AI in Drug Development

CDER Office of Medical Policy

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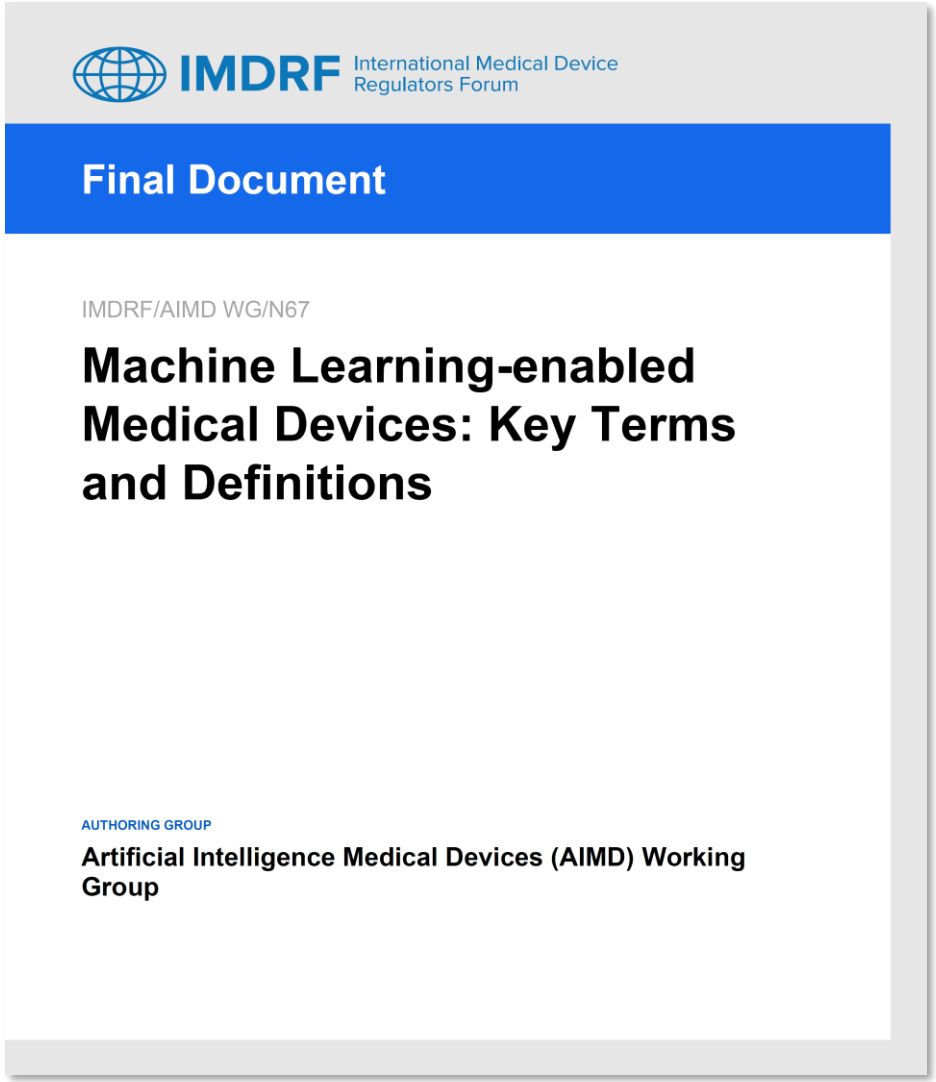
Image: https://www.imeche.org/news/news-article/the-human-s-digital-twin

Definitions are important: What is AI?

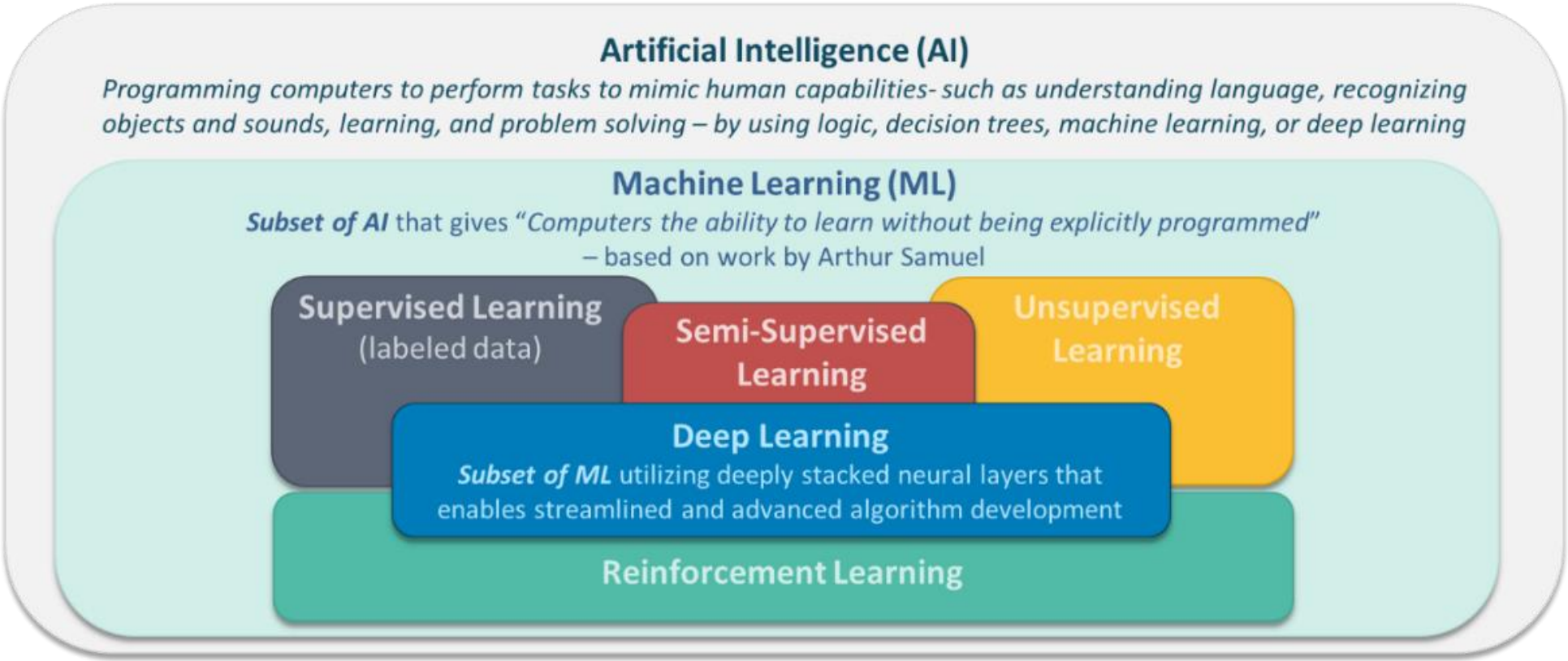
Artificial Intelligence (AI): a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions and making predictions



https://www.imdrf.org/documents/machine-learning-enabled-medical-devices-key-terms-and-definitions

Definitions are important: What is ML?

Machine Learning (ML): A subset of AI that allows ML models to be developed by ML training algorithms through analysis of data, without models being explicitly programmed



※ The descriptions within the diagram are not definitions, and are included to convey a general sense of the technology.

https://www.imdrf.org/documents/machine-learning-enabled-medical-devices-key-terms-and-definitions

Drivers behind the growth in AI health applications

- Large datasets (e.g., administrative data, EHRs, registries, etc.)
- Diverse and multimodal datasets (e.g., DHTs, genomic, laboratory, imaging, etc.)
- Improvements in data standards (e.g., ICD-10, LOINC, NDCs, UMLS, FHIR/HL7, OHDSI, etc.)
- Improved data interoperability and healthcare data exchange
- Increased computing power
- Advancements in data privacy persevering approaches
- Breakthroughs in methods (e.g., deep neural networks, reinforcement learning, Generative adversarial networks, Variational autoencoders, etc.) and causal inference approaches (e.g., structural causal models and causal Bayesian networks)

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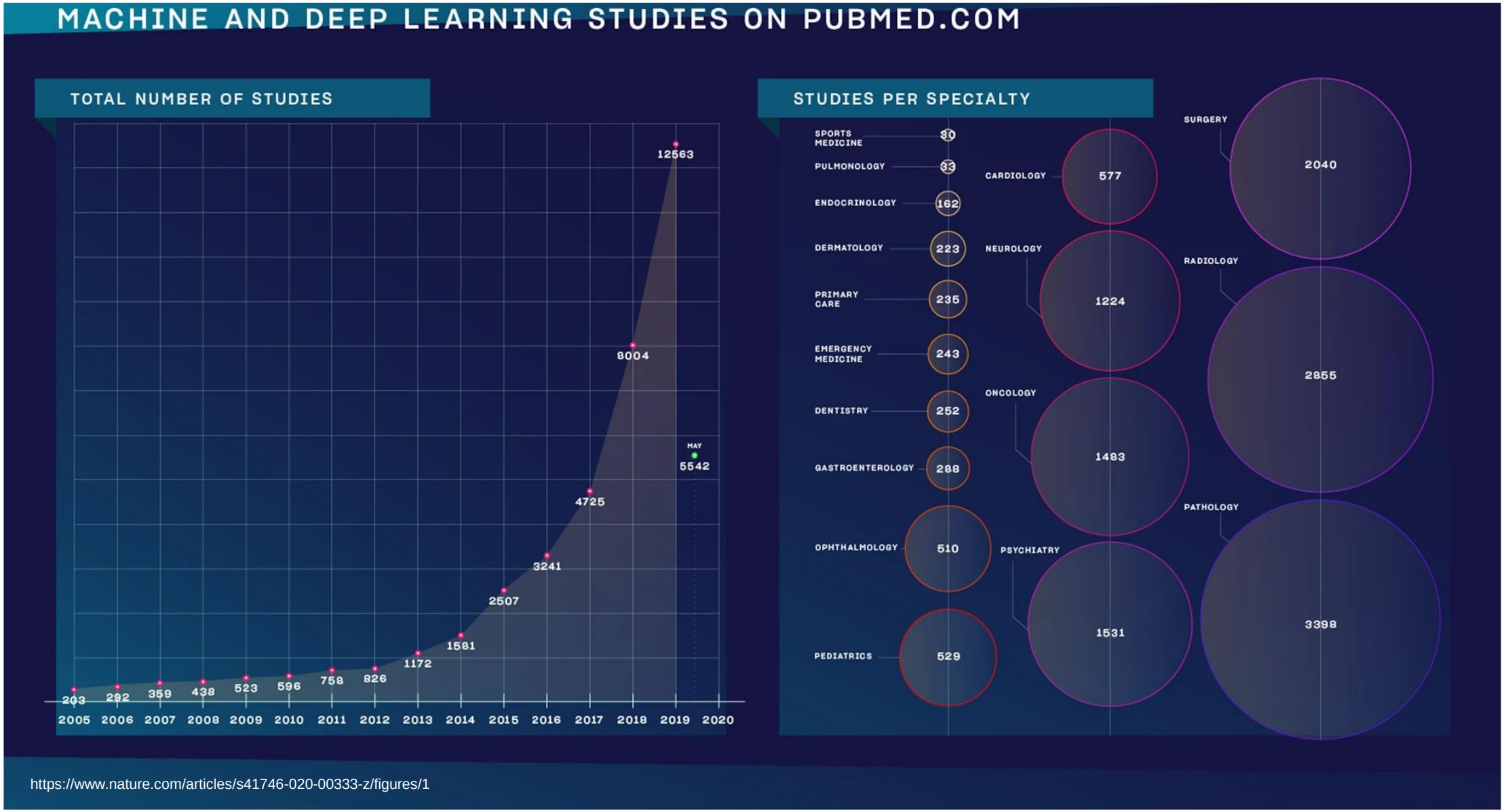
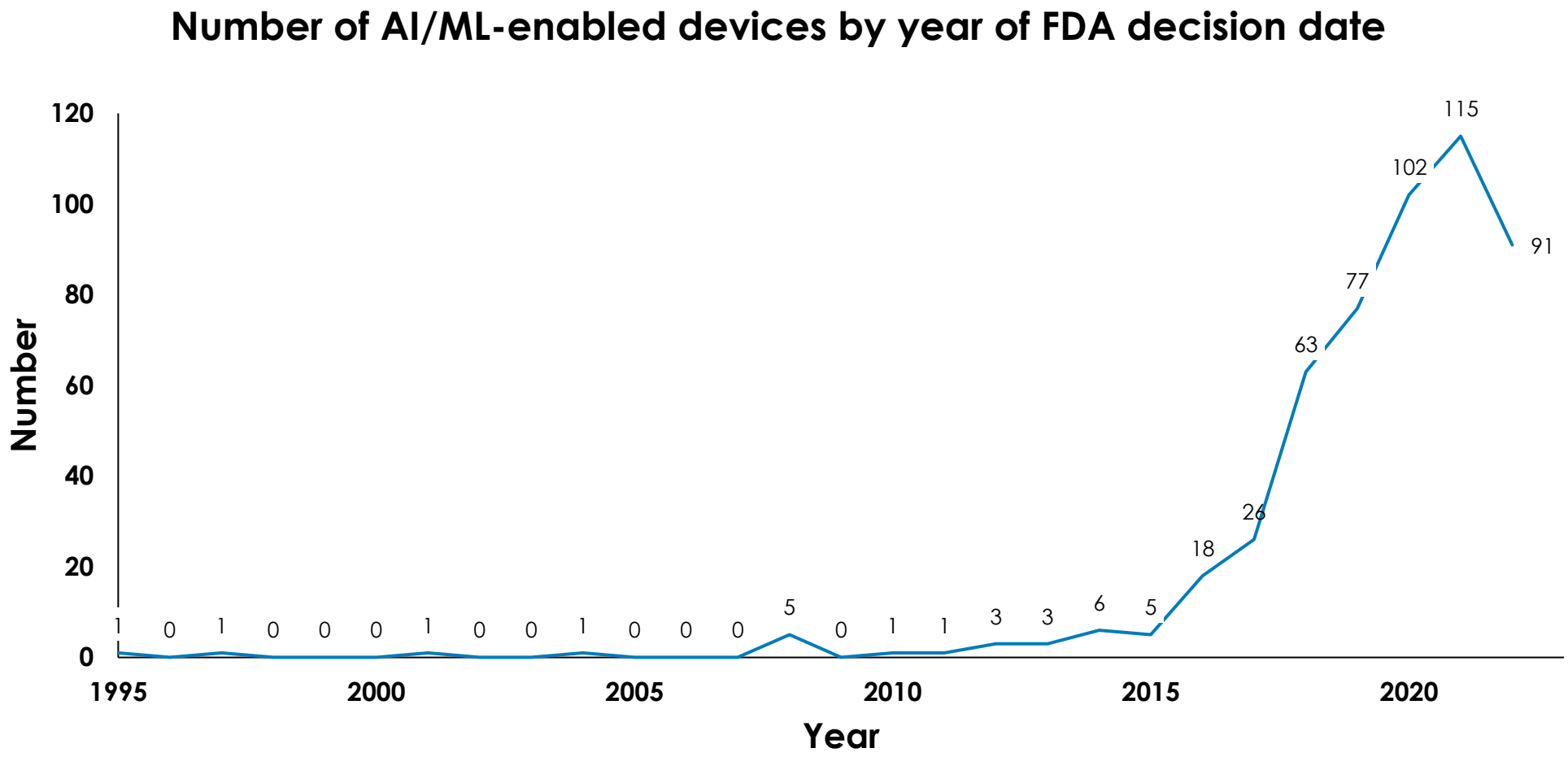
Number of medical AI studies by year from 2010 to 2020; and by medical specialties



https://www.nature.com/articles/s41746-020-00333-z/figures/1

FDA's CDRH has authorized over 500 AI/ML enabled devices



AI use across the drug development landscape

Discovery and Development

- Drug Target Identification, Selection, and Prioritization
- Compound Screening and Design

Preclinical Research

Pharmacokinetic (PK), pharmacodynamic (PD), and toxicologic studies

Clinical Research

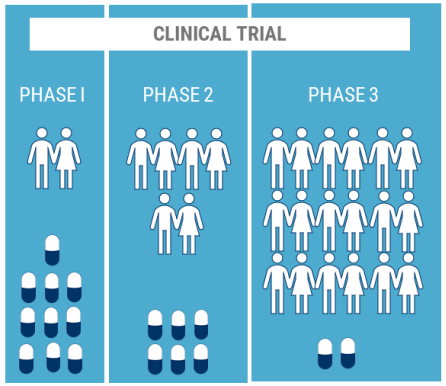


Image source: cbinsights.com

- Dose optimization
- Recruitment and selection
- Adherence
- Retention
- Site selection
- Data collection, management, and analysis
- Clinical endpoint assessment

Manufacturing and Post-Market Safety Monitoring

- Advanced pharmaceutical manufacturing
- Post-market safety surveillance or pharmacovigilance (PV)

FDA's CDER has seen a rapid increase in drug regulatory submissions with AI/ML components

Count of regulatory submissions for drug development with key terms "machine learning" or "artificial intelligence" from 2016 to 2021

	Year					
Submission Type (n)	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
IND	1	1	2	5	11	128
NDA, ANDA, BLA	-	-	1	2	2	2
DDT, CPIM	-	-	-	-	1	2

	Year					
Drug Development Stage (n)	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
Discovery and Development	-	-	-	-	1	3
Preclinical Research	-	-	-	-	-	8
Clinical Research	1	1	3	5	12	118
Post-Market Safety Monitoring	-	-	-	2	1	3

ABBREVIATIONS: Investigational New Drug (IND); New Drug Application (NDA), Abbreviated New Drug Application (ANDA), Biologics License Application (BLA); Drug Development Tool (DDT) Qualification Programs, Critical Path Innovation Meeting (CPIM)

SOURCE: Internal databases maintained by the FDA Center for Drug Evaluation and Research (CDER)

Q i Liu, R. H., Julie Hsieh, Hao Zhu, Mo Tiwari, Guansheng Liu, Daphney Jean, M. Khair ElZarrad, Tala Fakhouri, Steven Berman, Billy Dunn, Matthew Diamond, and Shiew-Mei Huang (2022). Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development from 2016 to 2021. Clinical Pharmacology & Therapeutics. (Accepted May 2022)

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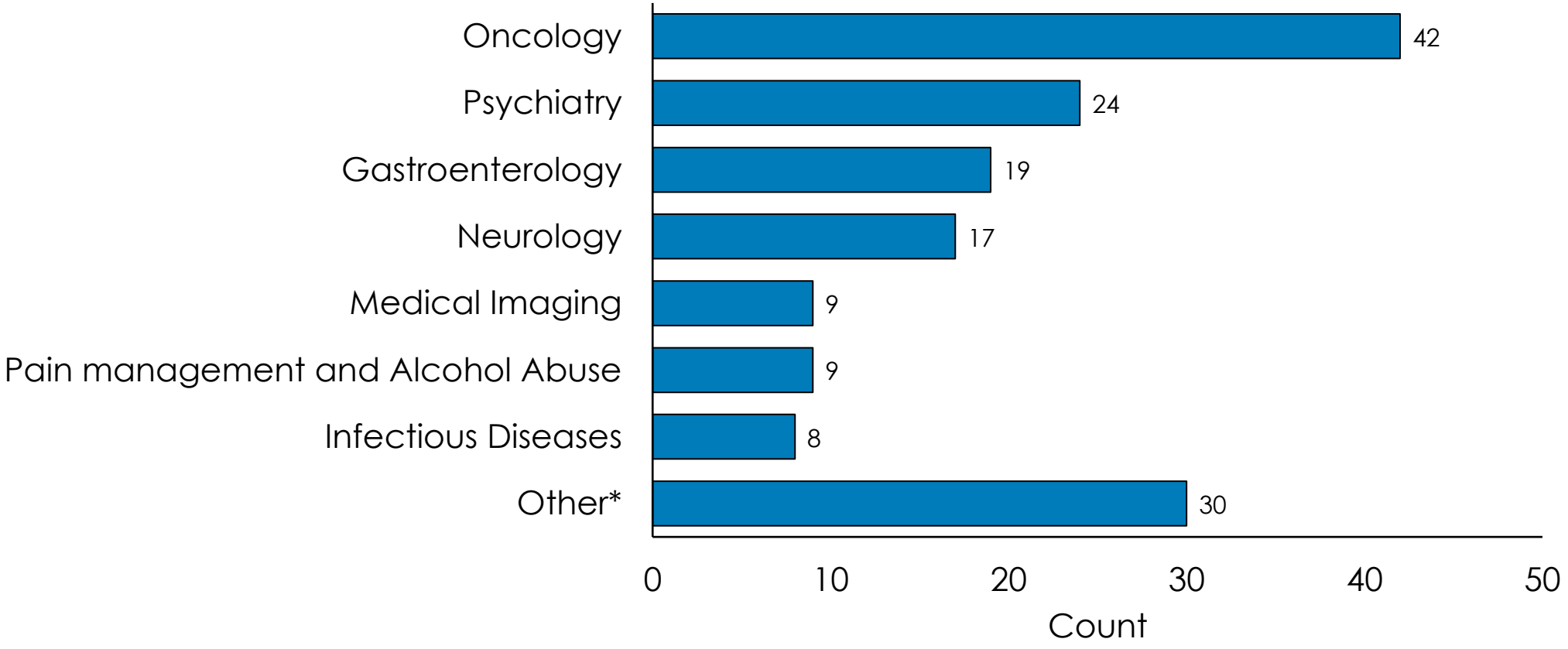
FDA's CDER has seen a rapid increase in drug regulatory submissions with AI/ML components

Regulatory submissions with key terms ML or AI by Therapeutic Area



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AI in drug development – challenges

- AI or ML approach can only ever be as good as the underlying data:
  - Scarcity of high-quality, large-scale, and fit-for-purpose datasets for development and testing
  - Identification and mitigation of bias in datasets
  - poor generalization due to dataset shift, to overfitting to confounders
- Black box algorithms
- Ensuring transparency to users
- Providing oversight/governance for adaptive algorithm
- Need for regulatory clarity in certain areas

Advancing regulatory science in this space can help us promote innovation and public health

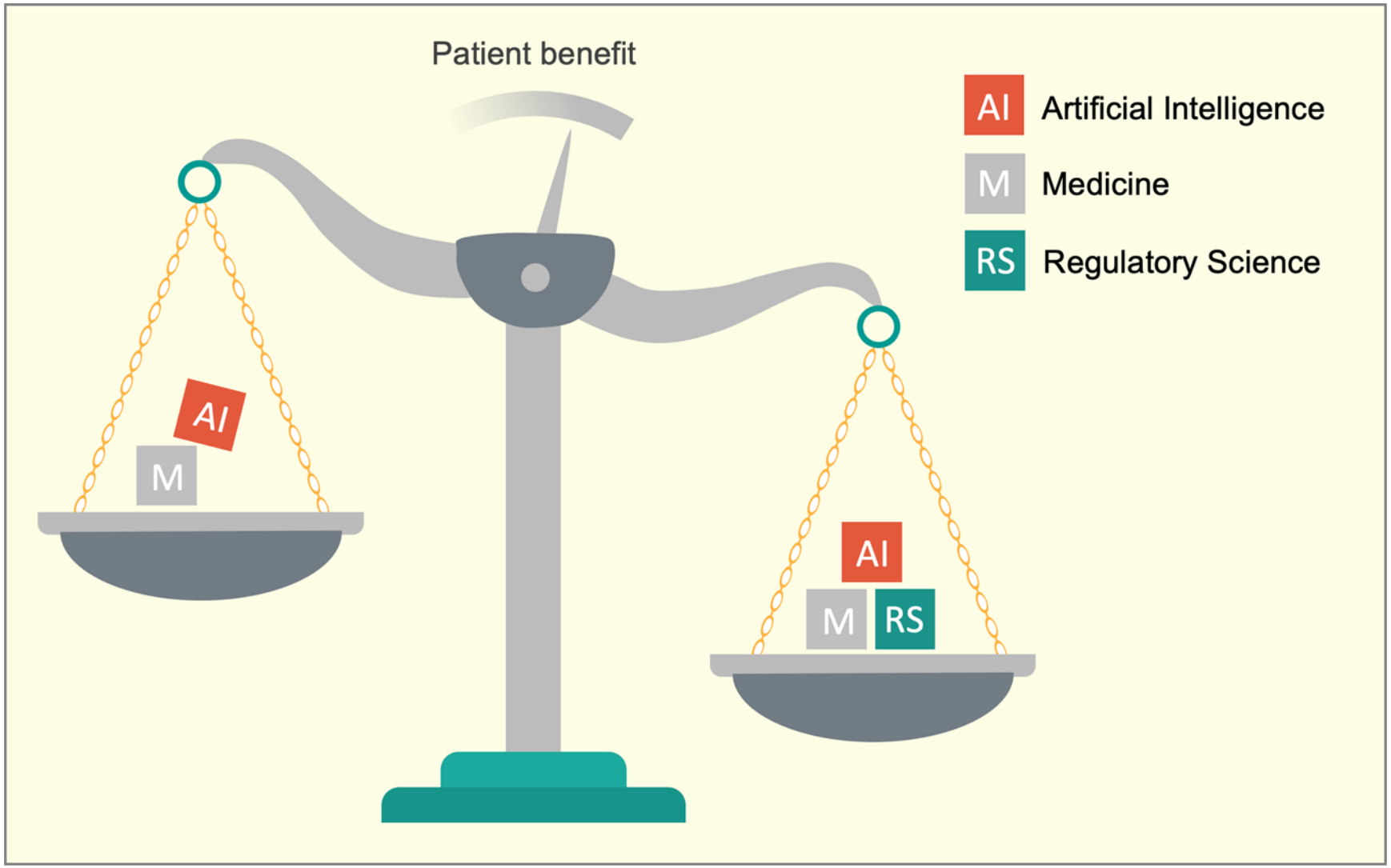

Image: https://www.nature.com/articles/s41746-022-00721-7

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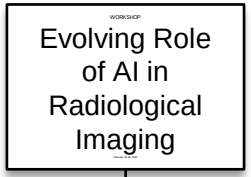
FDA's efforts in this area?
Center for Devices and Radiological Health (CDRH)

Published AI/ML-SaMD Discussion Paper

First joined Collaborative Community related to AI/ML

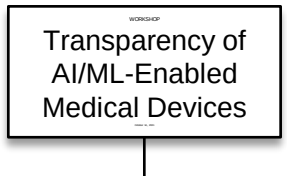


Public Workshop on AI/ML in Radiological Imaging

PEAC Mtg on Patient Trust in AI/ML Devices

Published AI/ML Medical Device Software Action Plan

Posted List of Currently Marketed AI/ML Devices



Public Workshop on Transparency of AI/ML Devices

Published GMLP Guiding Principles

2019 **2020** **2021**

Slide from Dr. Matthew Diamond, Chief Medical Officer for Digital Health, CDRH

CDRH's Good Machine Learning Practice for Medical Device Development: Guiding Principles

1. Multi-Disciplinary Expertise Is Leveraged Throughout the Total Product Life Cycle
2. Good Software Engineering and Security Practices Are Implemented
3. Clinical Study Participants and Data Sets Are Representative of the Intended Patient Population
4. Training Data Sets Are Independent of Test Sets
5. Selected Reference Datasets Are Based Upon Best Available Methods
6. Model Design Is Tailored to the Available Data and Reflects the Intended Use of the Device
7. Focus Is Placed on the Performance of the Human-AI Team
8. Testing Demonstrates Device Performance During Clinically Relevant Conditions
9. Users Are Provided Clear, Essential Information
10. Deployed Models Are Monitored for Performance and Re-training Risks Are Managed

https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles

FDA's efforts in this area?
Center for Drug Evaluation and Research (CDER)

- CDER actively collaborates with CDRH, CBER, and other centers on issues related to AI/ML in medical product development to ensure consistency whenever possible

- CDER established an AI Steering Committee in 2020 to facilitate effective use and sustainment of AI in CDER's decision-making and operations

- Next steps: workshops, white papers, discussion paper, harmonizing and tailoring GMLP to drug development, support development of regulatory science methods

- **Our goal: to develop and adopt a flexible risk-based regulatory framework that promotes innovation and protects patient safety**

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Thank you