is a method that applies the ISO 10993-17 toxicological risk assessment approach to medical device extractables screening data to assess systemic...

Biocompatibility and Toxicology

Chemicals List for Analytical Performance (CLAP)

Dataset | Lab Method

Chemicals List for Analytical Performance (CLAP)

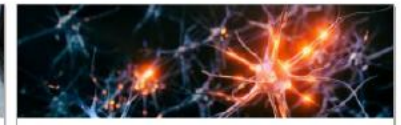
Biocompatibility and Toxicology | Materials and Chemical Characterization

Benchmark Validation Dataset for Laminar Flow in an Anatomical Vascular Model of the Inferior Vena Cava

Dataset

This tool provides a benchmark validation data set for laminar flow in an anatomical vascular model of the inferior vena cava (IVC).

Cardiovascular



EEG based Machine or Deep Learning Algorithms for TBI & Stroke Classification (EMATS)

Lab Method

This RST contains a set of machine or deep learning algorithms which can be utilized in the development of relevant medical devices to assist in the prediction of traumatic brain injury (TBI) an...

Neurology

Mock Circulatory Loop Generated Database for Dynamic Characterization of Pressure-based Cardiac Output Monitori...

Dataset

This RST is a database tool consisting of nine mock circulation loop (MCL)-generated datasets for characterizing three dynamic attributes of pressure-based cardiac output monitoring systems that...

Cardiovascular | Patient Monitoring and Control

A "threshold-based" Approach to Determining an Acceptance Criterion for Computational Model Validation

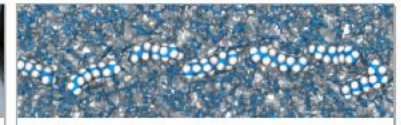
Computer Model

This RST, a "threshold-based" validation method, provides a means to determine an acceptance criterion for computational models. A "credible" computational model has the potential to provide ...

Cardiovascular

Strategy to Estimate Low to High Cycle Fatigue Transition of Nitinol for Fatigue to Fracture Test Planning

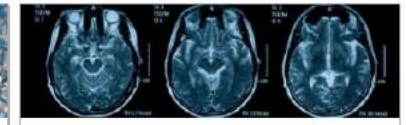
Lab Method



Device and Material Safety Evaluation Library (DAMSEL)

Dataset

The DAMSEL tool is a digital collection of published



VICTRE: In Silico Breast Imaging Pipeline

Computer Model

The Virtual Imaging Clinical Trials for Regulatory Evaluation (VICTRE) computer modeling pipeline is

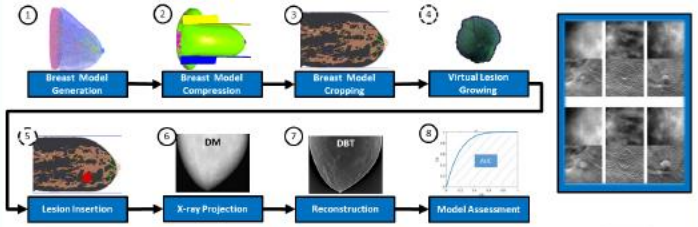
Targeted Box and Blocks Test (tBBT)

Clinical Outcome Assessment

A performance-based method requiring controlled grasping, transport, and release of objects that can

VICTRE PIPELINE

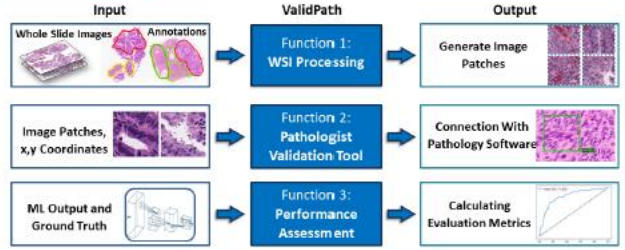
The simulating virtual images of the breast to reduce costs of clinical trials, including 3000 digital breast models in digital mammography (DM) and digital breast tomosynthesis (DBT) systems.



Badano, Aldo, et al. "Evaluation of digital breast tomosynthesis as replacement of full-field digital mammography using an in silico imaging trial." JAMA network open 1.7 (2018): e185474-e185474.

VALIDPATH

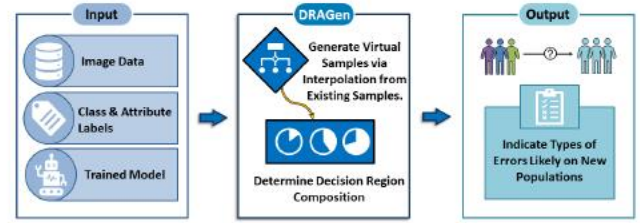
The whole slide image (WSI) processing and machine learning (ML) performance assessment tool.



Kahaki, Seyed, et al. "End-to-end deep learning method for predicting hormonal treatment response in women with atypical endometrial hyperplasia or endometrial cancer." Journal of Medical Imaging 11.1 (2024): 017502-017502.

DRAGen

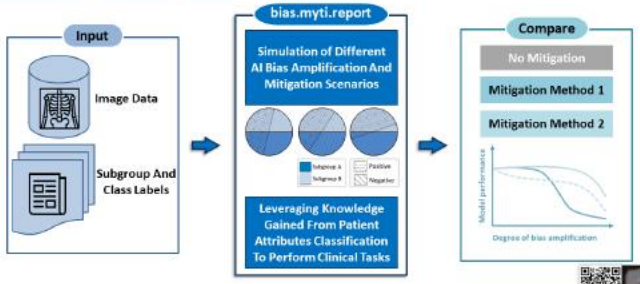
Decision Region Analysis for Generalizability: Assists in identifying the types of errors an AI model is likely to make when used on a new patient population.



Burgon, Alexis, et al. "Decision region analysis for generalizability of artificial intelligence models: estimating model generalizability in the case of cross-reactivity and population shift." Journal of Medical Imaging 11.1 (2024): 014501-014501.

bias.myti.report

Provides guidance for the AI developer to compare different bias mitigation methods through the systemic creation of AI models with varying degrees of bias.

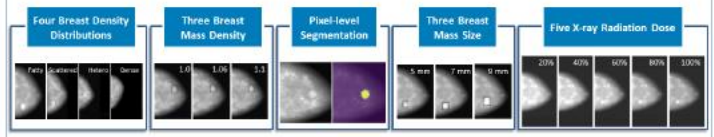


Burgon, Alexis, et al. "Manipulation of sources of bias in AI device development." Medical Imaging 2024: Computer-Aided Diagnosis. Vol. 12927. SPIE, 2024.

M-SYNTH

The synthetic digital mammography image dataset for comparative evaluation of artificial intelligence (AI) on a diverse population of cases, some of which may not be readily available in the clinic.

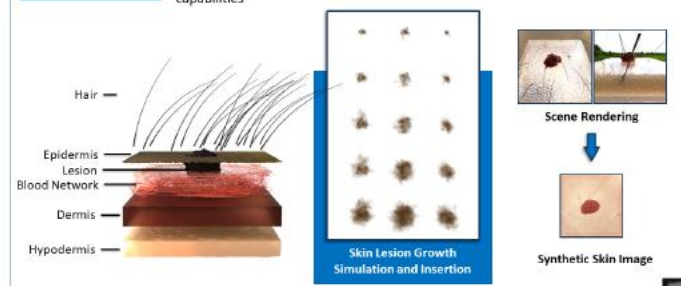
45,000 publicly available synthetic mammography images generated with various breast characteristics using different imaging device (x-ray) parameters



Sizikova, Elena, et al. "Knowledge-based in silico models and dataset for the comparative evaluation of mammography AI for a range of breast characteristics, lesion conspicuities and doses." Advances in Neural Information Processing Systems 36 (2024).

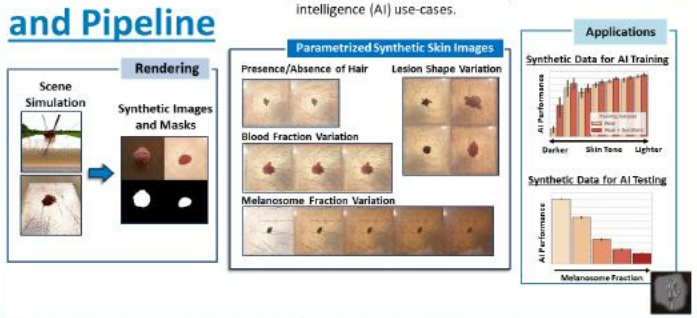
S-SYNTH

A knowledge-based multi-layer, multi-component, procedural skin model for generating synthetic images of skin conditions with full spectral capabilities



S-SYNTH Dataset and Pipeline

A parametrized data generation pipeline for creating synthetic skin images, along with an accompanying dataset of pre-generated examples and artificial intelligence (AI) use-cases.



WebXR Tools

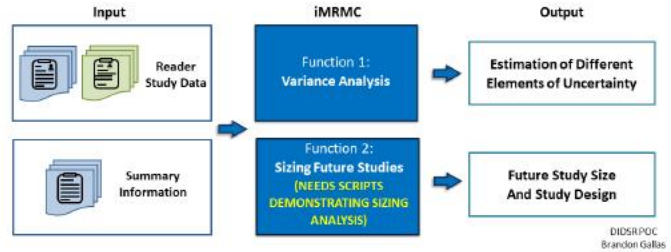
A tool for medical extended reality image quality assessment through creating customized scenes and patterns.

- ✓ Custom creation of patterns to evaluate image quality
- ✓ Universal and compatible with multiple headsets and technologies
- ✓ Shareable scenes for easy deployment
- ✓ Animations to study spatiotemporal effects

Collins, Brendan, Ryan Beams, and Miguel Lago. "Open-Source Pattern Creation Tool for Medical Extended Reality Image Quality Assessment." Journal of Open Source Software 9.93 (2024): 6021.

iMRMC

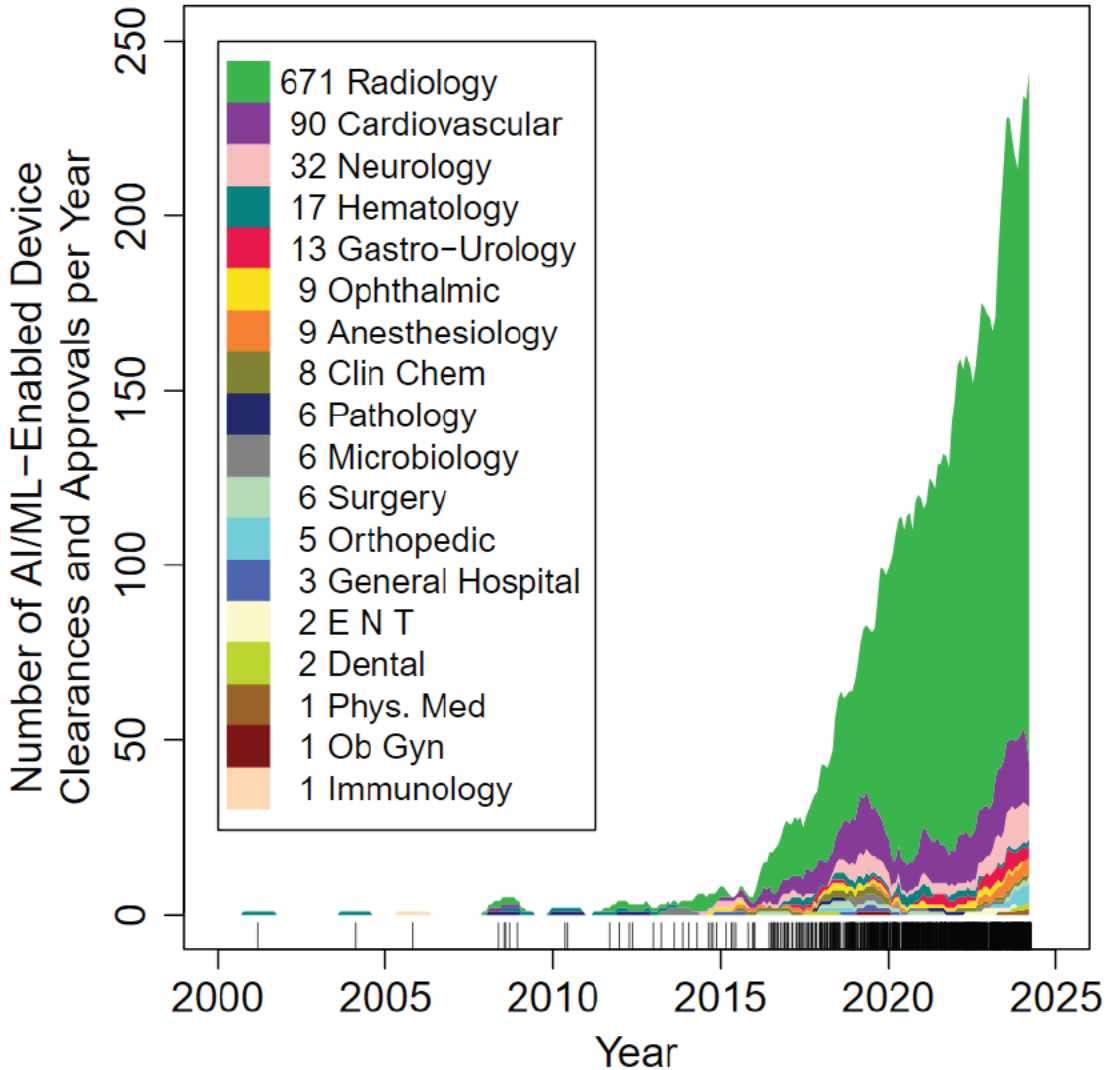
A software to perform statistical analysis on reader studies, where clinicians (readers) evaluate patient data (cases) to compare the effectiveness of two different modalities.



DIDSRPOC
Brandon Gallas

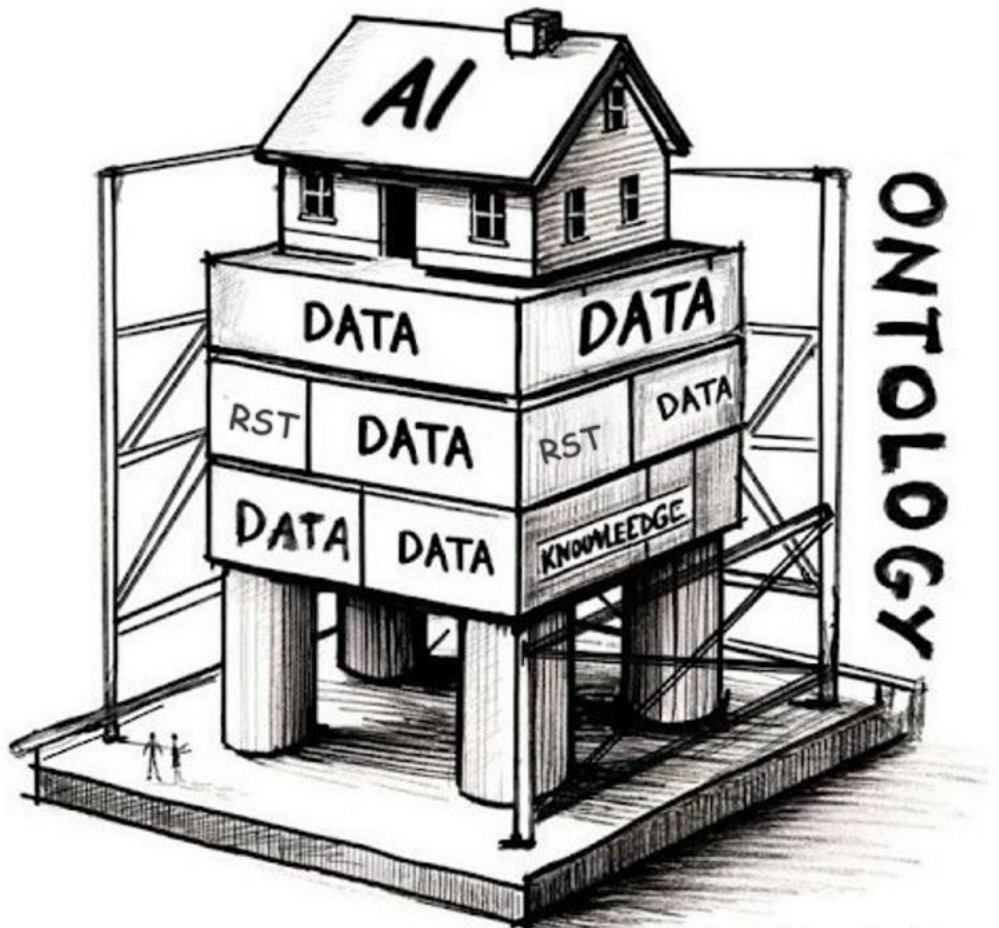
Gallas, Brandon D., et al. "A framework for random-effects ROC analysis: biases with the bootstrap and other variance estimators." Communications in Statistics—Theory and Methods 38.15 (2009): 2586-2603.

Why synthetics?



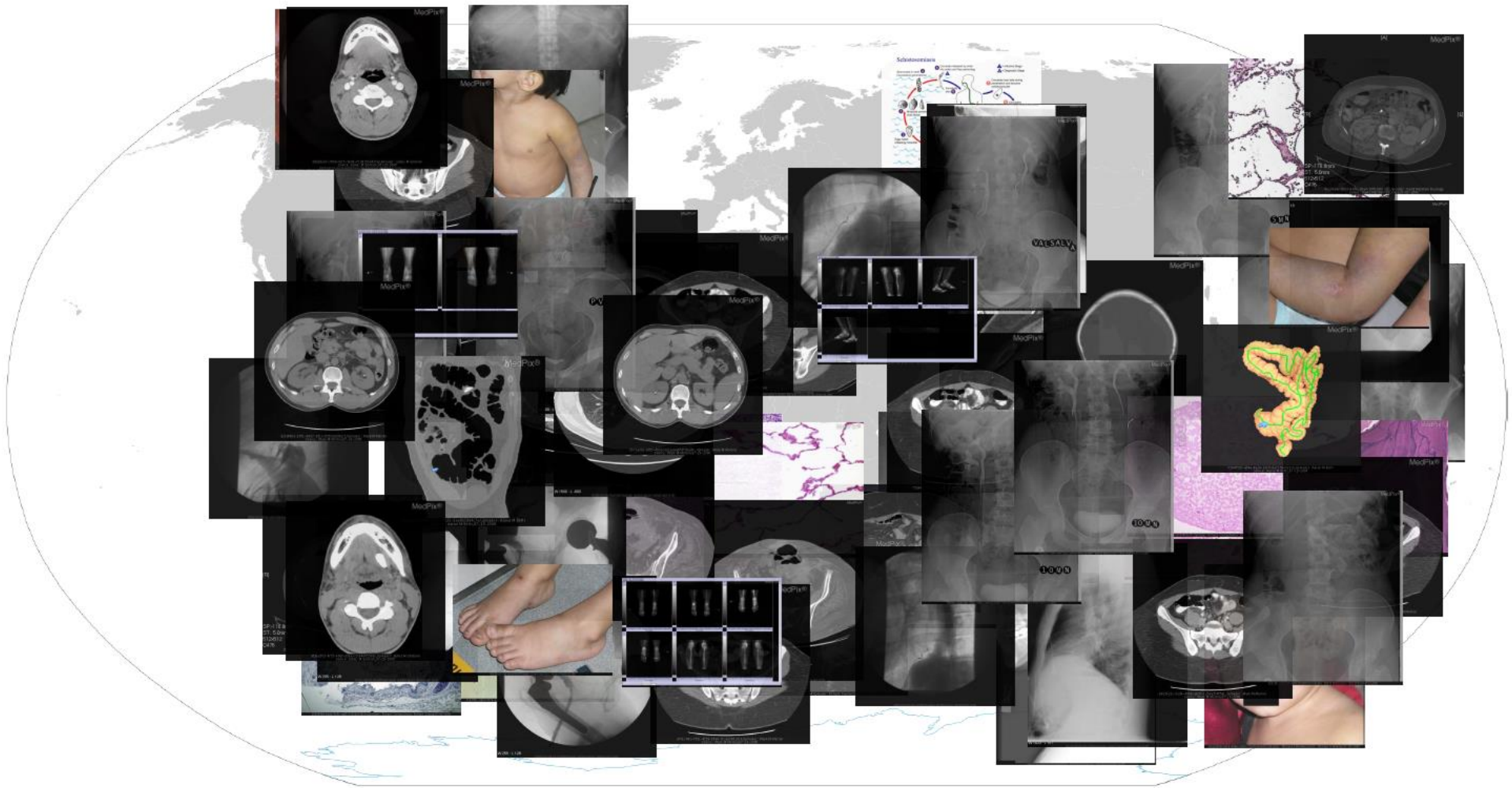
Courtesy of Frank Samuelson (DIDSR/OSEL/CDRH)

It's (almost) all about the data . . .



Credit: Stolen (and adapted) from the internet

data quality
data access
data representativeness
data privacy
data labels
data annotations
data context
data protocols
data collection
data formats
data sharing

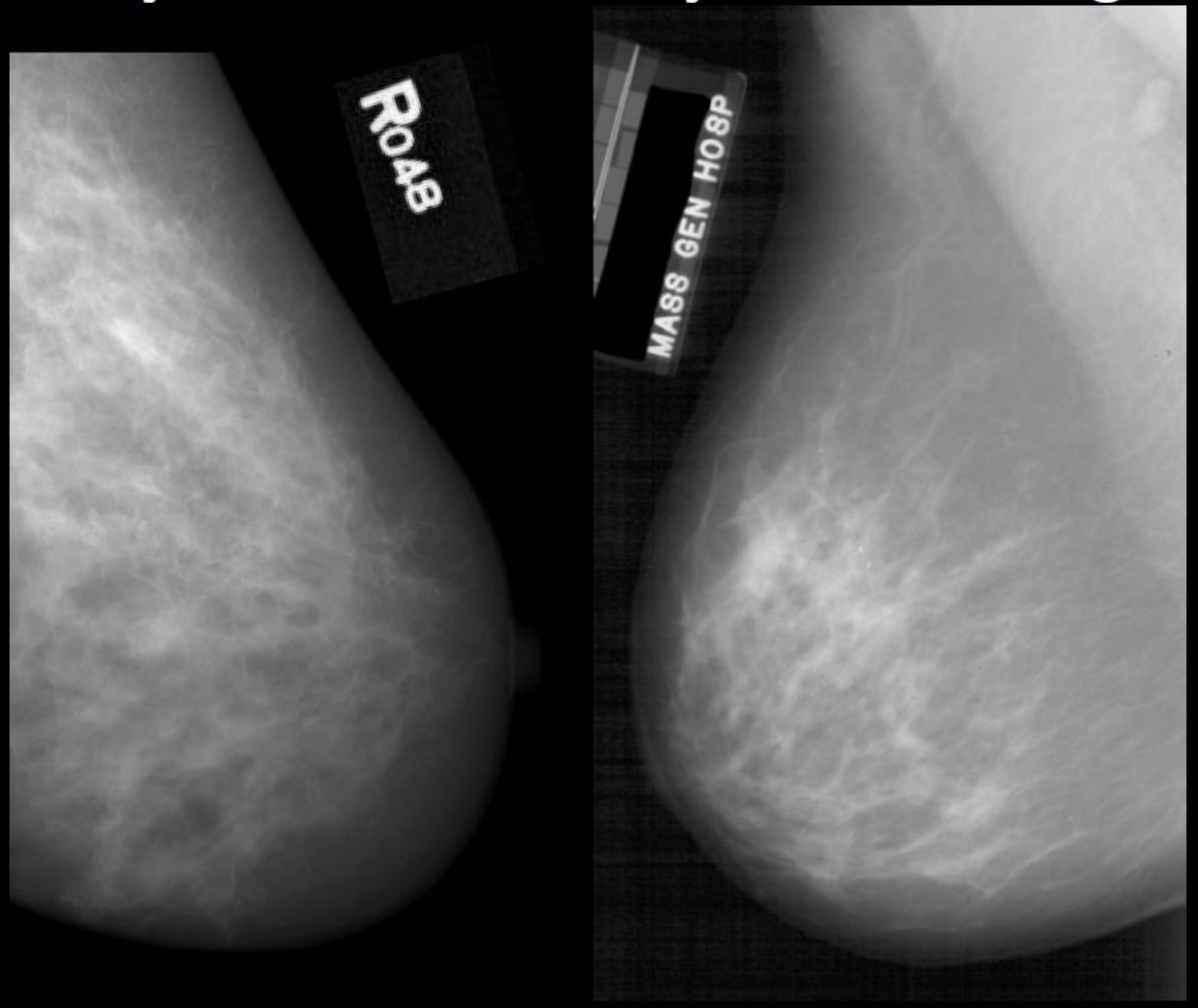


$\mathbf{10^4}$ cases $\times$ $\mathbf{10^4}$ devices $\times$ $\mathbf{10^2}$ iterations $\times$ $\mathbf{10^2}$ monitoring

Why synthetics?

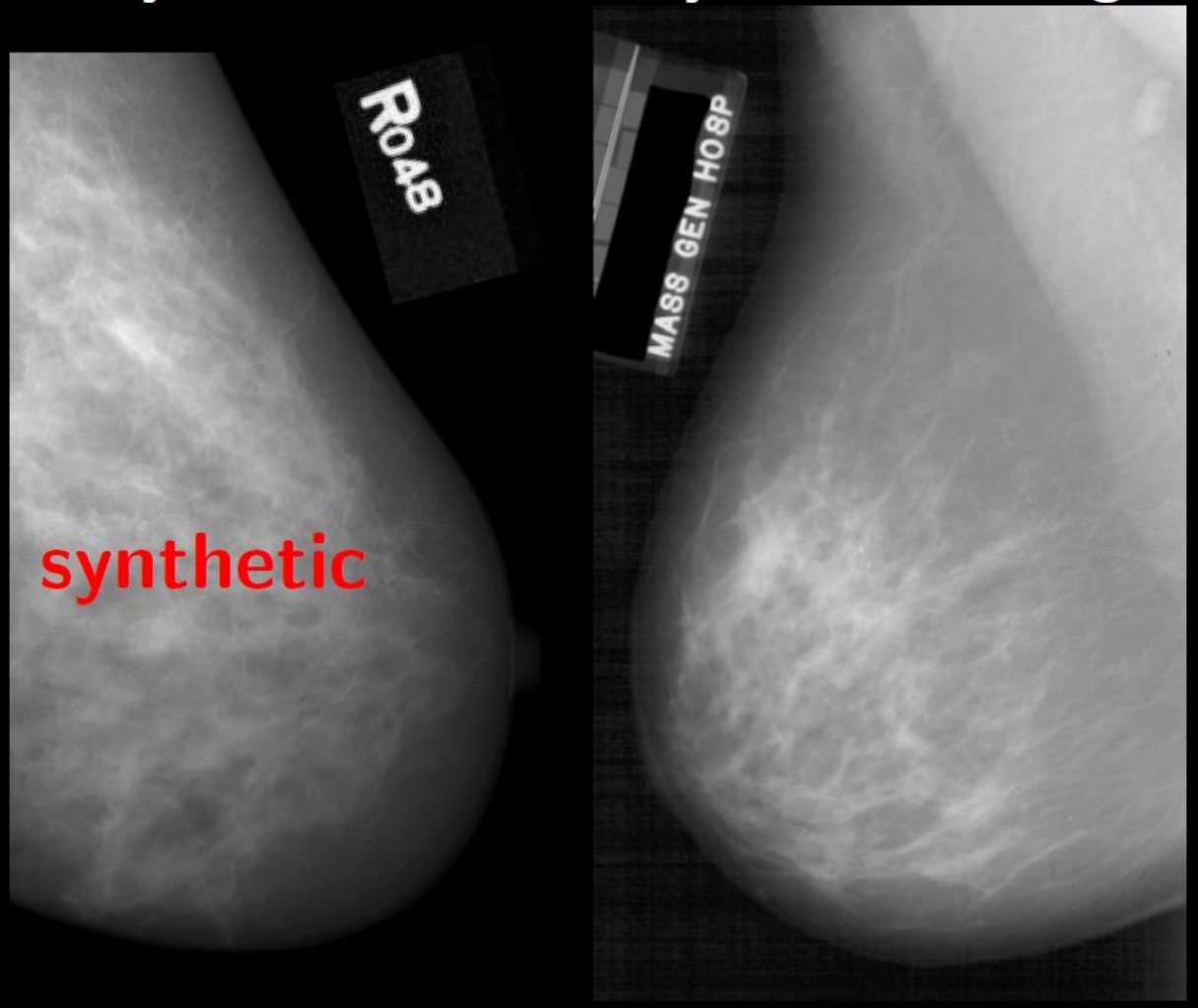
Unlimited samples
Exact labels by design (or, adjustable uncertainty)
Diversity (eg, rare conditions)
Representative and balanced cohorts
Safe for patients

Which mammography image is from a patient and not synthetic?
Raise your hand if you believe the synthetic image is on the right.



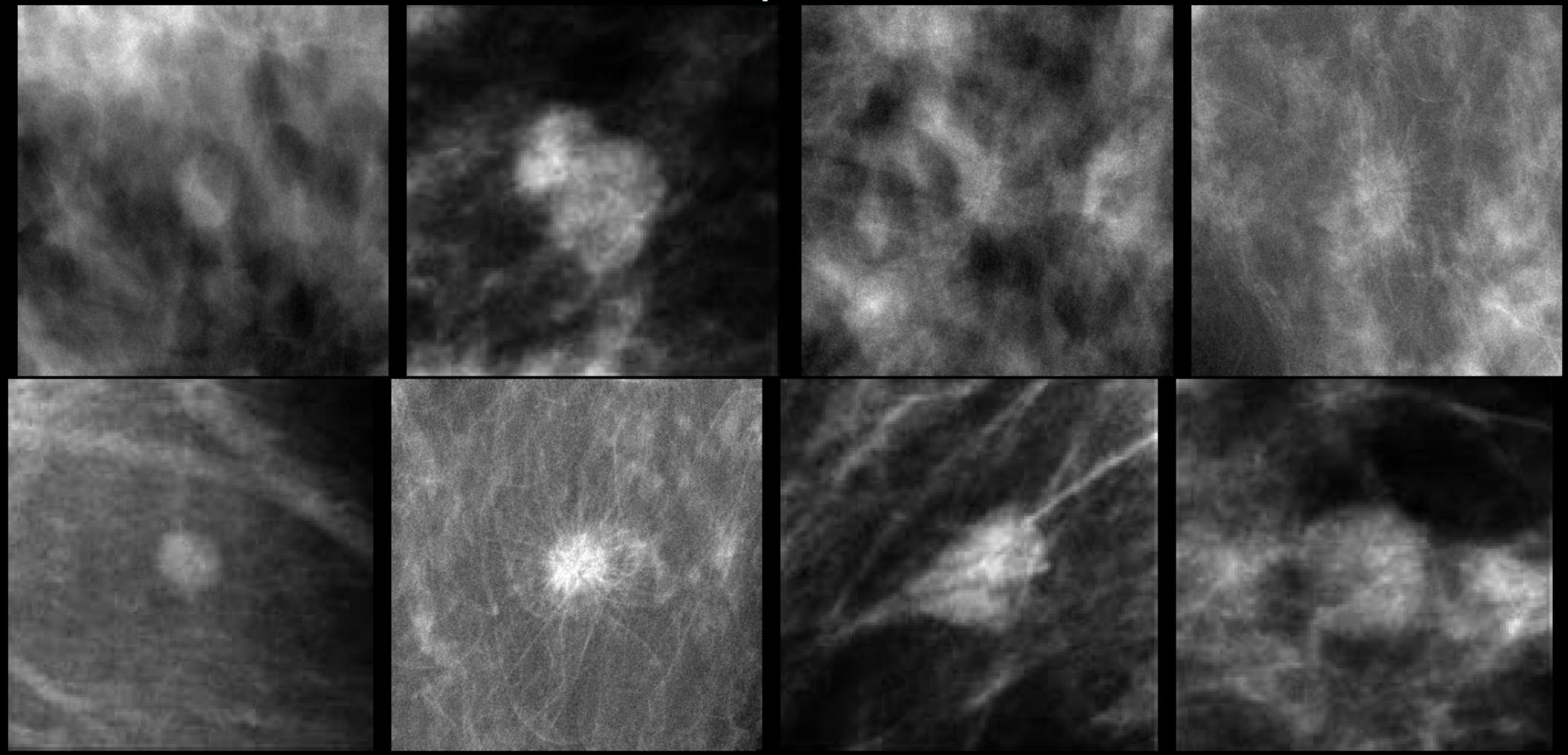
(left) (right)

Which image of a breast cancer lesion is from a patient and not synthetic?
Raise your hand if you believe the synthetic image is on the right.



(left) (right)

Who can find the 2 lesions from patients?



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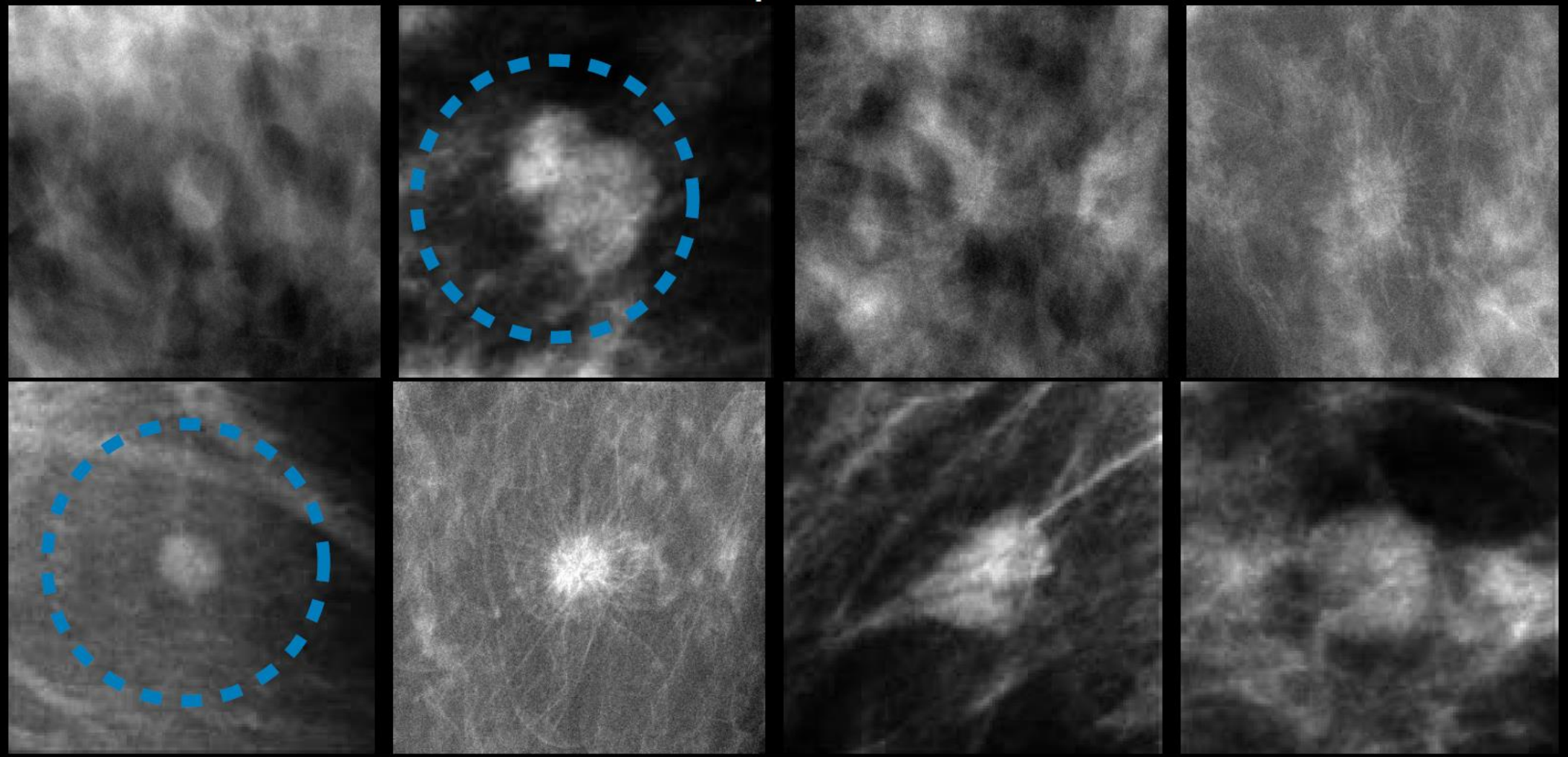
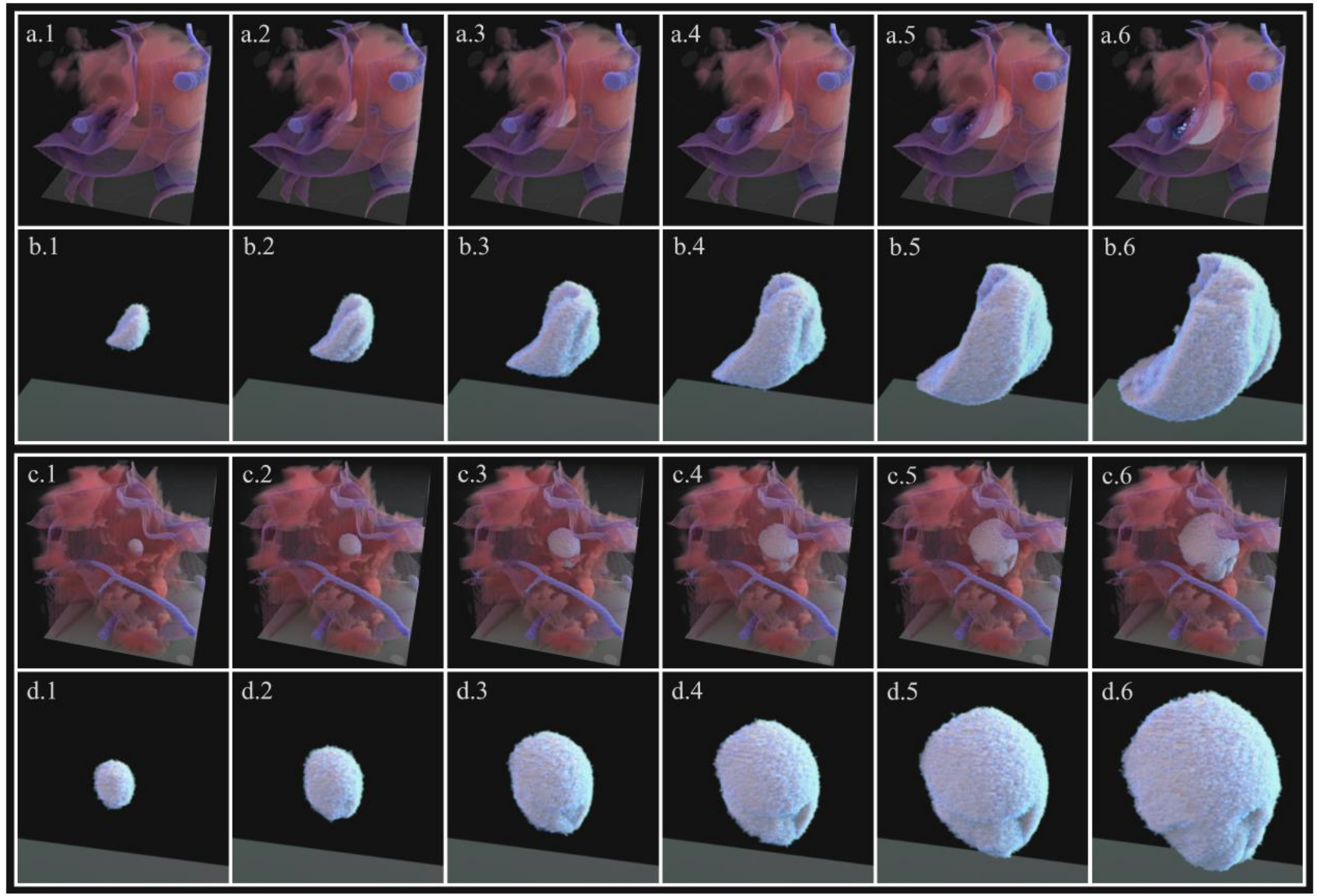
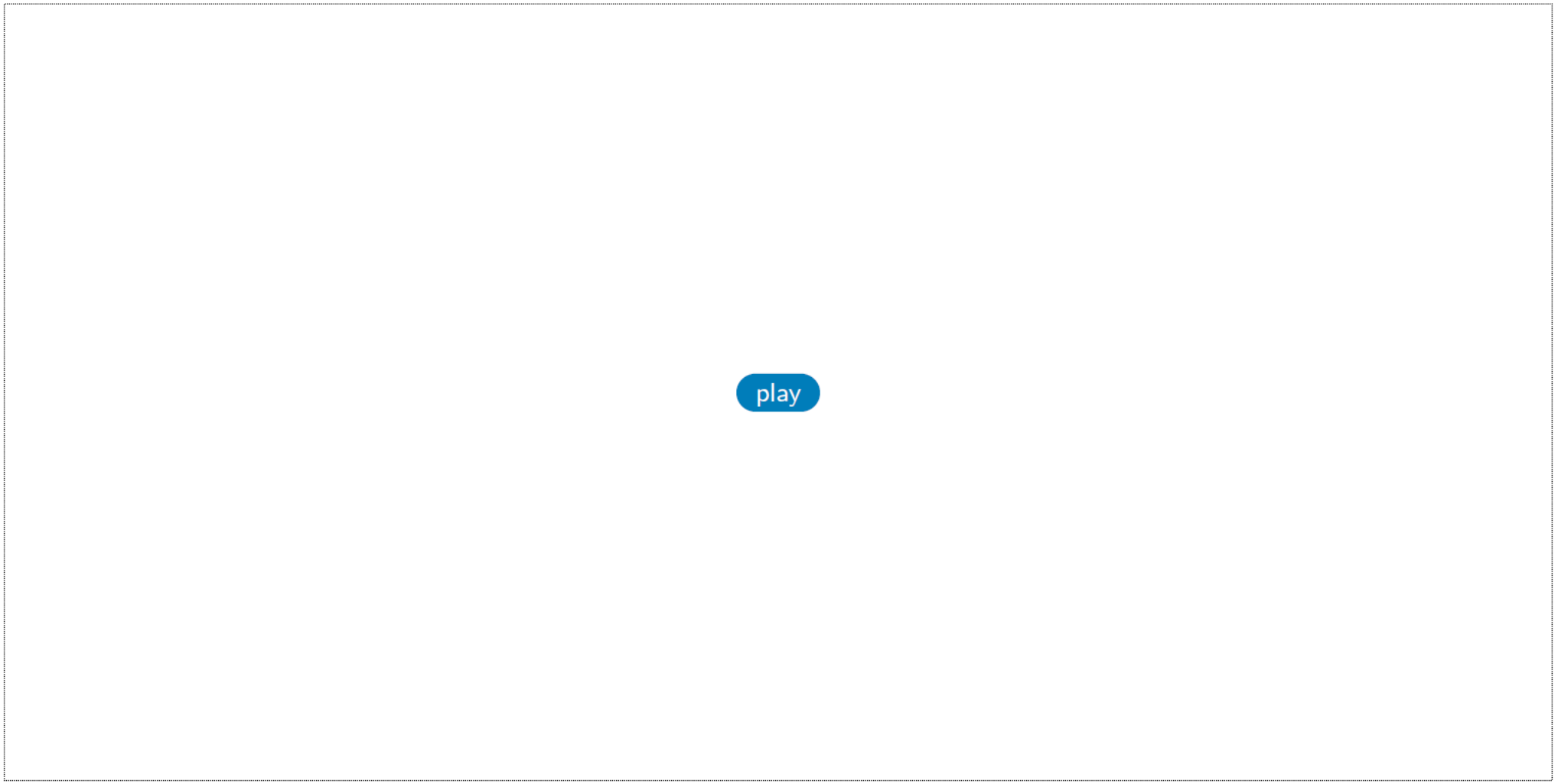




A Kim et al., SPIE Medical Imaging 2023.

Synthetic skin for evaluating skin lesion analyzers



Courtesy of Andrea Kim (DIDSR/OSEL/CDRH)

OVERVIEW: SPECTRAL RENDERING OF MULTI-LAYER SKIN MODELS

ANDREA S. KIM, MIGUEL A. LAGO, AND ALDO BADANO (DIDSR/OSEL/CDRH/FDA)

Time: 10-30 mins per set — Houdini

Procedural generation of blood network and multi-layer skin models

Surface noise parameters:
- Amplitude
- Roughness
- Turbulence

→ Hypodermis Model

Shortest path parameters:
- Thickness of dermis
- Start and end points
- Scatter seed number

→ Blood Network Model

Thickness parameter:
- Random range [1000u, 4000u]

→ Dermis Model

Thickness parameter:
- Random range [40u, 150u]

Dermis-Epidermis Junction:
- Papillary count [1000, 2000]
- Scatter seed number

Surface (top) noise parameter:
- Perlin noise offset

→ Epidermis Model

10 parameters:
- Hair density, length, bend Curve angle, rotation, thickness, scatter seed, etc.

→ Hair Model

Output: .obj
Procedural generation and export of models automated in python — python

python

Lesion growing simulation and export of models

Growing step	$S \sim U(1,2)$
Probabilities update	$G(\mu = 0, \sigma = 0.5)$
Cancer probability	$C_p = 0.0001$
Cancer iterations	$C_i = 10$
Maximum cancer recursion	$C_r = 2$

By Miguel Lago

→ Lesion Model

Output: .raw voxel array

→ No Lesion

Time: varies per resolution — Mitsuba

Establishment and spectral rendering of virtual environment

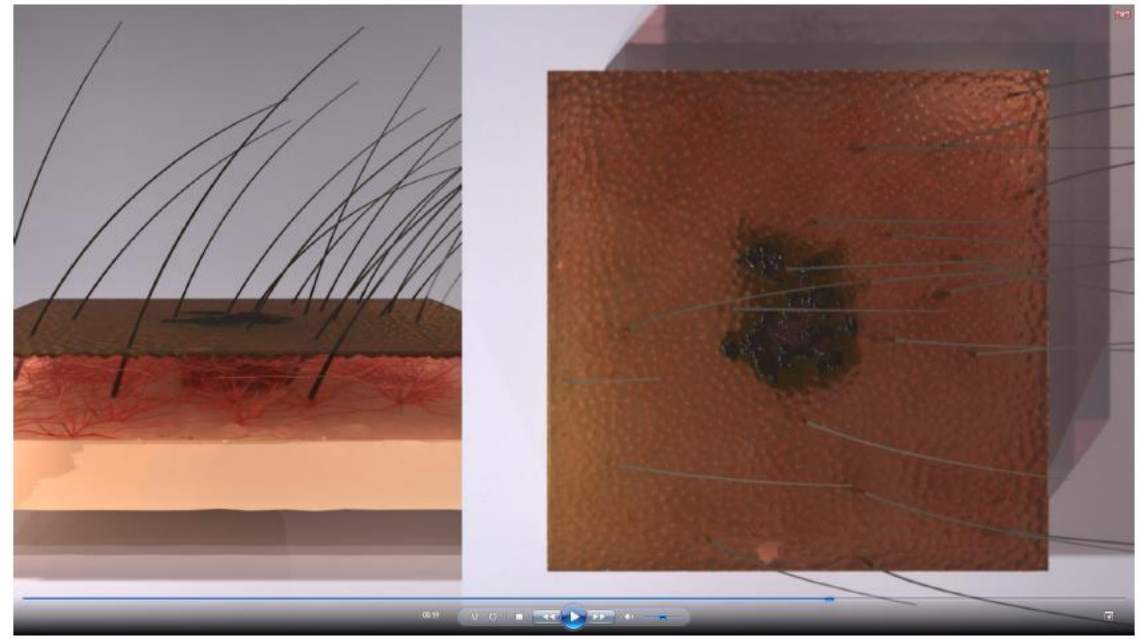
Camera Properties:
- Sensor type: Perspective
- Film: HDR Film (can set Sensor Response Function that defines the spectral sensitivity of the sensor)

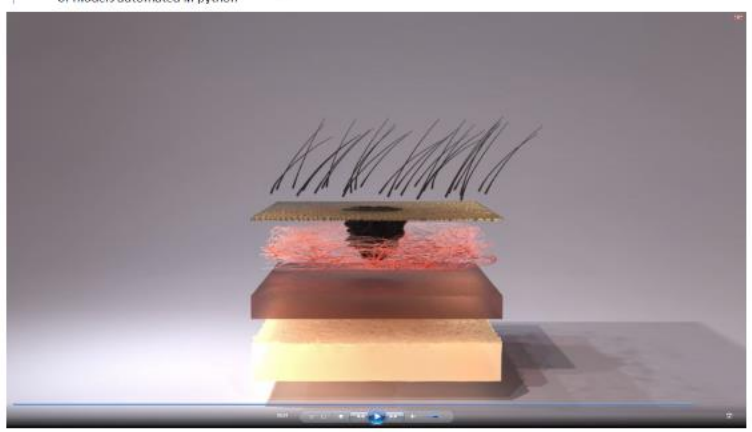
Source Light Properties:
- Emitter type: Area
- Emitter shape: Square at [0, 1, 0], pointing downwards (rotation [90, 0, 0])
- Radiance: D65
- Emitter radiance range: [360 nm, 830 nm]
- Emitter type 2: HDRI environment map

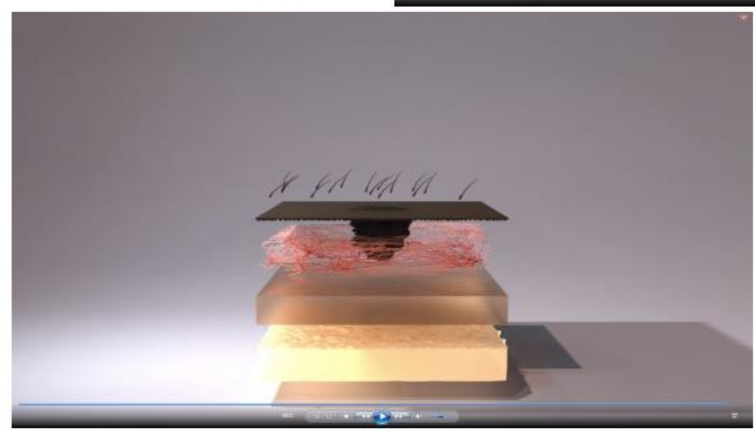
Rendering Properties:
- Integrator (the rendering technique): Volumetric path tracer with spectral multiple importance sampling (required for spectrally varying materials)

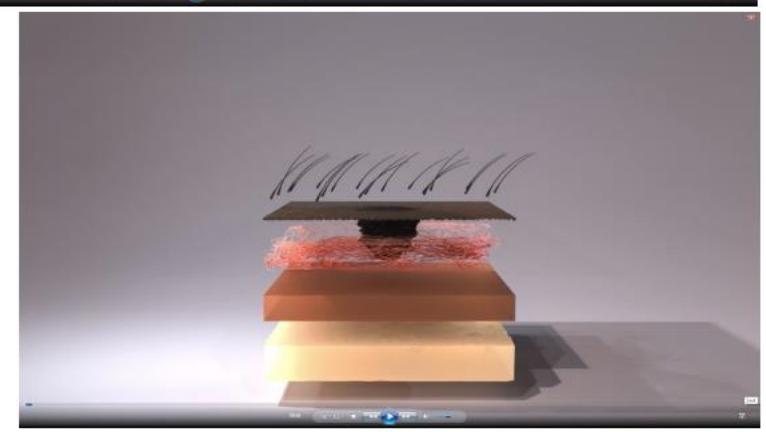
Optical properties for Lesion and Skin Models:
- Material type: Participating Media
  - Spectral Albedo Coefficients
  - Spectral Extinction Coefficients
- Surface Scattering Model/BSDF: Rough Dielectric
  - IOR
  - Alpha (surface roughness)

Output: .exr or .png
Scene scripted in jupyter notebook — python









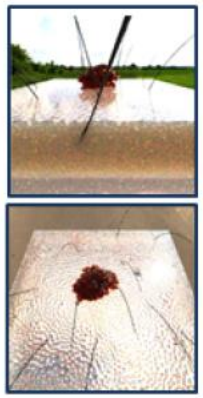
Courtesy of Andrea Kim (DIDSR/OSEL/CDRH)

S-SYNTH Dataset and Pipeline

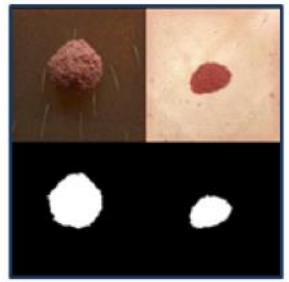
A parametrized data generation pipeline for creating synthetic skin images, along with an accompanying dataset of pre-generated examples and artificial intelligence (AI) use-cases.

Rendering

Scene Simulation

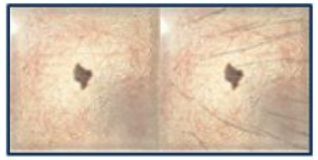


Synthetic Images and Masks

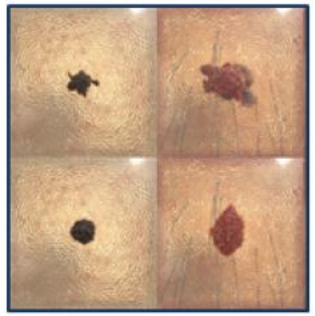


Parametrized Synthetic Skin Images

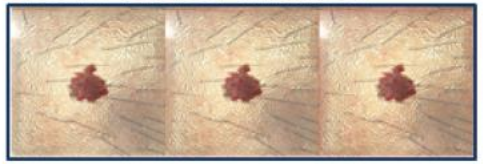
Presence/Absence of Hair



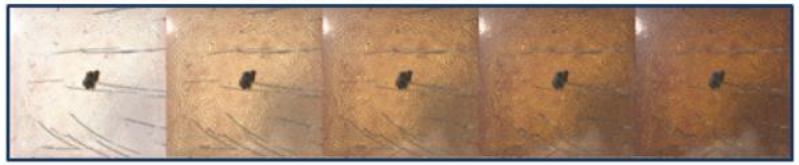
Lesion Shape Variation



Blood Fraction Variation

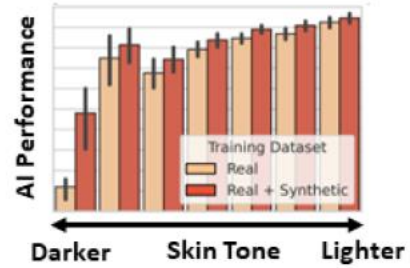


Melanosome Fraction Variation

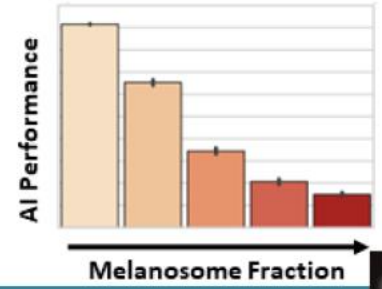


Applications

Synthetic Data for AI Training



Synthetic Data for AI Testing



Challenges in synthetic data models: fakes

DOWNLOAD PDF 92 12

Fake detection in AI-assisted image recovery using scanning Fourier Ring Correlation (sFRC)

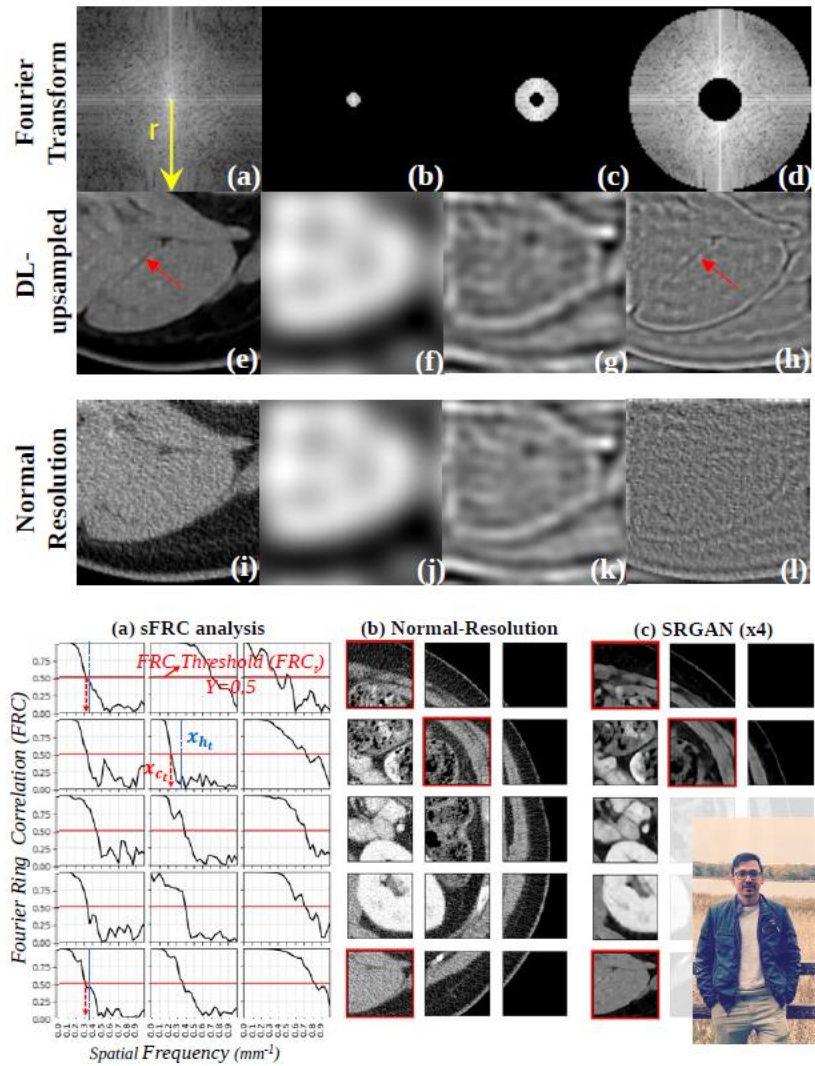
SIGNAL PROCESSING AND ANALYSIS

ARTIFACTS BIOMEDICAL IMAGING DEEP LEARNING FAKE DETECTION HALLUCINATION IMAGE QUALITY INVERSE PROBLEM MACHINE LEARNING SUBSAMPLED ACQUISITION SUPER-RESOLUTION

Prabhat Kc, Rongping Zeng, Nirmal Soni, aldo badano

Abstract

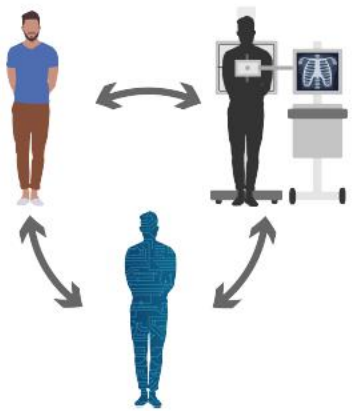
Deep learning (DL) methods are currently being explored to recover images from sparse-view, limited-data, and undersampled acquisitions in medical applications. Although DLbased solutions may appear visually appealing based on likability/subjective criteria (such as less noise, smooth features), they may also suffer from imperceptible fakes. This issue is further exacerbated by a lack of easy-to-use techniques and robust metrics for the identification of fakes in DL-based outputs. In this work, we propose performing Fourier Ring Correlation (FRC)based analysis over small patches and concomitantly scanning across DL-based outputs and their reference counterparts to identify fakes. We term the metrics as sFRC. We describe the rationale behind sFRC and provide its mathematical framework. The thresholds required for the sFRC can be set using predefined fake features or imaging theory-based fake maps. We use sFRC to identify fakes for two undersampled medical imaging problems (CT super-resolution and MRI subsampled recovery). We demonstrate the effectiveness of sFRC in finding fake features for the two imaging problems and its agreement with a different imaging theory-based method on fake feature maps. Finally, we quantify the incidences of fakes from DL-based methods relative to indistribution versus out-of-distribution data and the increment in subsampling rate.



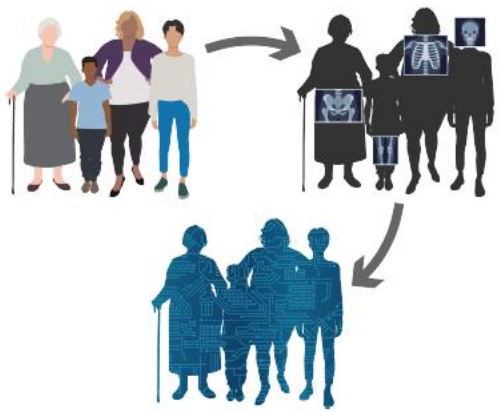
Digital humans

Individual models (non-stochastic)

Digital twins

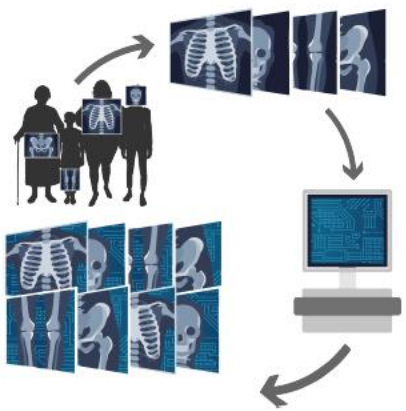


Digital families

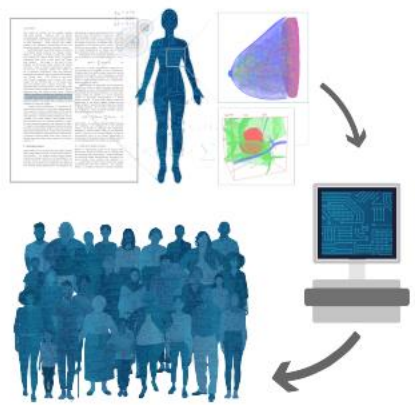


Population models (stochastic)

Data-driven



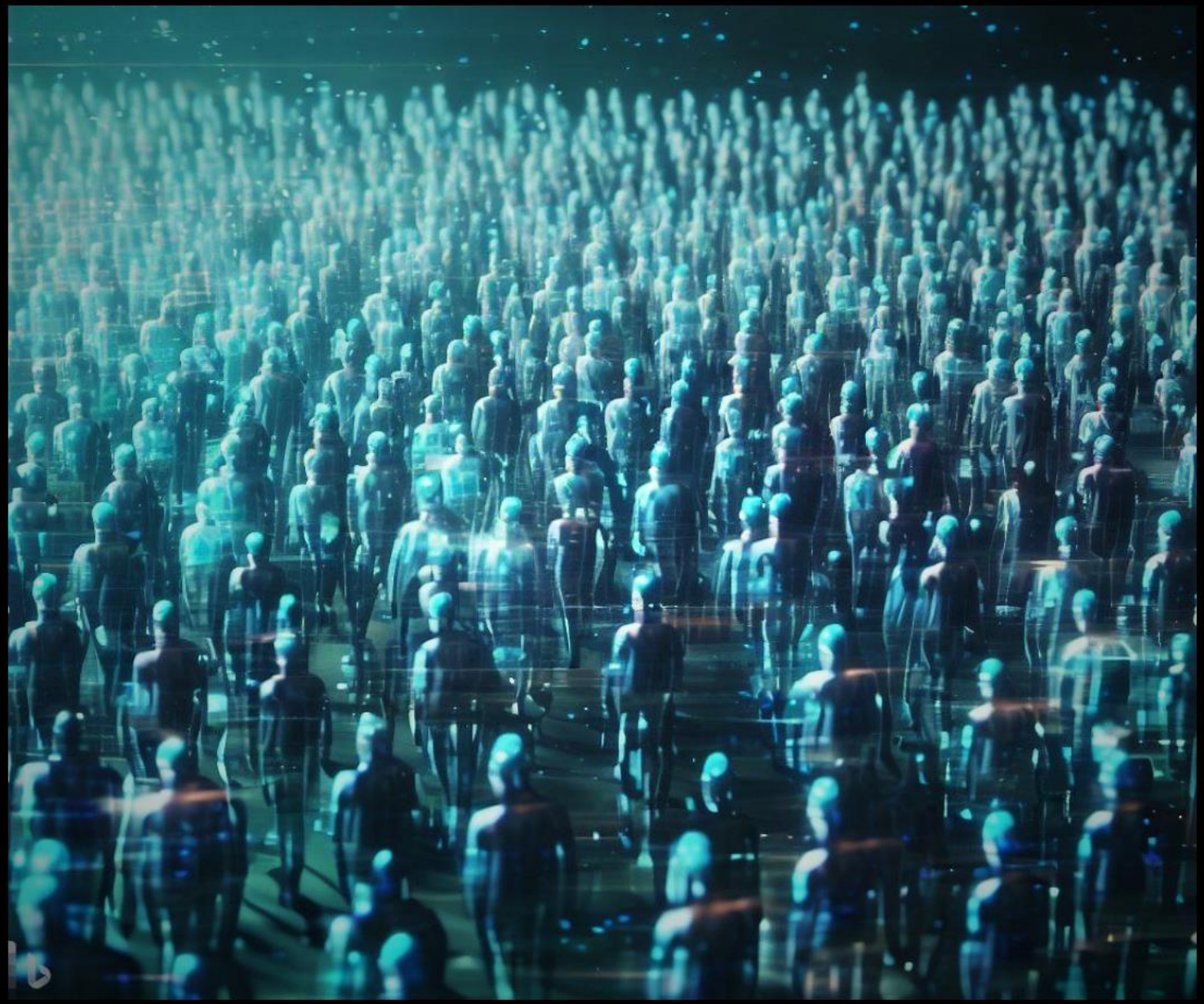
Knowledge-based



The stochastic digital human is now enrolling for in silico imaging trials - Methods for generating digital cohorts.

▸ A Badano et al. 2023 Prog. Biomed. Eng. 5 042002

Graphics designed by Andrea Kim (DIDSR/OSEL/CDRH)



The future of medical device evaluation is in silico

Tri-Agency NSF/NIH/FDA pilot FDT-Biotech

- Foundations for Digital Twins as Catalyzers of Biomedical Technological Innovation (FDT-BioTech) supports interdisciplinary research on mathematical/engineering foundations of DTs and synthetic data in biomedicine and healthcare with a focus on in silico models for evaluation of medical devices.
- Priorities include representations of physiology, **transferability, generalizability, robustness**, ethics, security, privacy, and **validation & sharing mechanisms**.
- The program encourages development of open-source tools.

Regulatory science priorities for medical DTs

1. Evaluation of data-driven models as DT components

VVUQ for data-driven models & guardrails against fakes and hallucinations

2. Continuous and multi-modal data sources

Models fixed but parameters updating, or models evolving with data

3. Patient-specific versus intended use population descriptions

From in silico distributions to patient-specific models and correctness at patient level post-deployment

4. Model transferability, generalizability, and robustness

Variability in clinical use, data acquisition, humans, and disease pathways

U.S. FOOD & DRUG ADMINISTRATION (& Devices)

▸ www.fda.gov/about-fda/cdrh-offices/office-science-and-engineering-laboratories

in aldobadano aldobadano

Kelly Brown-Plueschke

EMA

EDITH is a coordination and support action funded by the Digital Europe program of the European Commission under grant agreement n° 101083771

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Medicines Agency's support to innovation related to pharmaceutical developments

EDITH-CSA Ecosystem Meeting, 15-16 July 2024

Presented by Kelly Plueschke, European Medicines Agency –
Data Analytics and Methods Task Force (TDA-RWE)

What does EMA do?

Protect human and animal health

- ≈50 national regulatory authorities (27 Member States)
- European Medicines Agency
- European Commission

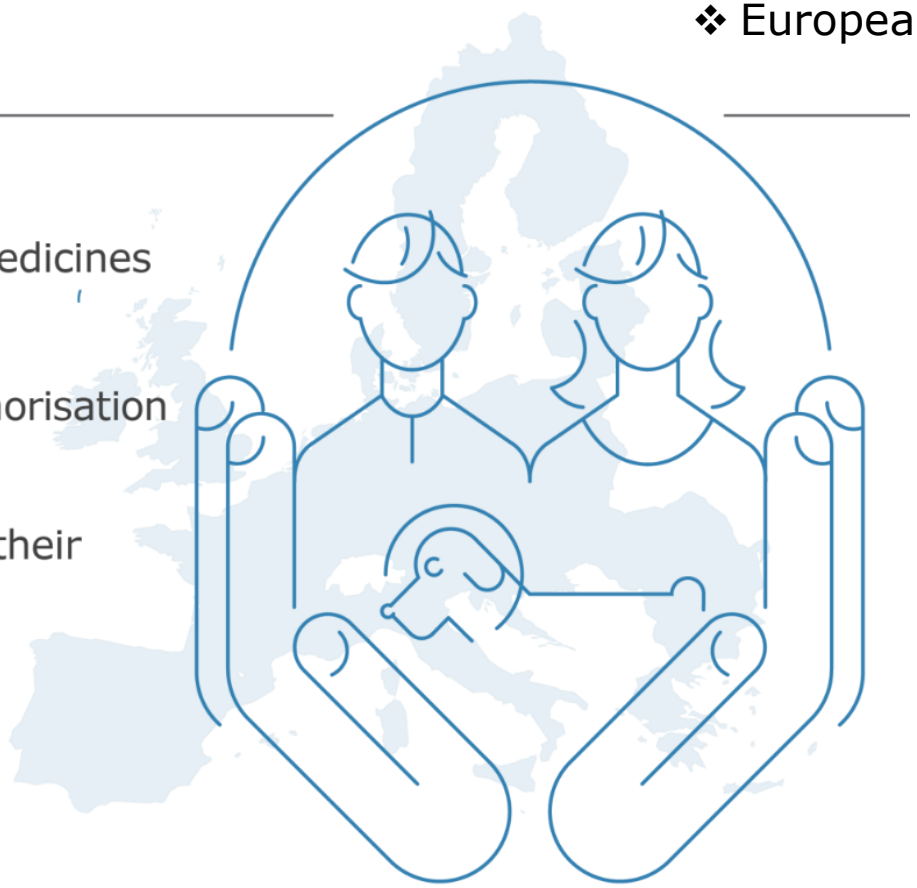
Facilitate development and access to medicines

Evaluate applications for marketing authorisation

Monitor the safety of medicines across their life cycle

ABC
XΨΩ

Provide reliable information on human and veterinary medicines to patients and healthcare professionals



Translation of European Pharma Innovation Strategies

EUROPEAN MEDICINES AGENCY

Catalysing the integration of science and technology in medicines development

FIVE GOALS for human medicines regulation

Enabling and leveraging research and innovation in regulatory science

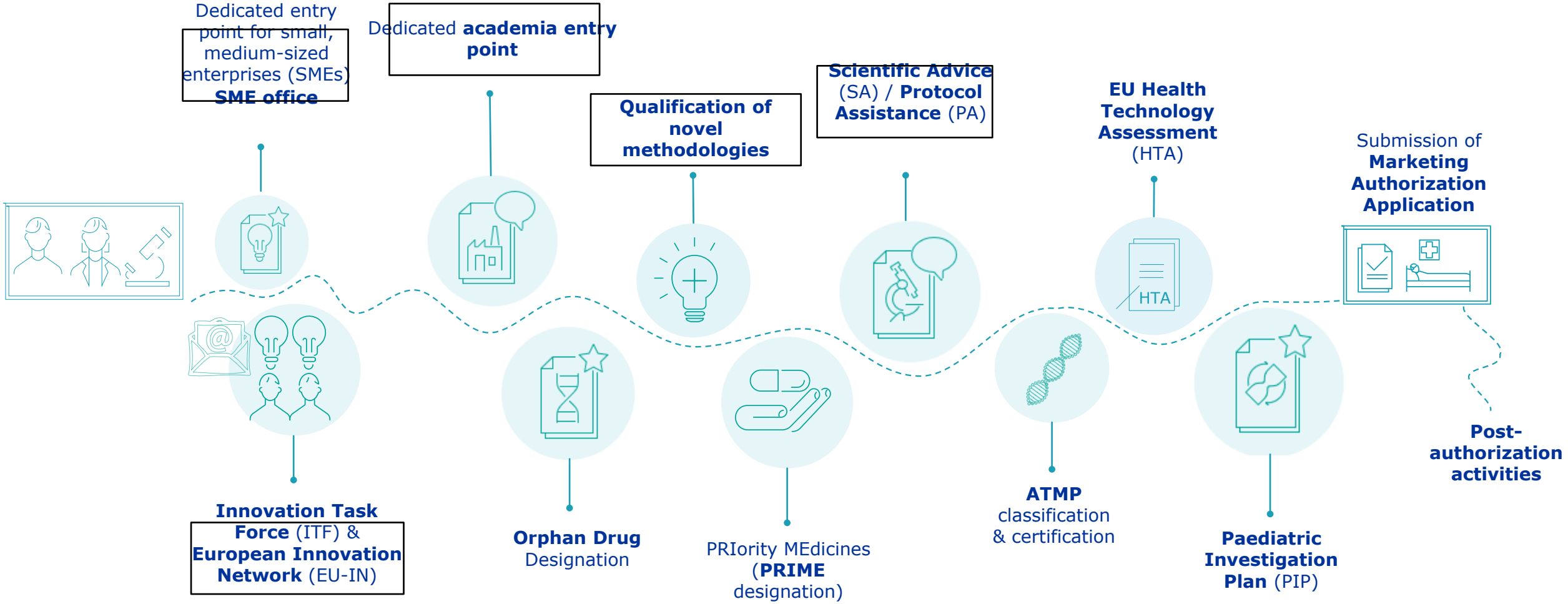
Driving collaborative evidence generation – improving the scientific quality of evaluations

Addressing emerging health threats and availability/therapeutic challenges

Advancing patient-centred access to medicines in partnership with healthcare systems

Ongoing revision of EU pharmaceutical legislation

EMA interactions across the medicine life cycle



Innovation Task Force (ITF) briefing meetings

EUROPEAN MEDICINES AGENCY

Multidisciplinary platform

Dialogue and orientation on innovative methods, technologies and medicines

Topics

- **Emerging therapies** (cell & gene therapies, targeted therapies, nano-medicines)
- **Emerging technologies** (digital / platform technologies, novel manufacturing)
- **Emerging methods** (organ-on-chip, 3Rs, new drug delivery systems, clinical trial methodology)

Support **innovative** drug development

Early informal dialogue with opinion leaders

1,5-hour discussion – *Free of charge*

Engage conversations on innovation in areas without existing guidance

First step to engage is submit completed 3-page template

itfsecretariat@ema.europa.eu - for human medicines
itfvet@ema.europa.eu - for veterinary medicines

Support to Academia

EMA **framework for collaboration with academia** since 2017:

- to translate **academic research** into novel methodologies and medicines
- ensure that the **best scientific expertise and academic research** is available to inform regulatory decision-making
- **collaborate on areas of research on regulatory science** (novel approaches, endpoints, methodologies)
- Academia@ema.europa.eu

Incentives for Academia:

- Protocol assistance **free-of-charge** to academic developers of orphan medicines
- EMA pilot: enhanced support to academic and non-profit developers of advanced therapy medicinal products (ATMPs)

EMA SME Office

EUROPEAN MEDICINES AGENCY

SME@ema.europa.eu
SME Helpline :
+31 (0)88 781 8787

SMEs are an important source of innovation

Support to SMEs

EU SME regulation(EC) No 2049/2005 of 15 December 2005

Aims to promote innovation and development of new medicines by SMEs

EMA SME Office launch in December 2005

- Dedicated contact point
- Assign EMA SME status
- Fee incentives
- Engage with EU bodies and stakeholders

SME user guide, Info days,
SME newsletters,
Mailings / announcements

Assistance to SMEs : Topics covered

- Scientific advice / protocol assistance
- Regulatory and procedural aspects
- Orphan drug designation, Paediatric requirements
- Access to SME incentives
- PRIME eligibility

Qualification of novel methodologies and biomarkers

EUROPEAN MEDICINES AGENCY

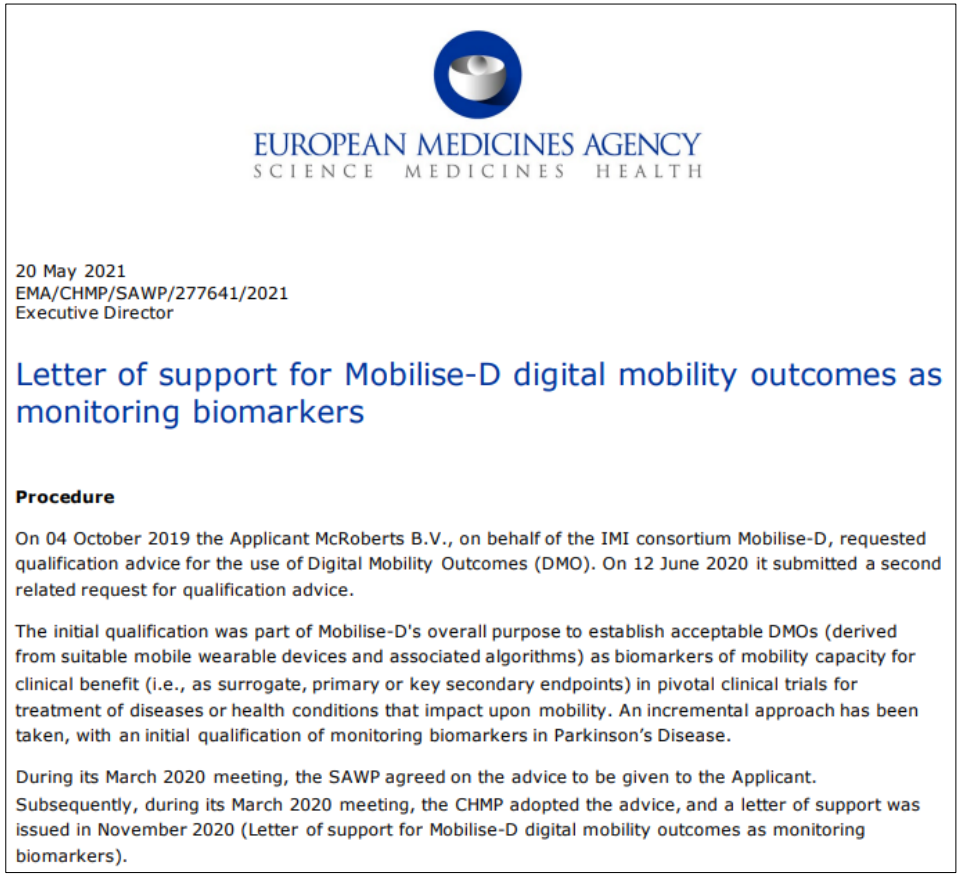
The CHMP can issue:

- an **opinion** (publicly available) on the **acceptability of a specific use of a method** in an R&D context based on the assessment of submitted data;
- an **advice** (confidential) on **future** protocols and methods for further method development towards qualification - **Letter of support** is possible

Aim: Speed up/optimise drug development

Examples:

- Biomarkers (predict toxicity, enrich patient population…)
- Surrogate clinical endpoints, digital technologies
- Patient and caregiver reported outcomes
- Patient/disease registries



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 May 2021
EMA/CHMP/SAWP/277641/2021
Executive Director

Letter of support for Mobilise-D digital mobility outcomes as monitoring biomarkers

Procedure

On 04 October 2019 the Applicant McRoberts B.V., on behalf of the IMI consortium Mobilise-D, requested qualification advice for the use of Digital Mobility Outcomes (DMO). On 12 June 2020 it submitted a second related request for qualification advice.

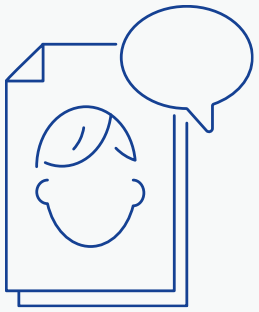
The initial qualification was part of Mobilise-D's overall purpose to establish acceptable DMOs (derived from suitable mobile wearable devices and associated algorithms) as biomarkers of mobility capacity for clinical benefit (i.e., as surrogate, primary or key secondary endpoints) in pivotal clinical trials for treatment of diseases or health conditions that impact upon mobility. An incremental approach has been taken, with an initial qualification of monitoring biomarkers in Parkinson's Disease.

During its March 2020 meeting, the SAWP agreed on the advice to be given to the Applicant. Subsequently, during its March 2020 meeting, the CHMP adopted the advice, and a letter of support was issued in November 2020 (Letter of support for Mobilise-D digital mobility outcomes as monitoring biomarkers).

Qualification of novel methodologies for medicine development

Opinions and letters of support published here

Scientific Advice and protocol assistance

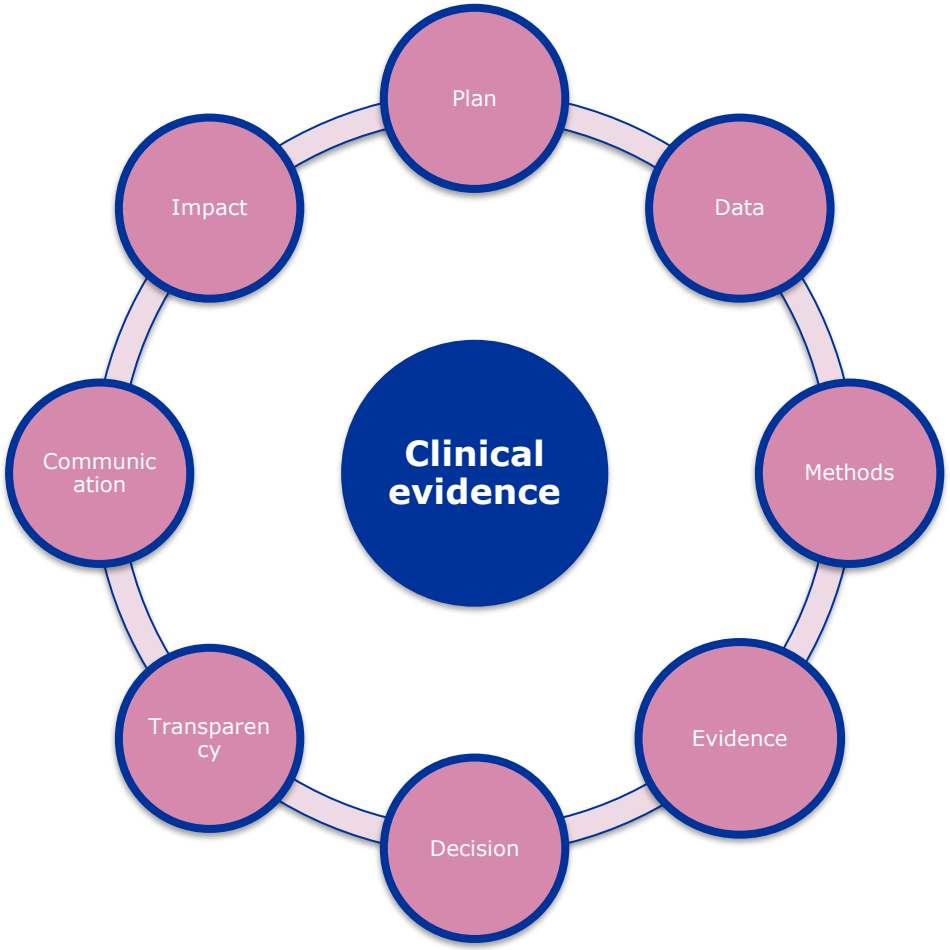


Scientific advice / protocol assistance

- Scientific advice can be provided on **any scientific question**
- Aim: advise developers on the **best way to generate robust evidence** (methods & study designs)
- < Quality, non-clinical and/or clinical >
- Protocol assistance for designated **orphan** medicinal products
- **At any time point** of the development (initial, follow up)
- Discussion on conditional approval/approval under exceptional circumstances
- **Parallel consultation** (EMA/HTA bodies)
- **Parallel Scientific Advice with FDA**

Clinical evidence: a vision to 2030

- Evidence generation is **planned** and **guided by data, knowledge and expertise**
- **Research question** drives evidence choice and embraces spectrum of data and methods
- Clinical trials remain core but are **bigger, better and faster**
- **Real world evidence** is enabled, and value is established
- The **patient voice** guides every step of the way
- Healthcare systems are supported in their choices
- High levels of **transparency** underpin societal trust

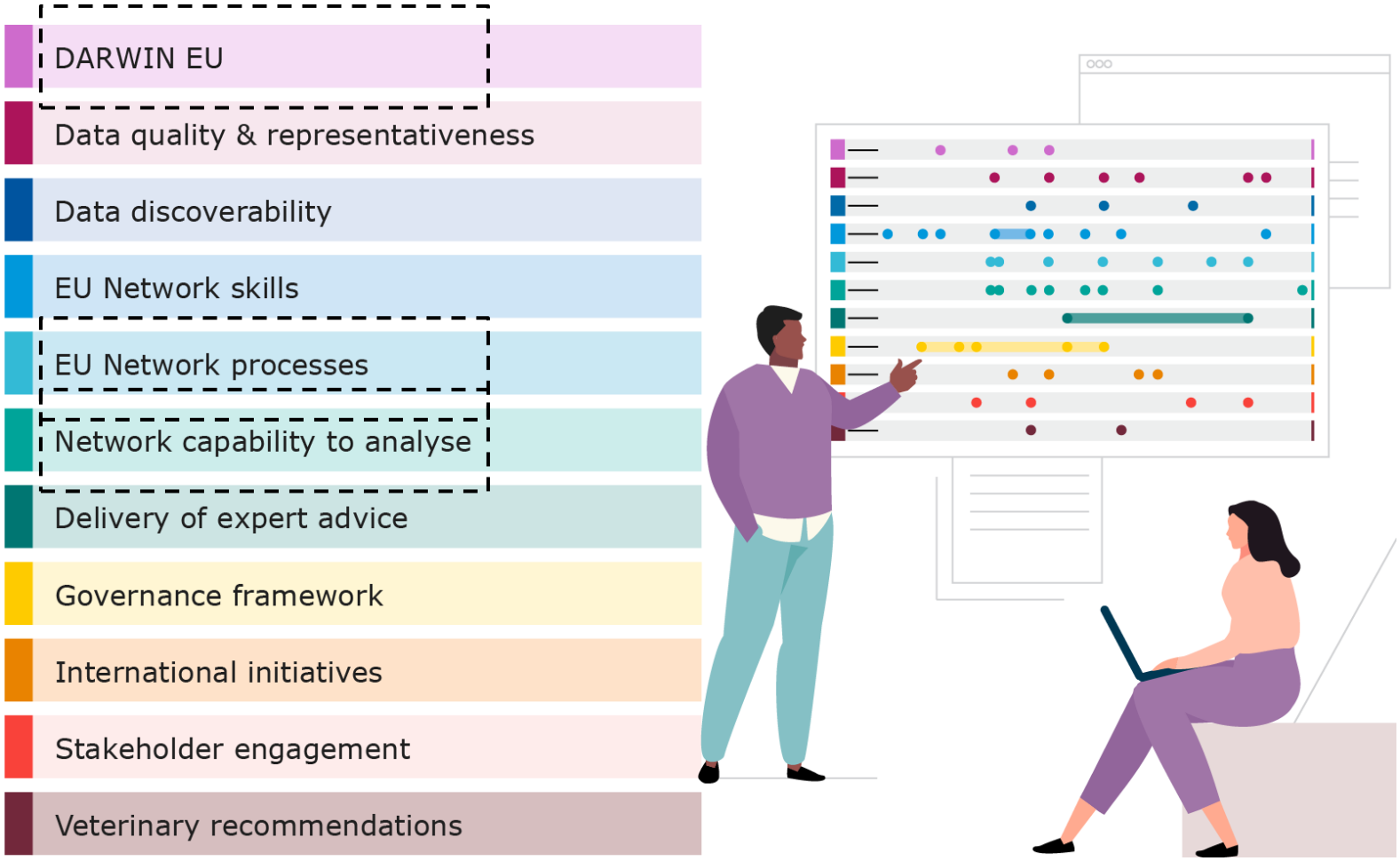


At the core of a successful MA dossier is excellent clinical evidence

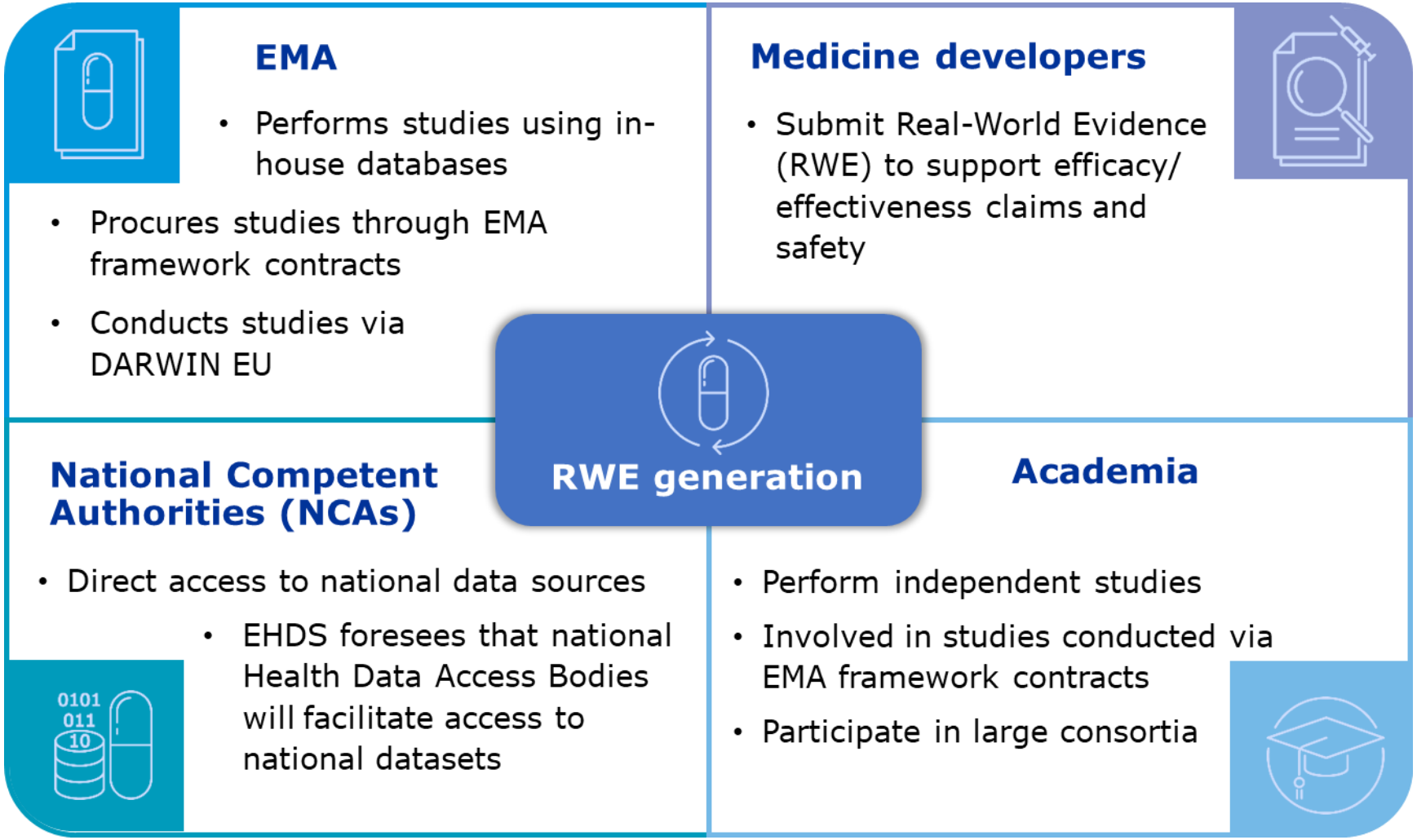
EMA/HMA Big Data Initiative

EU's current framework to unlock value, enable use of Real-World Data (RWD) and facilitate integration into regulatory decision-making

Big Data Steering Group workplan (BDSG)



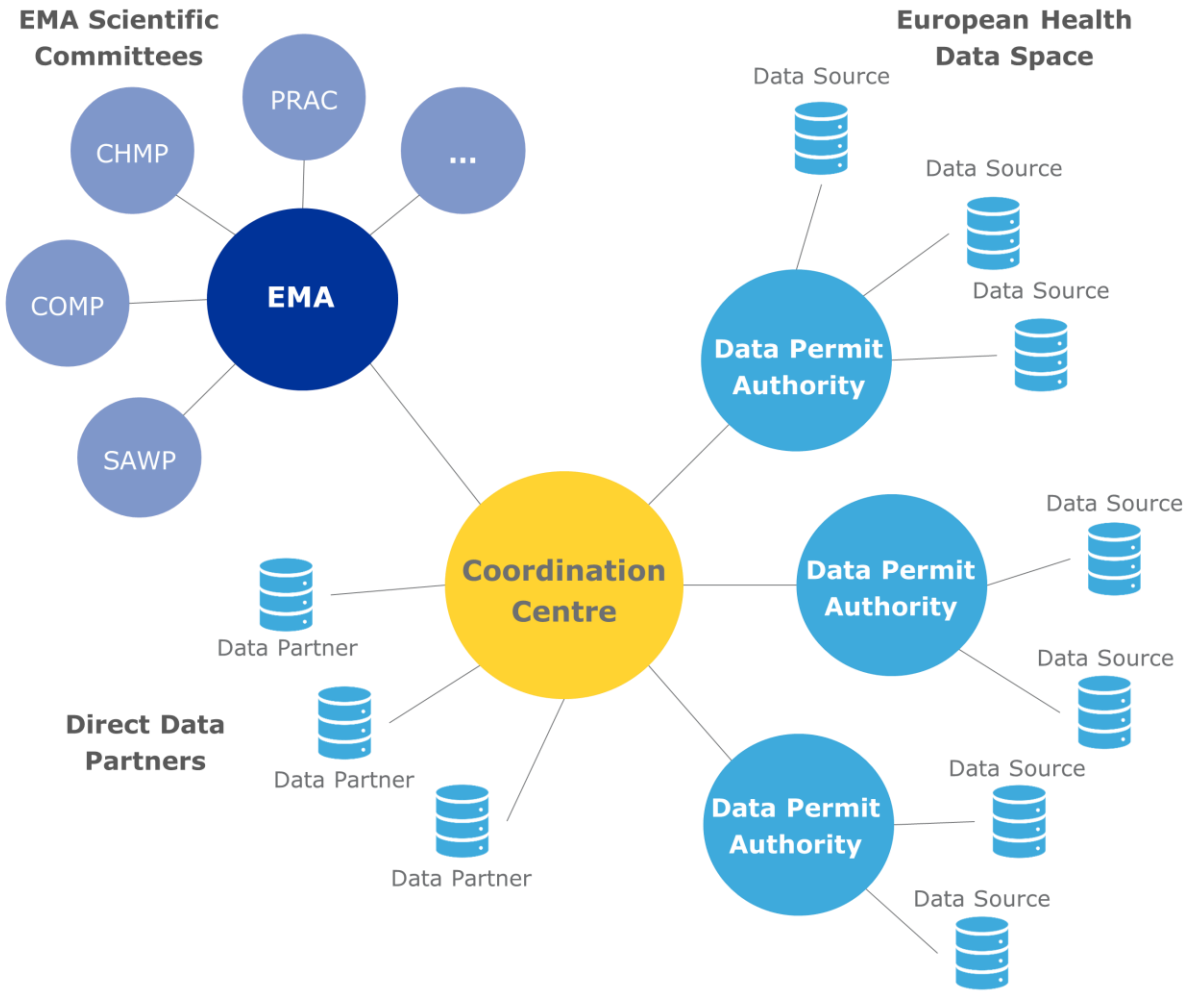
Who delivers RWE for regulatory purpose in the EU?



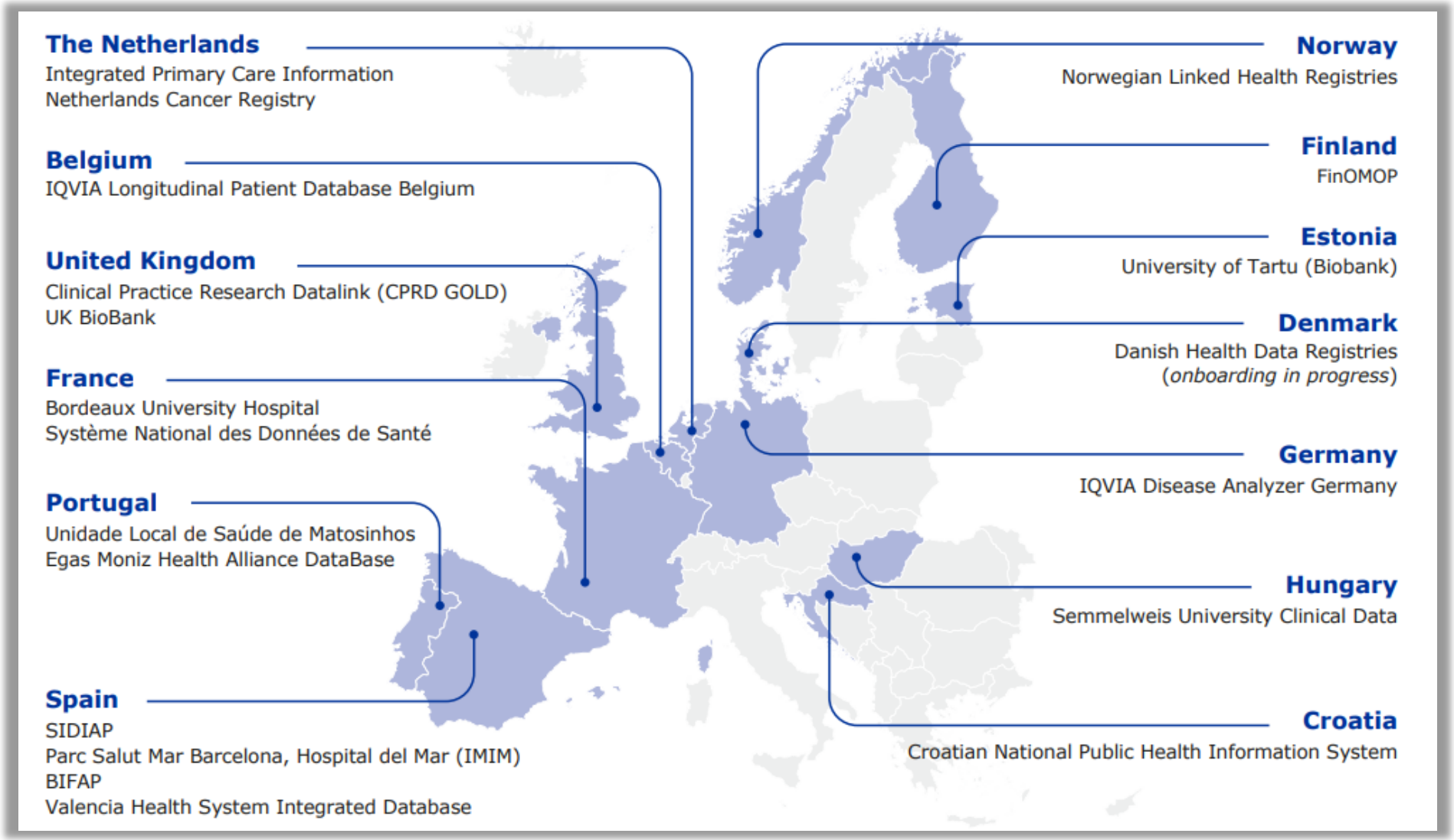
DARWIN EU® Data Analysis and Real-World Interrogation Network

Federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating **valid and reliable evidence from real-world healthcare data**

- Data stays **local**
- **Use of Common Data Model** (OMOP) to perform studies in a timely manner and increase consistency of results
- Data Analysis and Real-World Interrogation Network (DARWIN EU)



Data Analysis & Real-World Interrogation Network



Access to data from ~130 million patients in 2024 / ~40 Data partners by end of 2025

3 areas of EMRN* decision-making for which RWE can be requested

1 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

2 Support the planning and validity

- Design and feasibility of planned studies
- Representativeness and validity of completed studies

3 Investigate associations and impact

- Effectiveness and safety studies
- Impact of regulatory actions

* European Medicines Regulatory Network

European Health Data Space (EHDS)

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OBJECTIVES

Effective use of health data

SCOPE & EXPECTED IMPACT

Use of health data (primary, MyHealth@EU)	• Empower individuals to control their data • Standardization and mandatory certification of EHR systems • Voluntary labelling of wellness apps • European Electronic Health Record Exchange Format	**Single market for health data, data protection, free movement of people, digital goods and services**
Re-use of health data (secondary, HealthData@EU)	• Health data access bodies • Purposes for use and forbidden use • Data permits, secure environments, no identification	**Facilitated Research & Innovation** **Better Policy Making**

MEANS

Legal / Governance

Quality of data

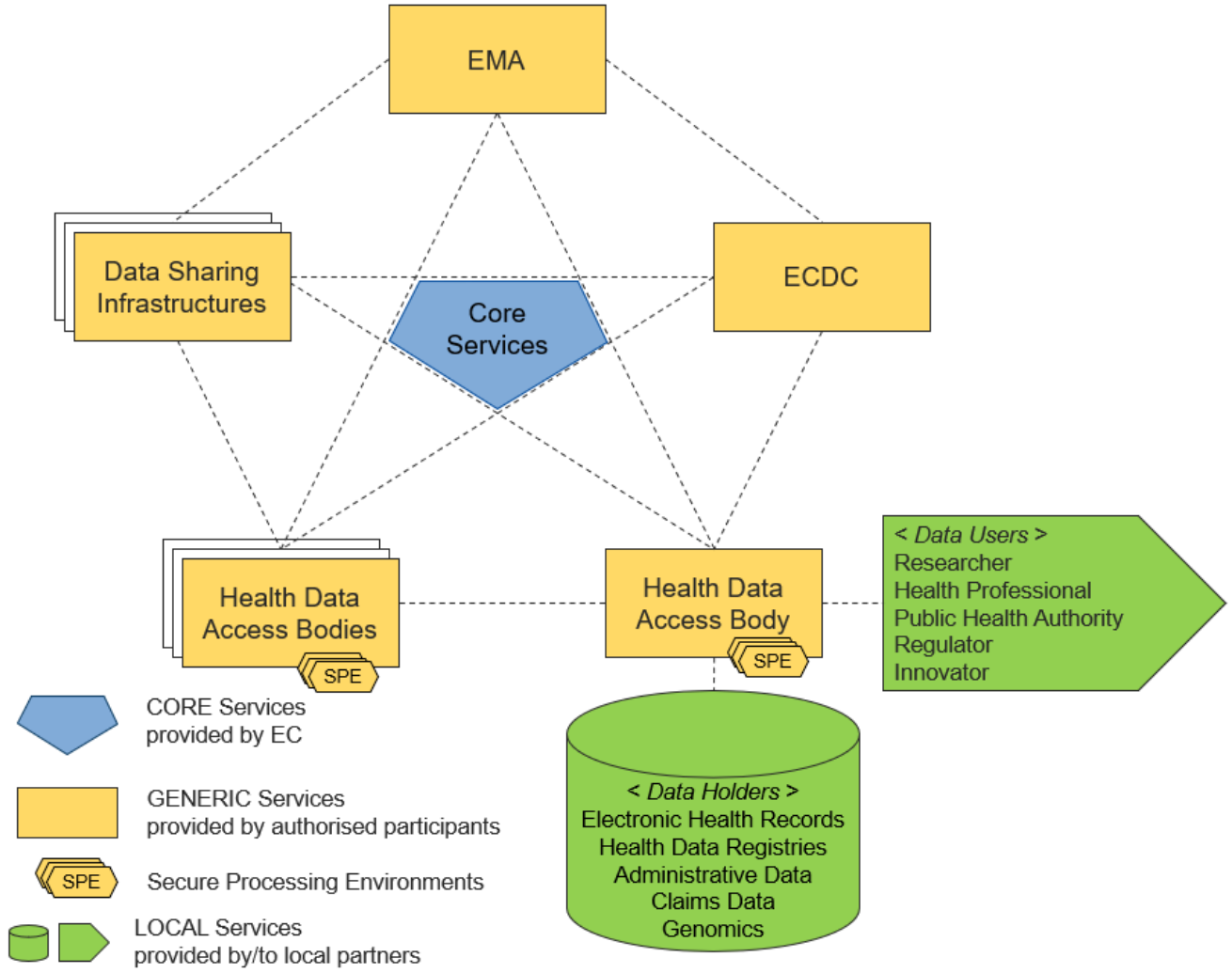
Infrastructure

Capacity building/digitalisation

HealthData@EU: a vision

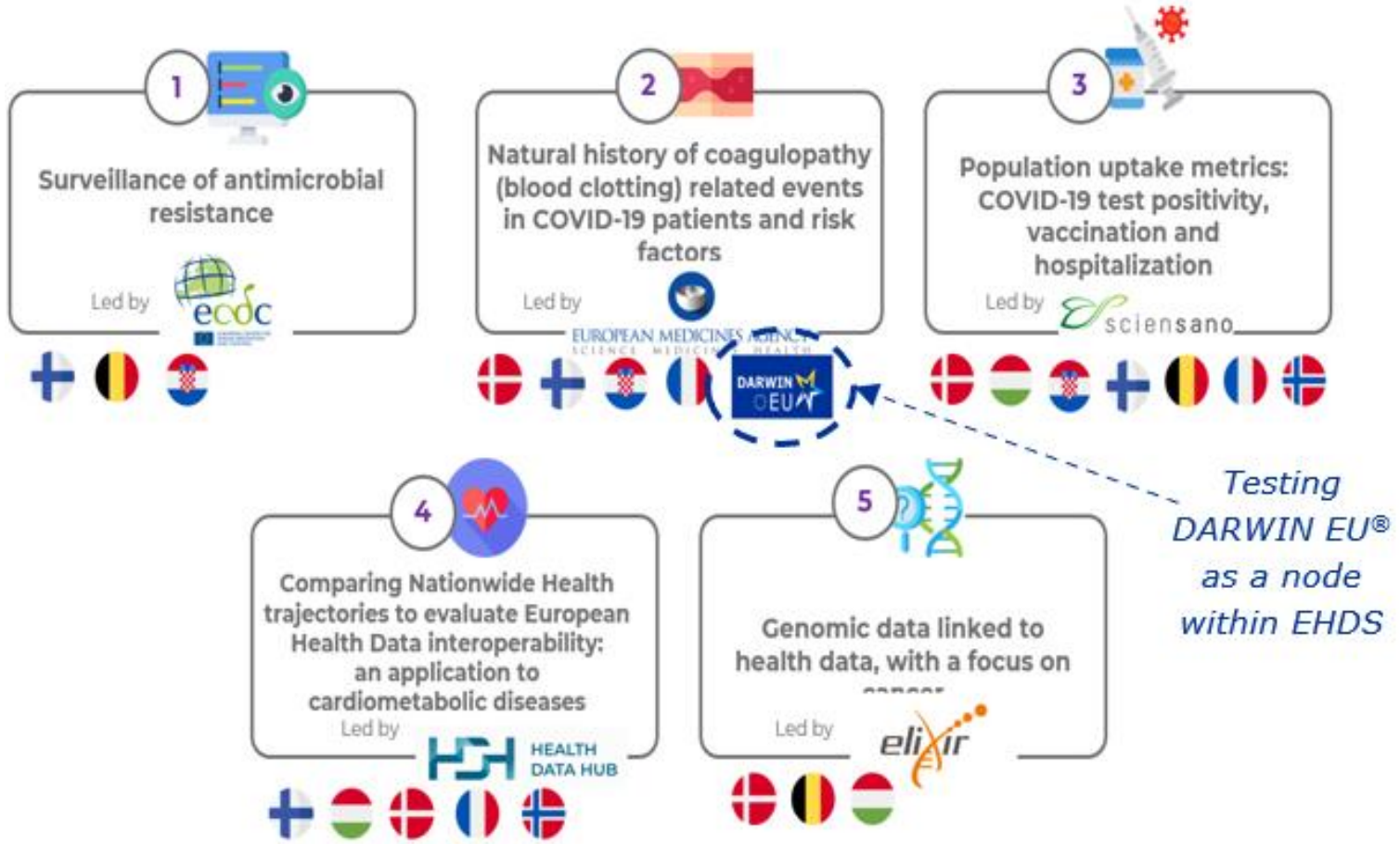
EUROPEAN MEDICINES AGENCY

- **Build new infrastructure for secondary uses of health data**
- Connecting health data access bodies and data sharing infrastructures
- Several health data access bodies are established, or are in the process, across Member States

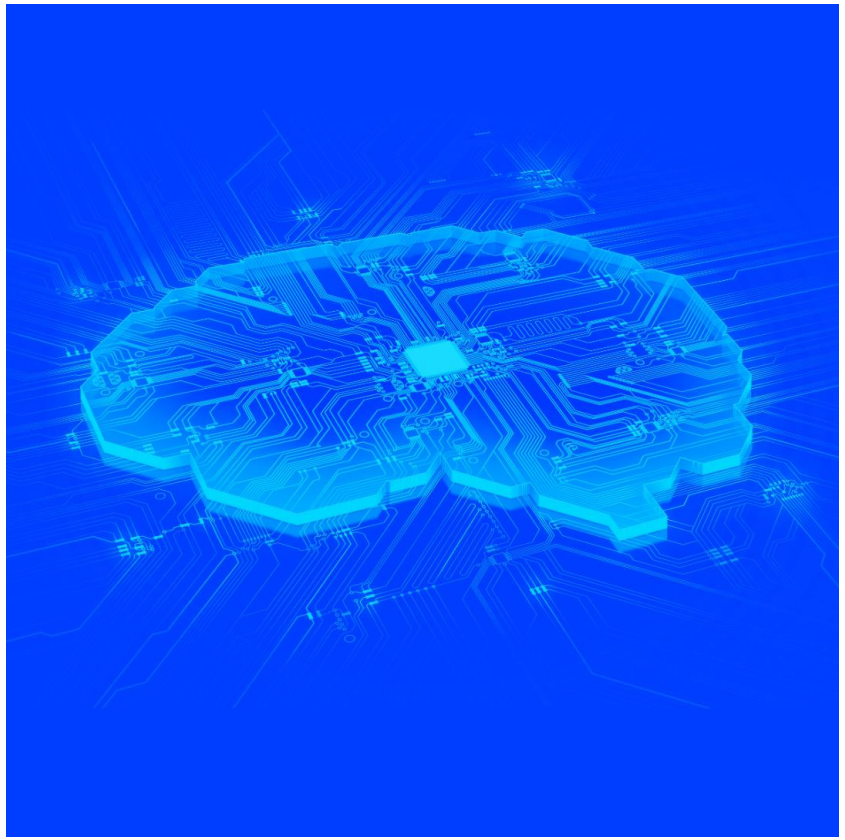


EHDS pilot: DARWIN EU use case

- HealthData@EU (EHDS2 pilot) kicked off: **Five use cases** selected to inform the design, development, and deployment of EHDS2
- **DARWIN EU® - use case on blood clots in Covid-19 patients**
  - Contributors: research teams and data nodes from Finland, France, Denmark and Croatia
  - Integration of DARWIN EU® will be tested



AI is a catch all term for statistical tools and techniques that allow computers to learn rules and identify patterns from data with minimal human oversight, and occasionally, to execute actions (semi)automatically.



The European Medicines Regulatory Network's AI vision aims to establish a medicines regulatory system leveraging AI for **enhanced personal productivity**, **process automation**, **improved data insights**, and **strengthened decision-making** for the betterment of public and animal health.

EMA Management Board

December 2023

AI ACT

The Promise of AI | AI promise across the medicine lifecycle

Greater efficiency /productivity

- Automate processes
- Address scalability issues
- Leverage personal assistants (chatbots)

Do more things, faster

Reduce error

- Facilitate access to information
- Reduce human cognitive load

Provide information at the fingertip

Expose data

- Transform text data into structured data
- Reduce dimensionality of data
- Imputation of missing data

Structure and summarise information

Expand insights

- Probabilistic phenotyping
- Synthetic control arms
- Clinical prediction modelling
- Confounding adjustment
- Digital endpoints
- Heterogeneity of treatment effects

Predict probability of events

Guidance | AI Reflection Paper

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SCIENCE MEDICINES HEALTH

13 July 2023
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Draft

Draft agreed by Committee for Medicinal Products for Human Use (CHMP) Methodology Working Party	July 2023
Draft adopted by CVMP for release for consultation	13 July 2023
Draft adopted by CHMP for release for consultation	10 July 2023
Start of public consultation	19 July 2023
End of consultation (*deadline for comments*)	31 December 2023

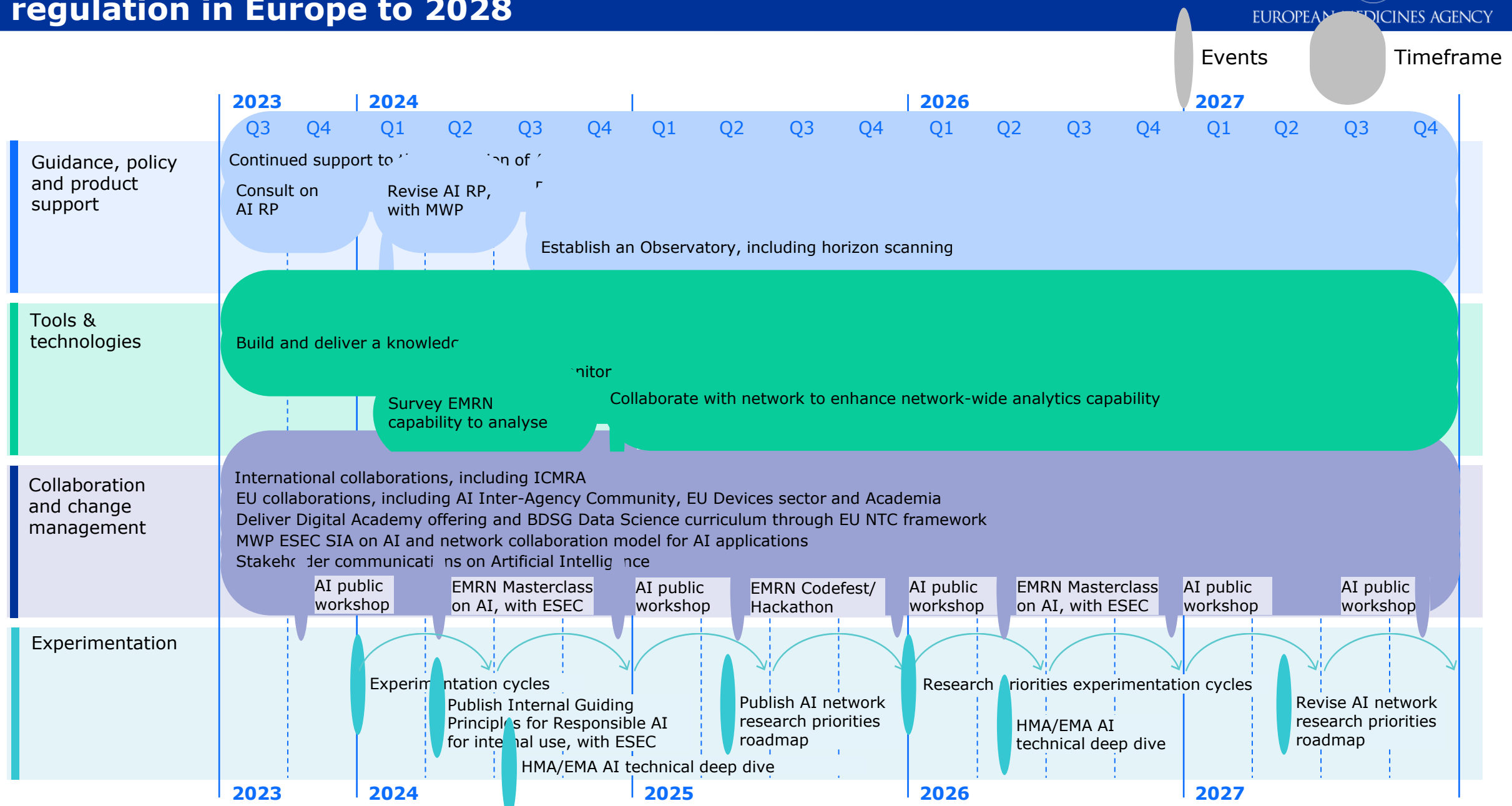
Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	*Artificial intelligence, AI, machine learning, ML, regulatory, medicine, human medicinal product, veterinary medicinal product*

Reflection paper on the use of AI in the medicinal product lifecycle

Table of contents

Multi-annual AI workplan to guide the use of AI in medicines regulation in Europe to 2028



Take home messages

- Innovative medicines and innovative tools are essential to provide patients with best and safest care
- EMA provides extensive guidance on support to innovation
- Several opportunities for interactions throughout medicines lifecycle
- The earlier interactions take place, the better!
- We need to embrace the wide spectrum of data and methods whilst ensuring their fitness for purpose to generate best evidence possible for regulatory decision-making

Thank you!

Any questions?

Acknowledgements: Falk Ehmann, Helene Casaert, Luis Pinheiro

Please contact me: kelly.plueschke@ema.europa.eu

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Send us a question Go to www.ema.europa.eu/contact

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Nada Alkhayat

European Commission, DG SANTE

EDITH

EDITH is a coordination and support action funded by the Digital Europe program of the European Commission under grant agreement n° 101083771

Regulatory science and policy update on the EU MDR/IVDR and the AI Act

EDITH Final Ecosystem Meeting on building the VHT - 16 July 2024

Medical Device and In Vitro Diagnostic medical device regulations (MDR and IVDR) – Regulations (EU) 2017/745 and 2017/746

Artificial Intelligence Act – Regulation (EU) 2024/1689

Nada Alkhayat

DG SANTE – D3 Medical devices

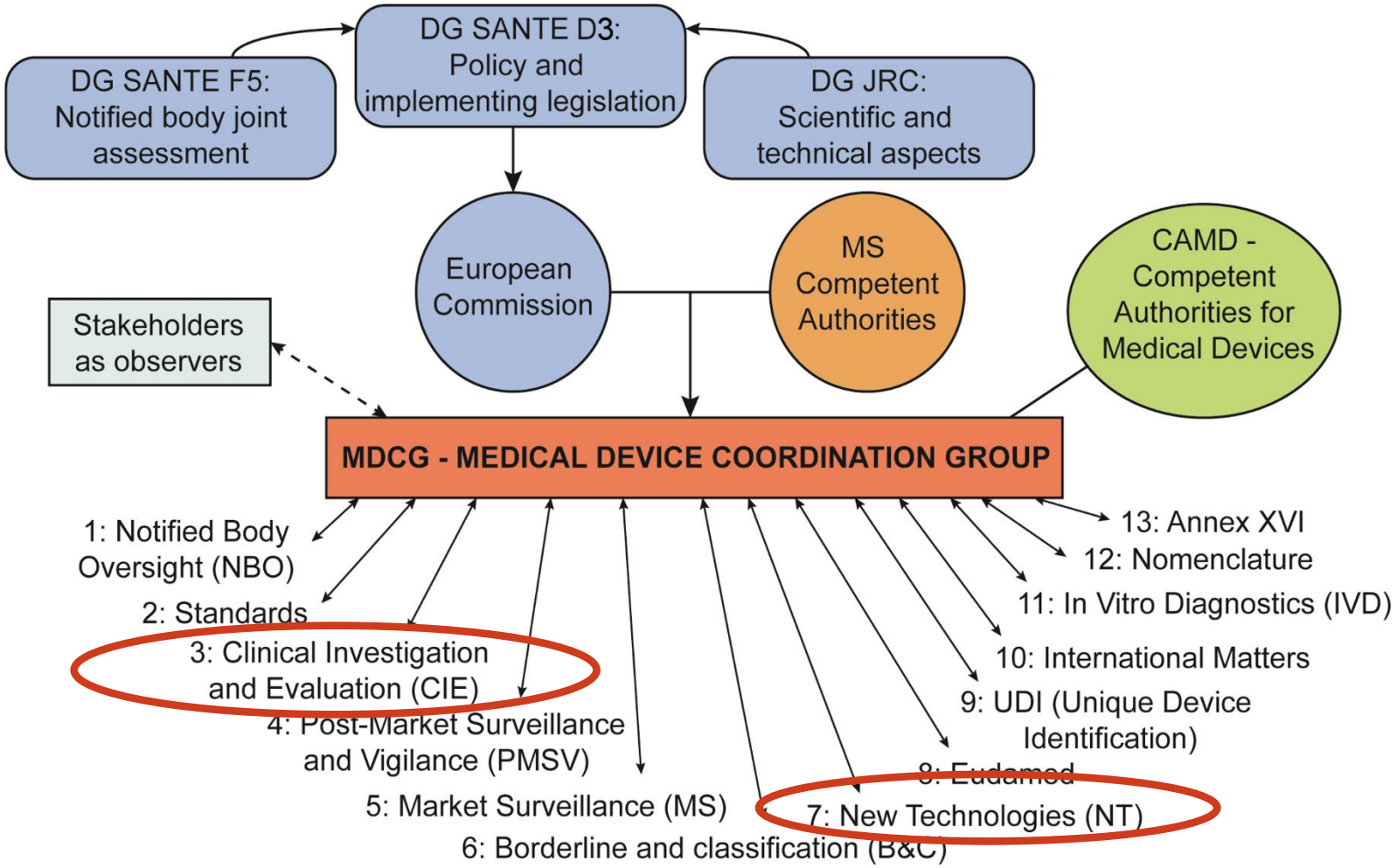
Agenda

- 1. EU MDR/IVDR
- 2. Key MDCG Guidance for software and AI enabled medical devices
  - 2.1. Qualification & Classification ; 2.2 Cybersecurity 2.3 Clinical Evaluation /Performance Evaluation
- 3. Additional requirements from the AI Act

EU MDR/IVDR

European Commission

Governance



- **MDCG**: advise and assist COM and Member States to implement Regulations
- **MDCG Subgroups** (13): 100+ guidance and other documents

European Commission

Impacts of the Regulations (MDR/IVDR) on medical device software

Increased Expectations

New regulations impose higher standards and requirements on medical device manufacturers, emphasizing enhanced compliance measures.

Software Classification Rules

Specific classification rules introduced for software within the medical device space, outlining distinct categorization criteria.

Post-Market Surveillance & Vigilance

Heightened focus on Post-Market Surveillance (PMS) and Vigilance to ensure ongoing monitoring and reporting of device performance and safety.

Risk Management Emphasis

Significant emphasis placed on robust risk management practices to identify, assess, and mitigate potential hazards associated with medical devices.

Lifecycle Approach

Adoption of a comprehensive lifecycle approach towards medical devices, emphasizing continuous monitoring and improvement .

European Commission

General Safety and Performance Requirements (GSPR): Annex I

01

IT Security

Incorporate robust IT security measures to safeguard against cyber threats and unauthorized access.

02

Verification and Validation

Conduct thorough verification and validation processes to ensure the efficacy and safety of the medical device.

03

Risk Control Measures

Implement comprehensive risk control measures to mitigate potential hazards and ensure patient safety.

04

Documentation

Maintain detailed documentation of the device's design, development, and testing phases to facilitate traceability and compliance.

05

Information & Labelling

Ensure accurate and informative labeling of the medical device to provide users with essential usage and safety information.

European Commission

Critical Aspects —

Secure Design and Manufacture

Emphasizing Safety, Security, and Effectiveness Throughout the Lifecycle

1

Early Development Stages

Safety, security, and effectiveness considerations should be integrated from the initial stages of development.

2

Continuous Monitoring

Maintain a holistic approach by monitoring and enhancing safety, security, and effectiveness throughout the product lifecycle.

MDR/ IVDR life-cycle approach

European Commission

Key MDCG Guidance for software and AI enabled medical devices

2.1. Qualification & Classification ;

2.2 Cybersecurity;

2.3 Clinical Evaluation /Performance Evaluation.

European Commission

Impacts of the Regulations (MDR/IVDR) – cont.

MDCG guidance specific to software:

Reference	Title	Publication
MDCG 2020-1	Guidance on clinical evaluation (MDR) / Performance evaluation (IVDR) of medical device software	March 2020
MDCG 2019-11	Qualification and classification of software - Regulation (EU) 2017/745 and Regulation (EU) 2017/746	October 2019
MDCG 2019-16	Guidance on cybersecurity for medical devices	December 2019

European Commission

2.1. Qualification & Classification

European Commission

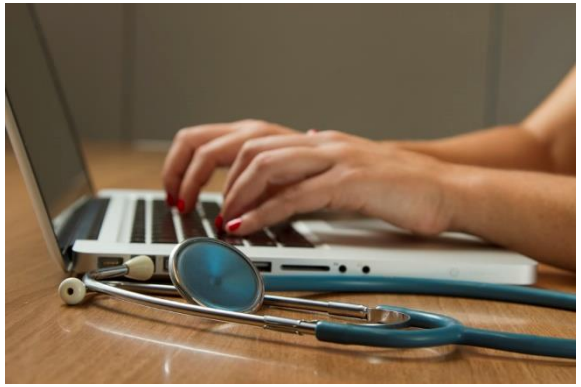
MDCG 2019-11

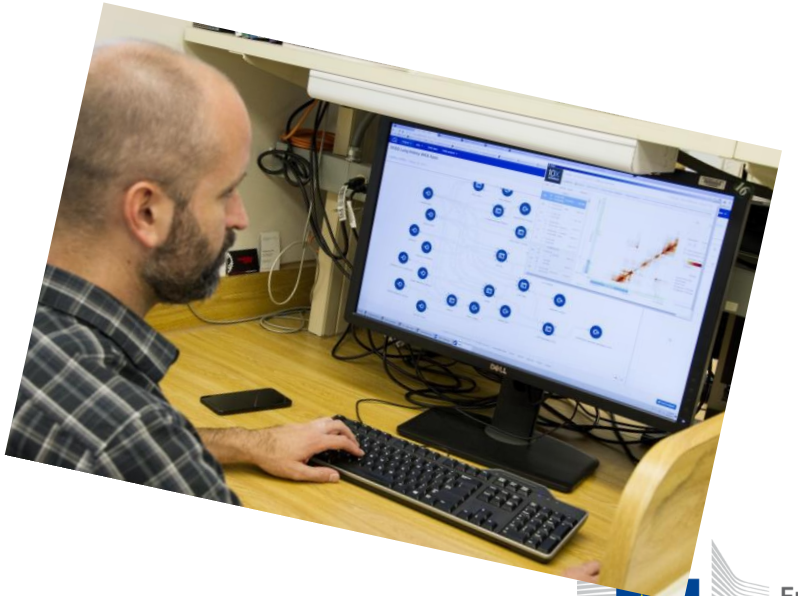
Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR

European Commission

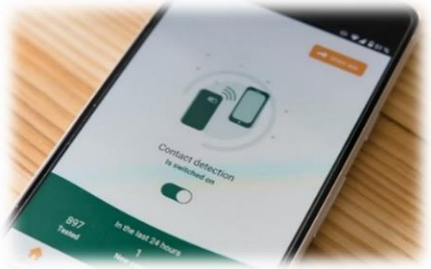
Qualification as MDSW

- Medical device software is software that **is intended** to be used, **alone or in combination**, for a purpose as specified in the definition of a "**medical device**" in the MDR or IVDR, regardless of whether the software is **independent** or **driving or influencing** the use of a device.





What is a medical device?



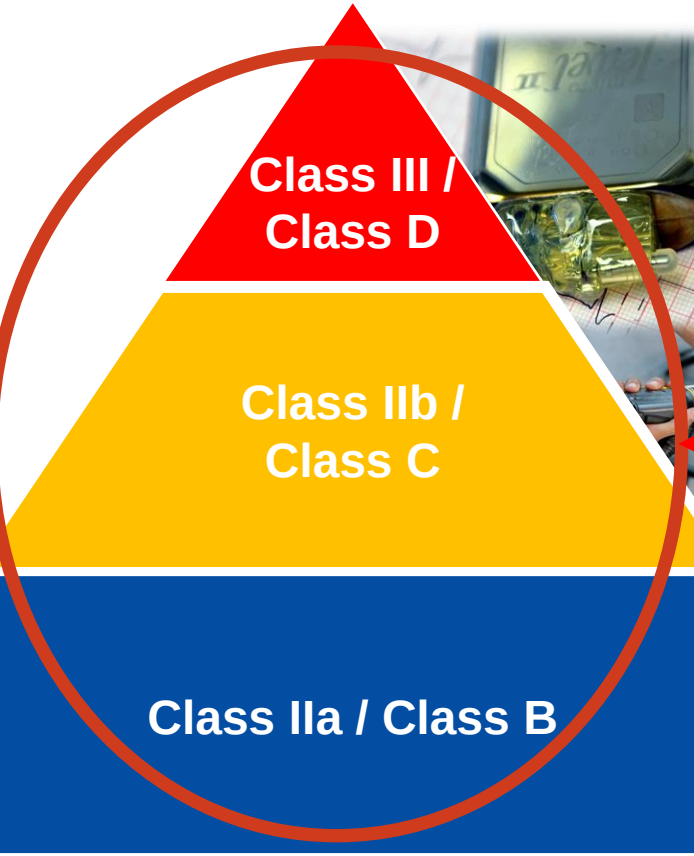
any instrument, apparatus, appliance, **software,** implant, reagent, material or other article intended by the **manufacturer to be used, alone or in combination**, for human beings for one or more of the following specific medical purposes:

- **diagnosis, prevention**, **monitoring, prediction, prognosis, treatment or alleviation** of **disease**,
- **diagnosis, monitoring, treatment, alleviation** of, **or compensation** for, **an injury or disability**,
- **investigation,** replacement or modification of the anatomy or of a physiological or **pathological process or state**,
- **providing information** by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

European Commission

Risk Classes



Classification – Rule 11 and IMDRF risk categorisation

		Significance of Information provided by the MDSW to a healthcare situation related to diagnosis/therapy		
State of Healthcare situation or patient condition		High Treat or diagnose ~ IMDRF 5.1.1	Medium Drives clinical management ~ IMDRF 5.1.2	Low Informs clinical management (everything else)
	Critical situation or patient condition ~ IMDRF 5.2.1	Class III Category IV.i	Class IIb Category III.i	Class IIa Category II.i
	Serious situation or patient condition ~ IMDRF 5.2.2	Class IIb Category III.ii	Class IIa Category II.ii	Class IIa Category I.ii
	Non-serious situation or patient condition (everything else)	Class IIa Category II.iii	Class IIa Category I.iii	Class IIa Category I.i

2.2 Cybersecurity

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Medical Device
Medical Device Coordination Group Document MDCG 2019-16

MDCG 2019-16
Guidance on Cybersecurity for medical devices

December 2019

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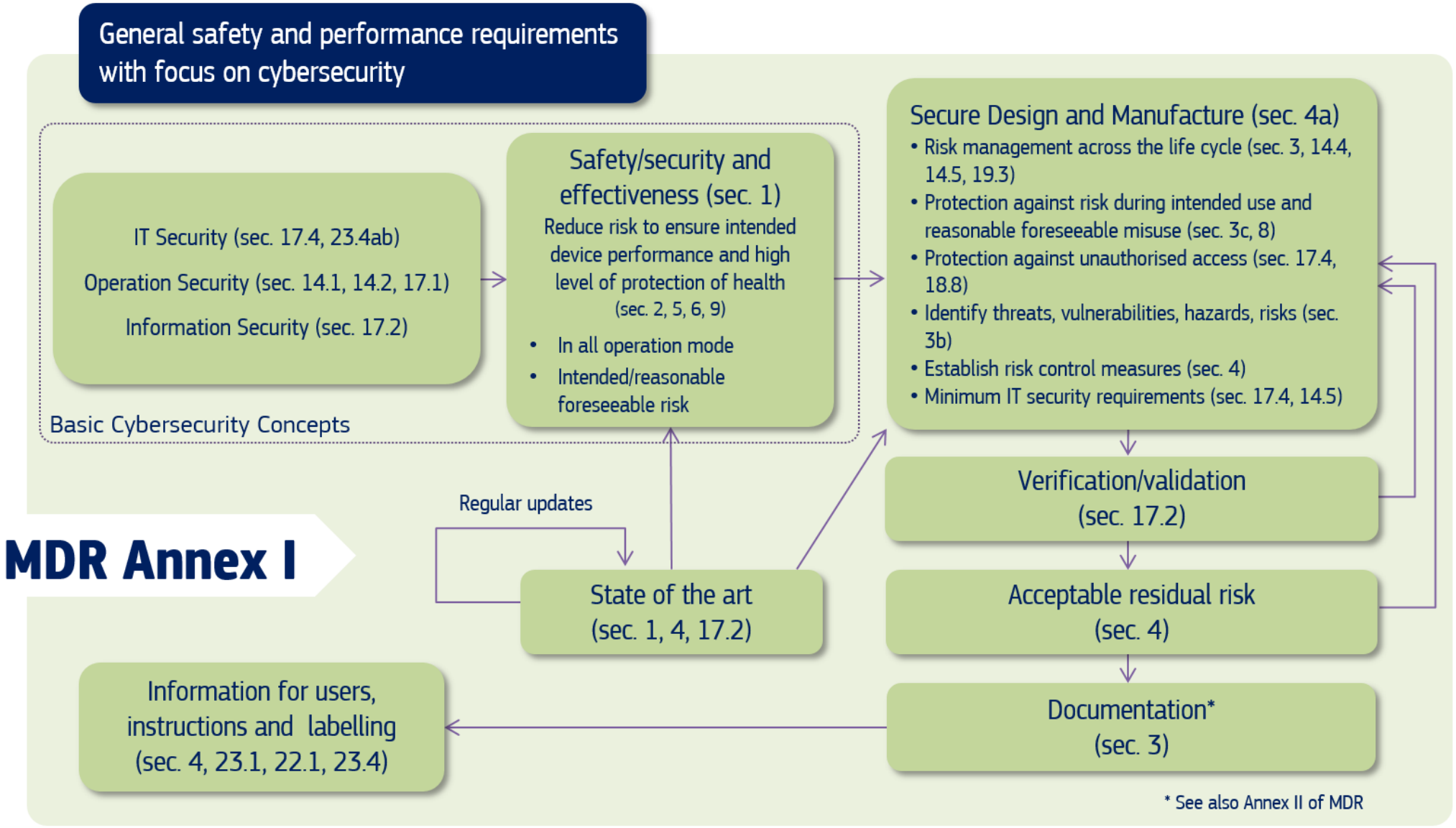
Guidance on cybersecurity for medical devices – MDCG 2019-16



Risk Management and V&V activities

including mitigatin risks to Mitigating risks to confidentiality, integrity, and availability Strategically safeguarding the confidentiality, integrity, and availability of sensitive patient data stored and transmitted through medical devices to prevent unauthorized access or manipulation.

Addressing cybersecurity risks at the design stage

Implementing security protocols and features during the initial design phase of medical devices to proactively address potential cyber threats and vulnerabilities.

Evaluating security and safety risks

Conducting comprehensive evaluations to assess both security and safety risks associated with medical devices, ensuring that cybersecurity measures do not compromise patient safety or device functionality.

Clinical Evaluation and Conformity Assessment

Implementing security protocols and features during the initial design phase of medical devices to proactively address potential cyber threats and vulnerabilities.

Post-Market Surveillance

Trend reporting and monitoring of devices

Gathering post-market information

Collecting and analyzing real-world data and feedback post-market release to identify any cybersecurity incidents, vulnerabilities, or performance issues and implement necessary updates or patches.

2.3 Clinical Evaluation /Performance Evaluation

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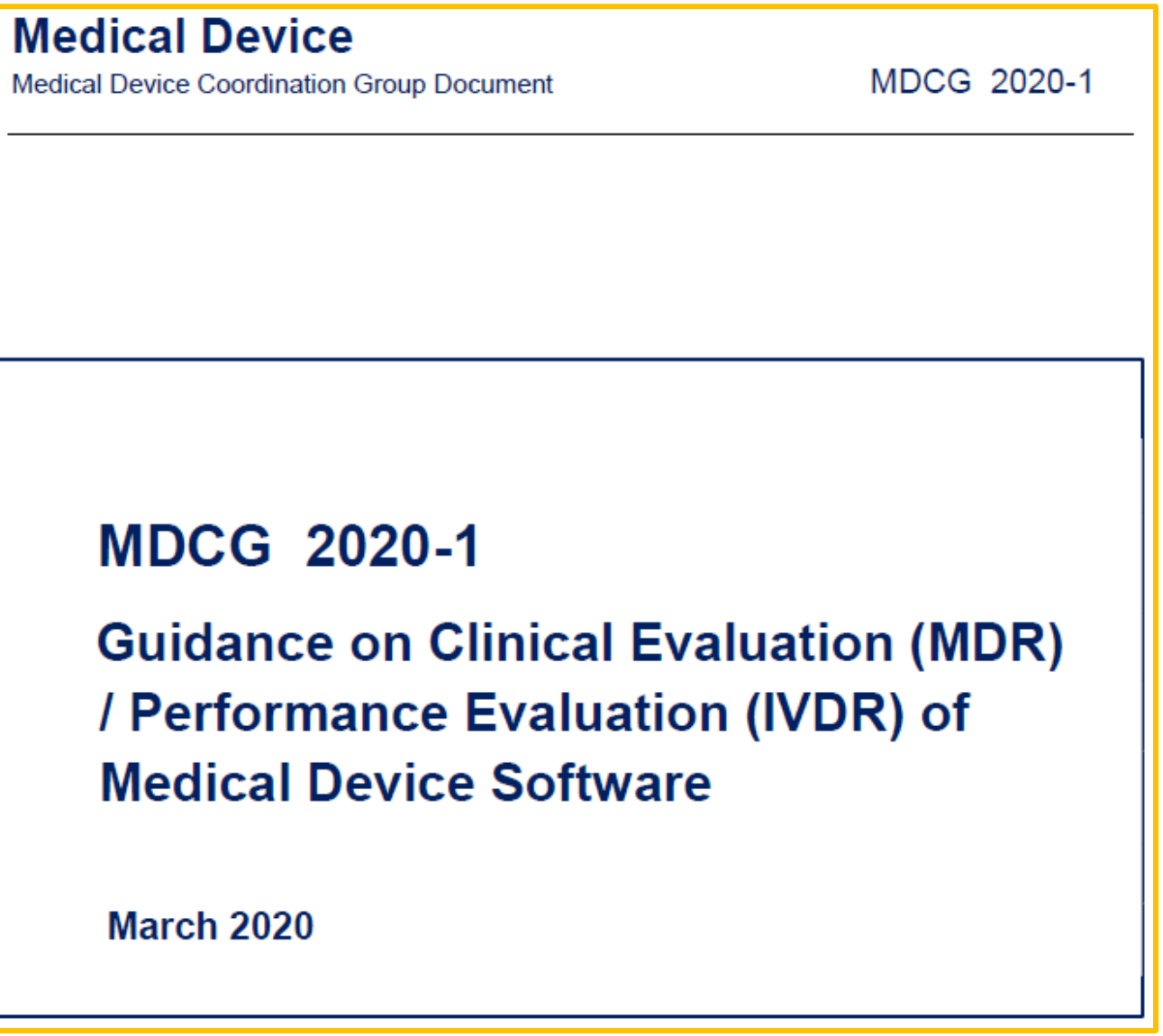
Medical Device
Medical Device Coordination Group Document
MDCG 2020-1
MDCG 2020-1
Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software
March 2020


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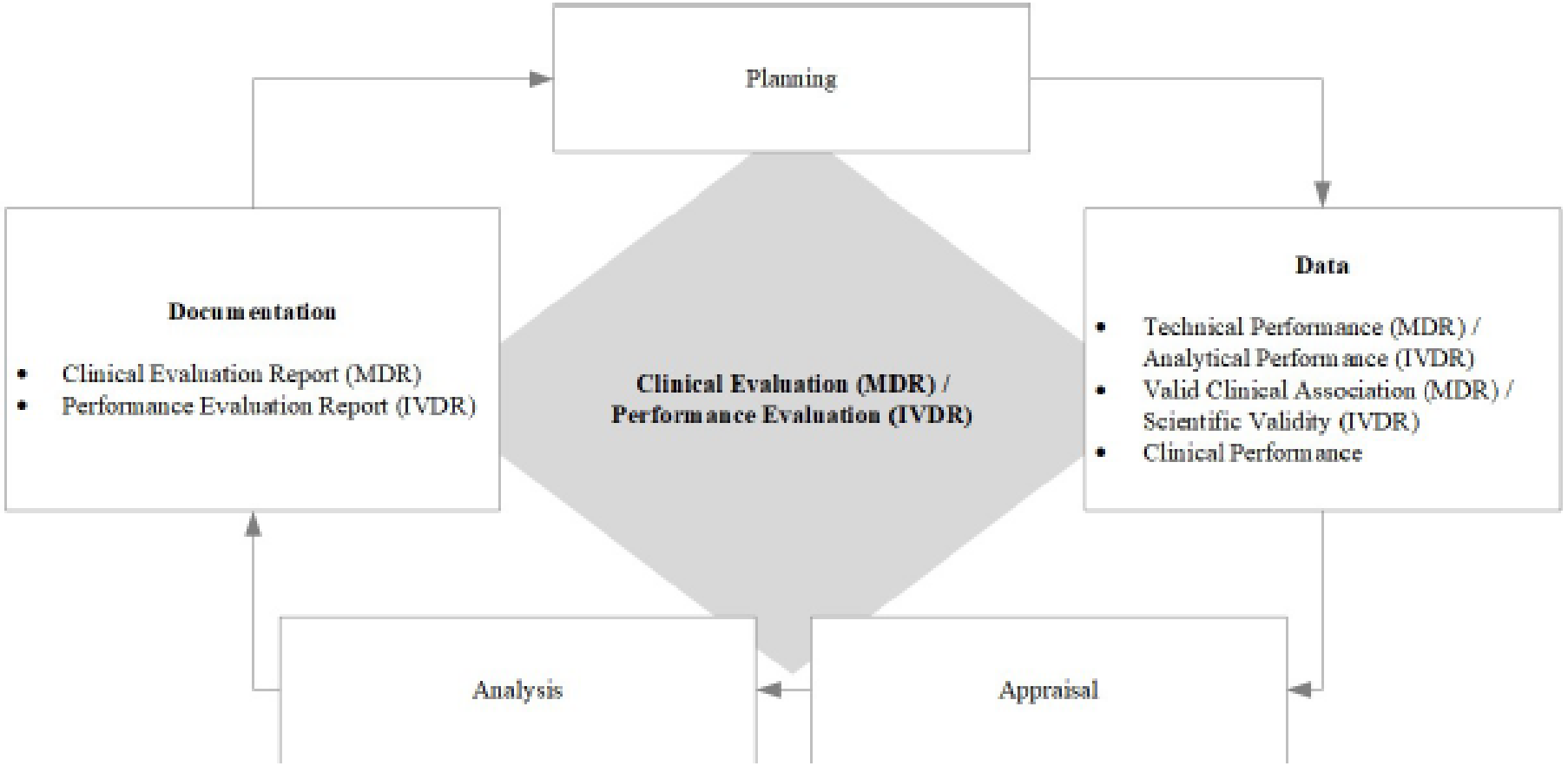
Different MDSW and how Clinical/Performance Evaluation should be conducted

Model of Software	CLINICAL EVALUATION (MDR) / PERFORMANCE EVALUATION (IVDR) - **scope**
MDSW (with independent intended purpose and claimed CLINICAL BENEFIT)	MDSW only
MDSW (with intended purpose and claimed CLINICAL BENEFIT related to driving or influencing a medical device for a medical purpose)	MDSW and the driven or influenced medical device [Notes 1,2]
Software driving or influencing the use of a medical device (with no independent intended purpose or independent claimed CLINICAL BENEFIT)	Driven or influenced medical device including the software (component or accessory)

Overview on Clinical Evaluation/Performance Evaluation of MDSW



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Pillars of Clinical Evaluation/Performance Evaluation

- Valid clinical association/Scientific validity
- Technical performance/Analytical performance
- Clinical Performance

Additional requirements from the AI Act

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AI Act: Main Operational Elements

New Legislative Framework (NLF)
Product Safety Legislation +

*** Pre-market ***

Mandatory Requirements (harmonized standards) + Conformity Assessment

*** Post-market ***

monitoring

risks to health, safety and fundamental rights

1. **risk management system** for AI systems *[Art. 9 AI Act]*
2. **governance and quality of datasets** used to build AI systems *[Art. 10 Data and data governance]*
3. **record keeping -** built-in logging capabilities in AI systems *[Art. 11 Technical documentation and Art. 12 record-keeping]*
4. **transparency and information** to the users of AI systems *[Art. 13 Transparency and provisions of information to users]*
5. **human oversight** of AI systems *[Art. 14 Human oversight]*
6. **accuracy** specifications for AI systems *[Art. 15 Accuracy, robustness and cybersecurity]*
7. **robustness** specifications for AI systems *[Art. 15 Accuracy, robustness and cybersecurity]*
8. **cybersecurity** specifications for AI systems *[Art. 15 Accuracy, robustness and cybersecurity]*
9. **quality management system** for providers of AI system *[Art. 17]*
10. **conformity assessment** for AI systems *[Art. 19 + Art. 43 Conformity Assessment]*

Interplay between MDR/IVDR and AIA

Requirements for high-risk AI – including medical devices (Title III, chapter 2)

Establish and implement an iterative **risk management** process (identify & mitigate risks)

- Use high-quality **training, validation and testing datasets**
  Implement **data governance procedures**
- Establish **documentation** in Annex IV and design the system with **logging** features (traceability & auditability)
- Ensure appropriate degree of **transparency and interpretability** of the system by design & provide users with **information** (on how to use the system, its capabilities and limitations, potential risks etc.)
- Enable **human oversight** aimed to minimize residual risks (measures built into the system and/or to be implemented by users)
- Ensure **robustness**, **accuracy** and **cybersecurity** throughout the lifecycle

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NB! Harmonised technical standards developed by ESOs will support providers to demonstrate compliance.

High-risk AI Systems in the healthcare area

HIGH-RISK AI SYSTEMS IN AIA

1 **SAFETY COMPONENTS OF REGULATED PRODUCTS (OR AI SYSTEMS WHICH ARE PRODUCTS BY THEMSELVES)**

2 **CERTAIN (STAND-ALONE) AI SYSTEMS – SPECIFIC USE-CASES - IN THE FOLLOWING AREAS (ANNEX III)**

- ✓ Biometric identification and categorisation of natural persons
- ✓ Management and operation of critical infrastructure
- ✓ Education and vocational training
- ✓ Employment and workers management, access to self-employment
- ✓ **Access to and enjoyment of essential private services and public services and benefits**
- ✓ Law enforcement
- ✓ Migration, asylum and border control management
- ✓ Administration of justice and democratic processes

HEALTHCARE-RELATED HIGH-RISK AI SYSTEMS

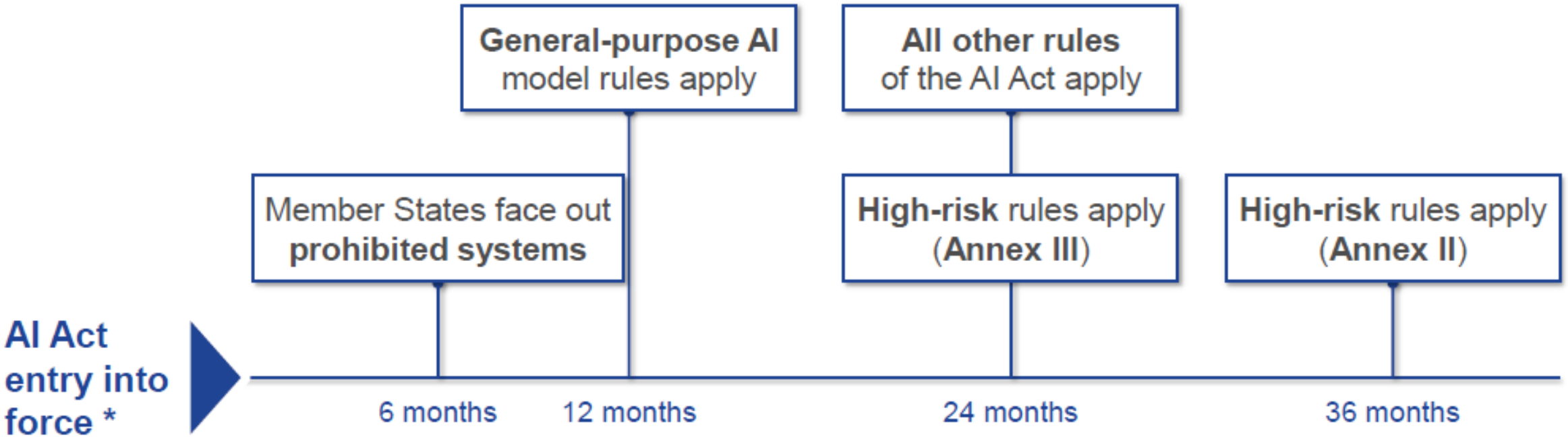
- **AI systems which are safety components of medical devices** (e.g. AI system exerting a safety function in relation to a remote-controlled surgical system)
- **AI systems which are medical devices by themselves** (e.g. AI systems providing information for diagnosis or treatment)

JOINT APPLICATION OF AIA AND MEDICAL DEVICE REGULATIONS

- "AI systems intended to be used to dispatch, or to establish priority in the **dispatching of emergency first response services, including by** firefighters and **medical aid, as well as of emergency healthcare patient triage systems** " have been already listed in Annex III under this category

NB: The list of standalone use-cases is being reviewed on a yearly basis

The AI Act enters into application in a gradual approach



*Following its adoption by the European Parliament and the Council, the AI Act shall enter into force on the twentieth day following that of its publication in the official Journal.

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Thank you!

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Coffee Break

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