INTERNATIONAL CONSORTIUM *for* INNOVATION & QUALITY *in* PHARMACEUTICAL DEVELOPMENT

MACHINE INTELLIGENCE FOR QUANTITATIVE MODELING IN DRUG DISCOVERY & DEVELOPMENT APPLICATIONS WORKSHOP

15-16 September 2022

Keynote Speaker

Dr. Qi Liu

Associate Director for Innovation & Partnership in the Office of Clinical Pharmacology (OCP), OTS, CDER

US Food & Drug Administration

Application of Artificial Intelligence/Machine Learning (AI/ML) in Drug Development

15 September 2022

Presenter: Qi Liu, Ph.D., M.Stat., FCP
Associate Director for Innovation & Partnership
Office of Clinical Pharmacology/OTS/CDER/FDA

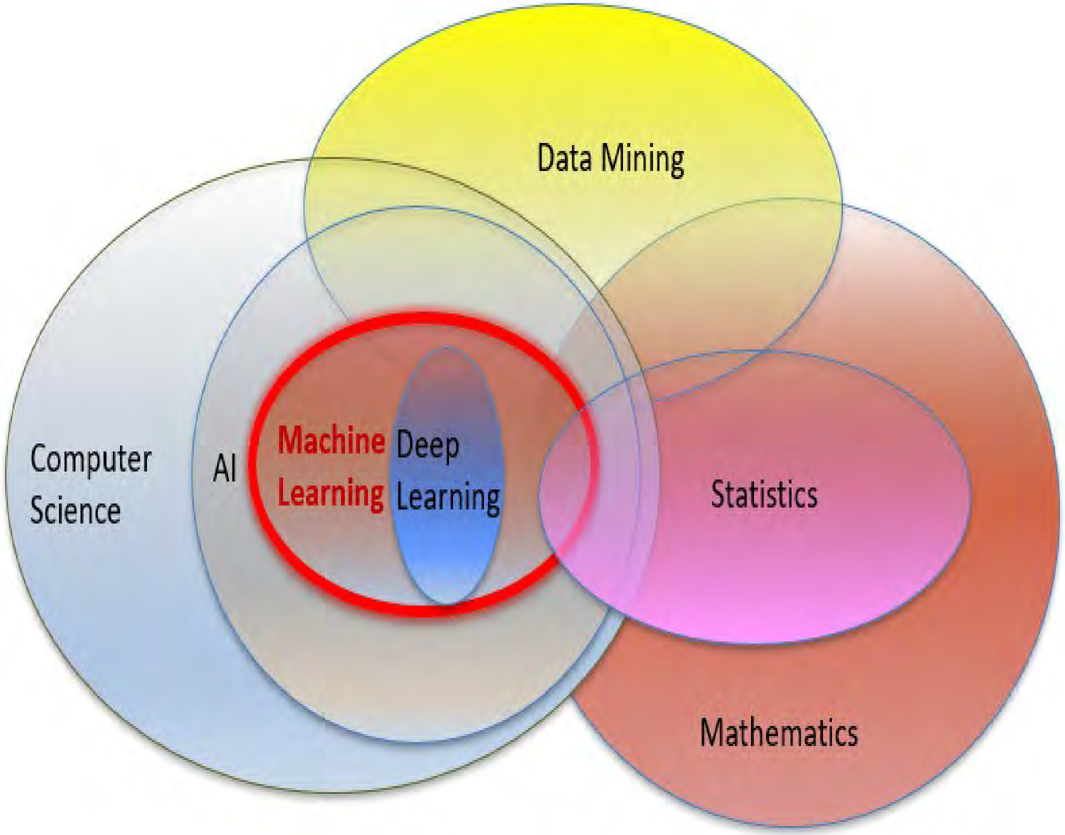
Why are we talking about AI/ML today?

- The application of AI/ML in drug development is expanding rapidly.
- Oncology has the highest number of regulatory submissions with AI/ML components.
- AI/ML have the potential to improve the efficiency of drug development and advance precision medicine, but they also have unique challenges.

Outline

- Background
- AI/ML related submissions to FDA
- Challenges related to the applications of AI/ML
- Regulatory considerations for AI/ML in drug development (still evolving)
- Examples:
  1. ML for Patients Risk Stratification/Management
  2. ML-based Enrichment Trial Design
- AI/ML related activities in the Office of Clinical Pharmacology and how we developed our capacity

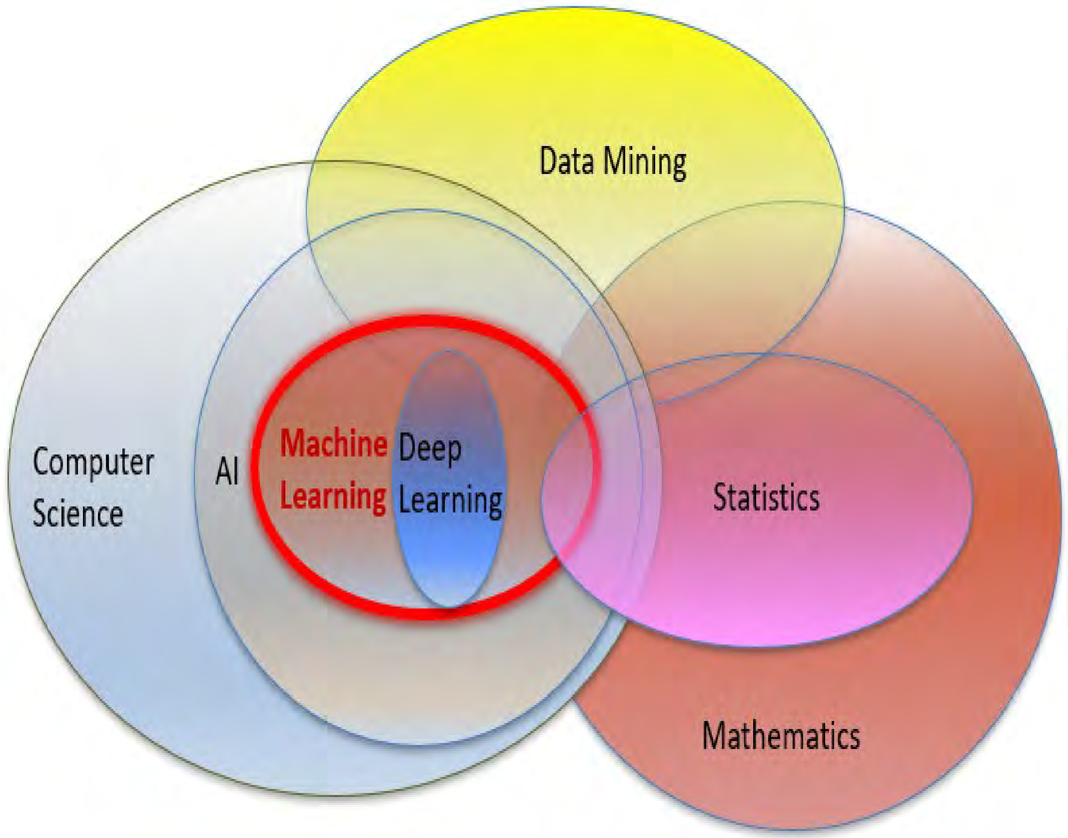
Definition of Machine Learning (ML)

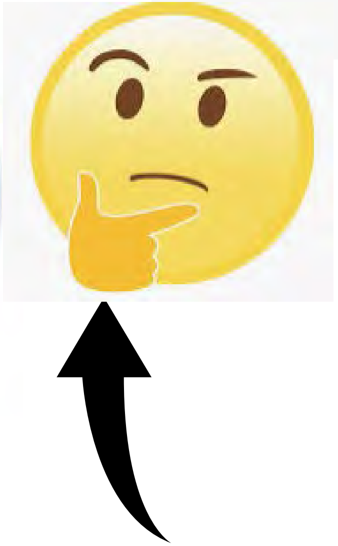


- The field of study that gives computers the ability to learn without being explicitly programed - Arthur Samuel
- A Computer program learns from experience E with respect to some class of tasks T and performance measure P, if P improves with E - Tom Mitchell

The algorithm's performance improves with accumulating data

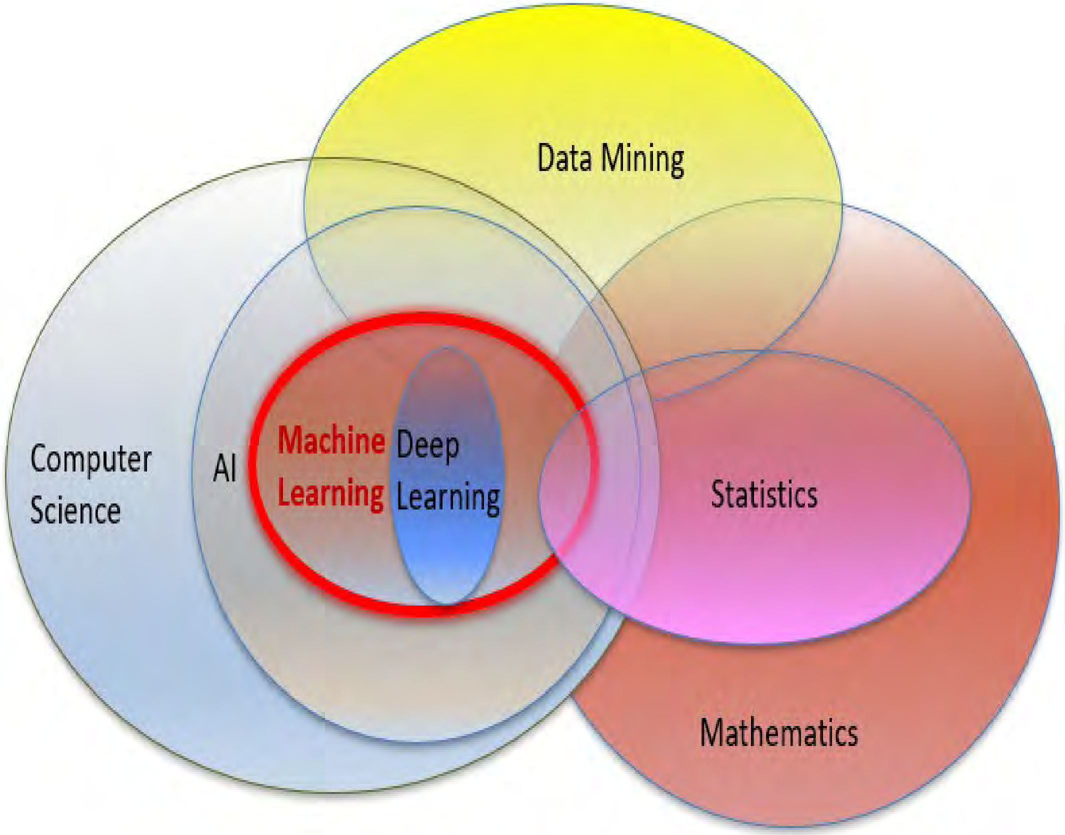
Definition of Machine Learning (ML)

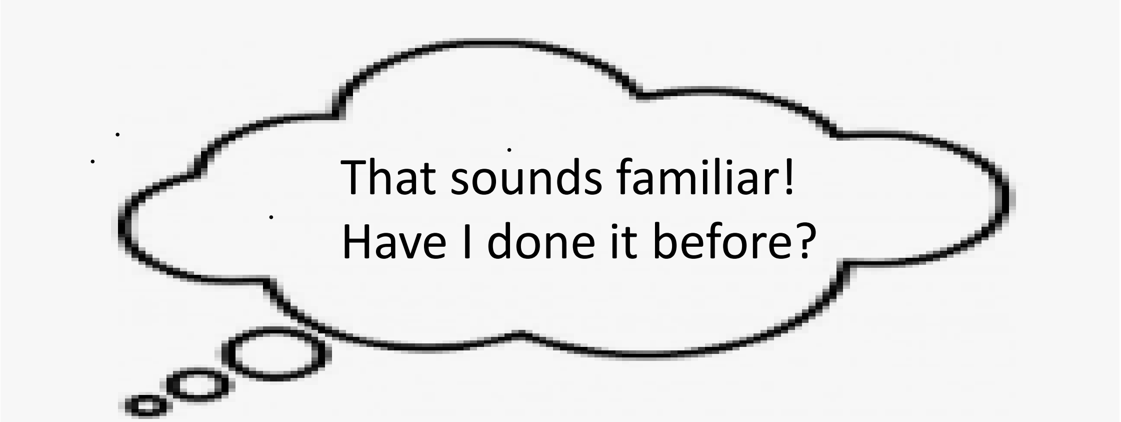




The algorithm's performance improves with accumulating data

Definition of Machine Learning (ML)



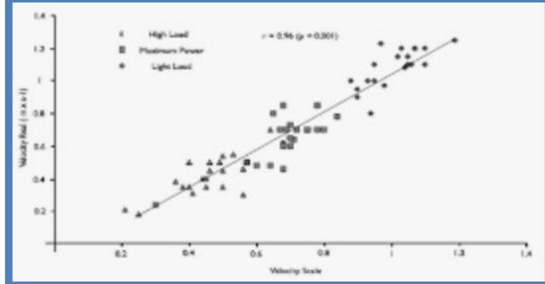
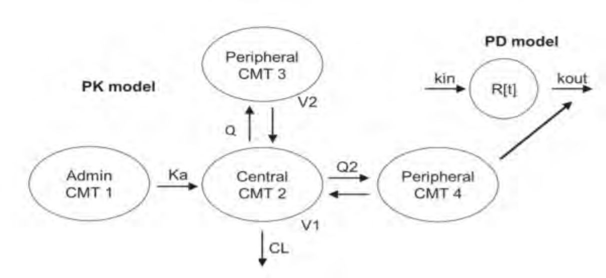
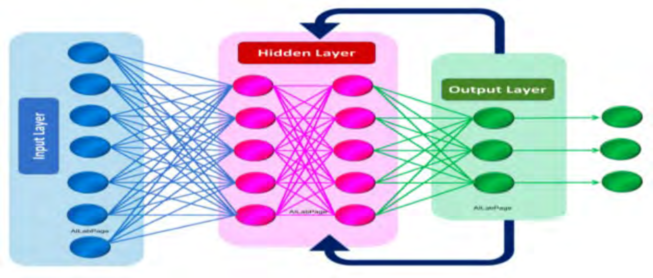


The answer is probably yes! ☺

In fact, ML has a lot of overlap with statistical and pharmacometric modeling!

The algorithm's performance improves with accumulating data

So, What is New This Time?

<table>
<tr><th>The Traditional Statistical/Pharmacometric Modeling</th><th>The Newer Machine Learning Approach</th></tr>
<tr><td>

</td><td>
</td></tr>
<tr><td>Explicit model structure defined with domain knowledge and assumptions</td><td>Very General/Flexible Model structure, with less reliance on domain knowledge and assumptions</td></tr>
<tr><td>Tend to excel at handling data with a small or moderate number of independent variables</td><td>Tend to excel at handling data with a large number of independent variables (i.e., features),
can also handle new types of data such as imaging</td></tr>
<tr><td>Easier to interpret/explain or draw statistical inference</td><td>Harder to interpret/explain or draw statistical inference;
More focused on prediction performance</td></tr>
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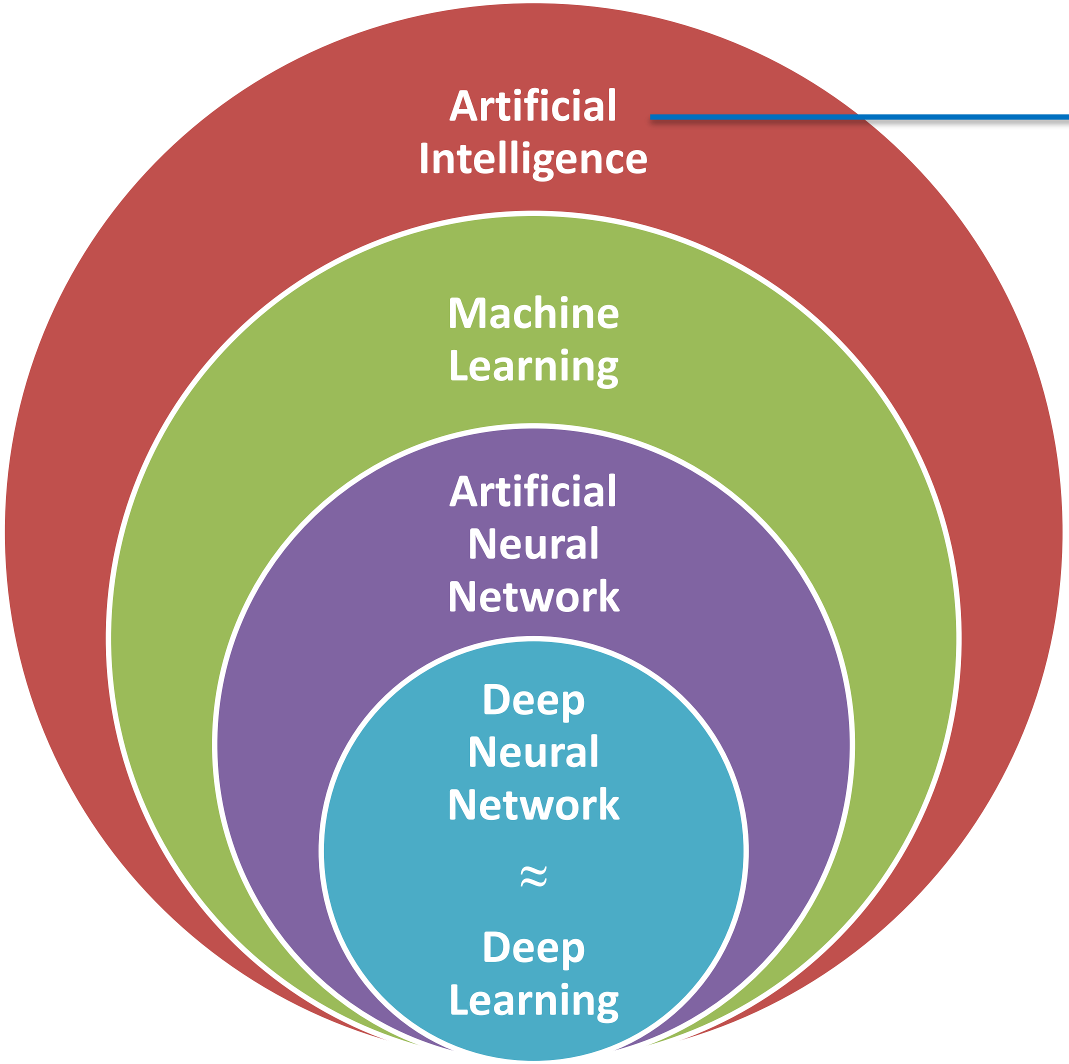
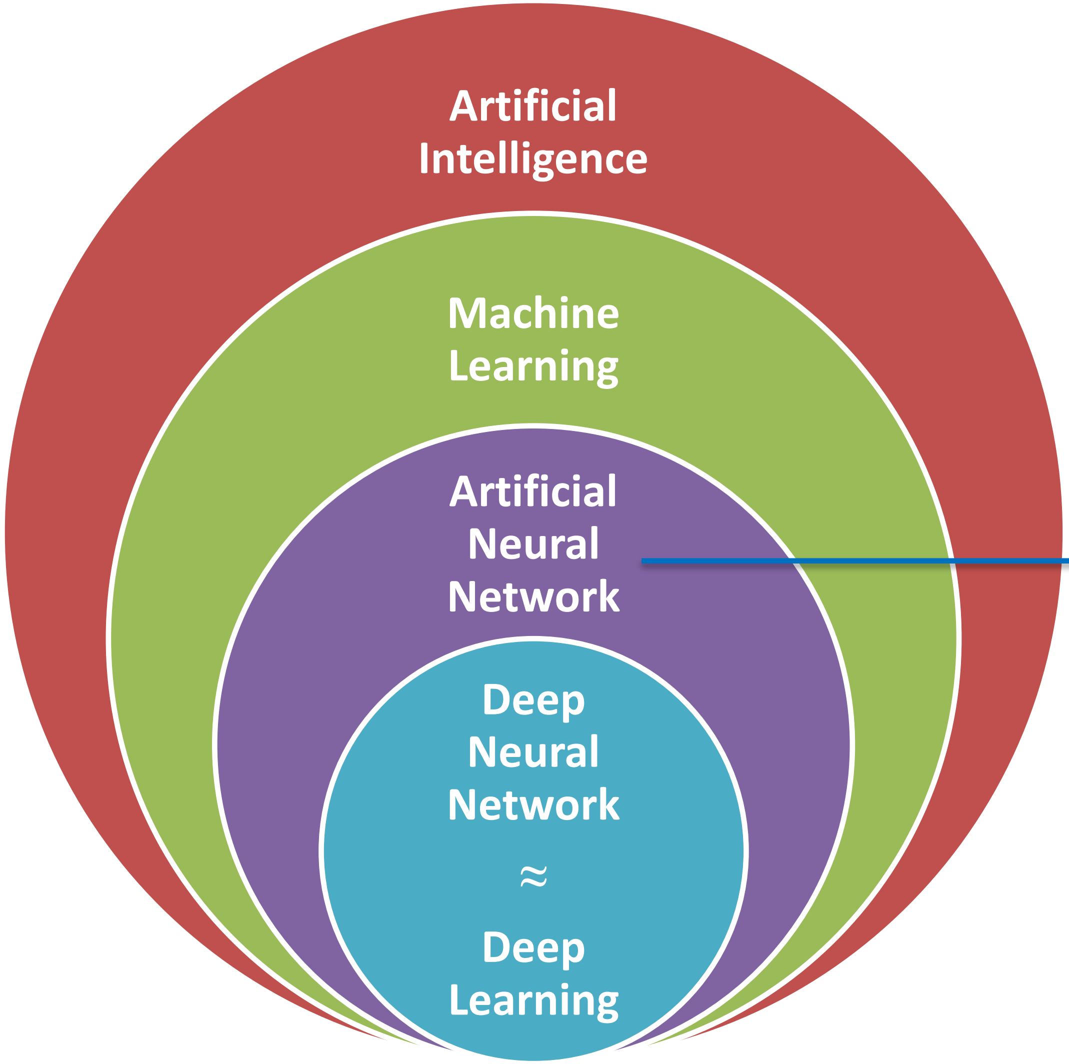
Machine Learning and Related terminology

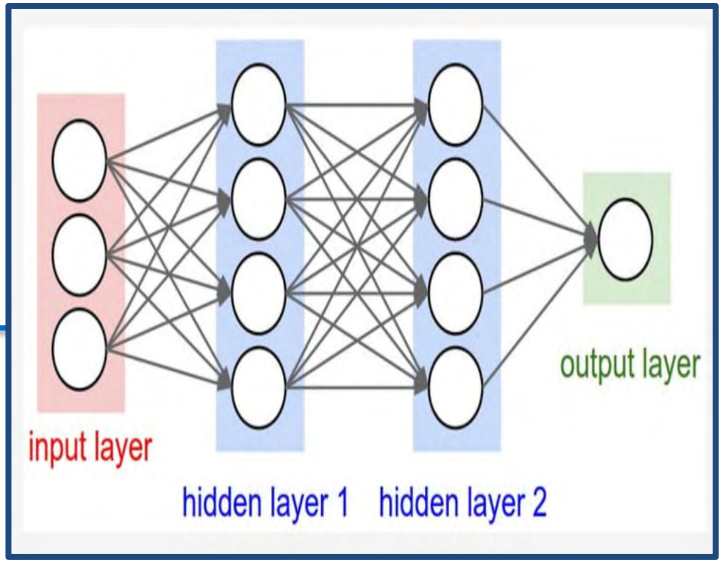


The science and engineering of making intelligent machines -John McCarthy

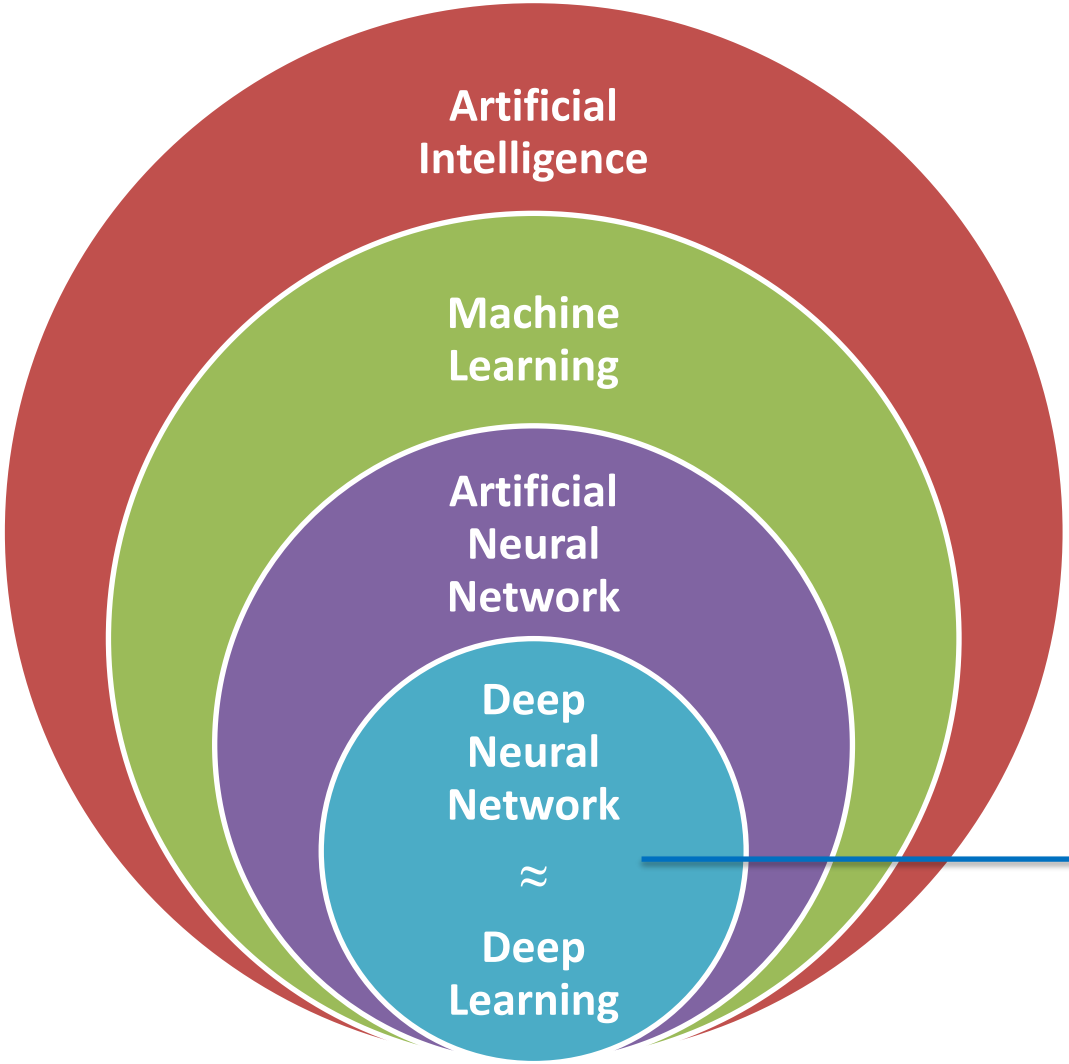
The theory and development of computer systems able to perform tasks normally requiring human intelligence, in order to deliver solutions that can automate routine tasks, draw data-based insights, or augment human activities. https://www.hhs.gov/sites/default/files/final-hhs-ai-strategy.pdf.

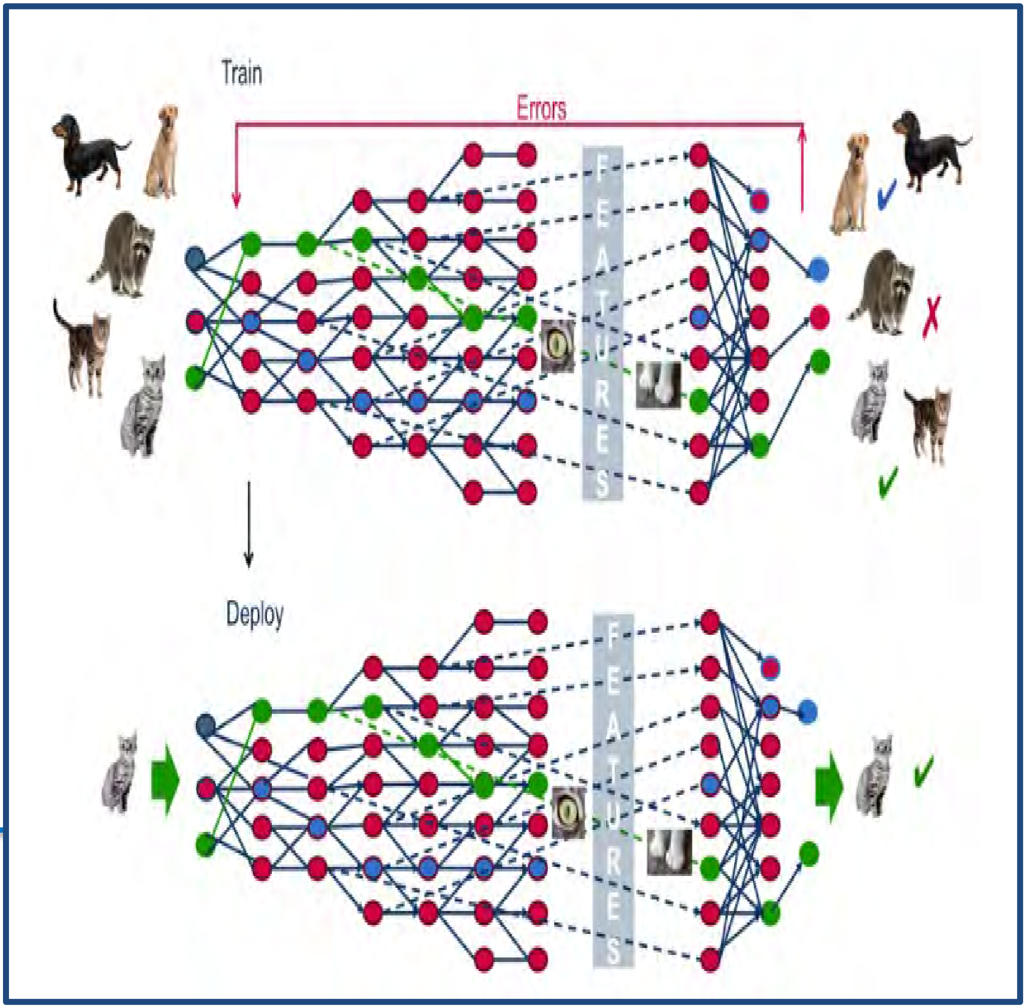
Machine Learning and Related terminology



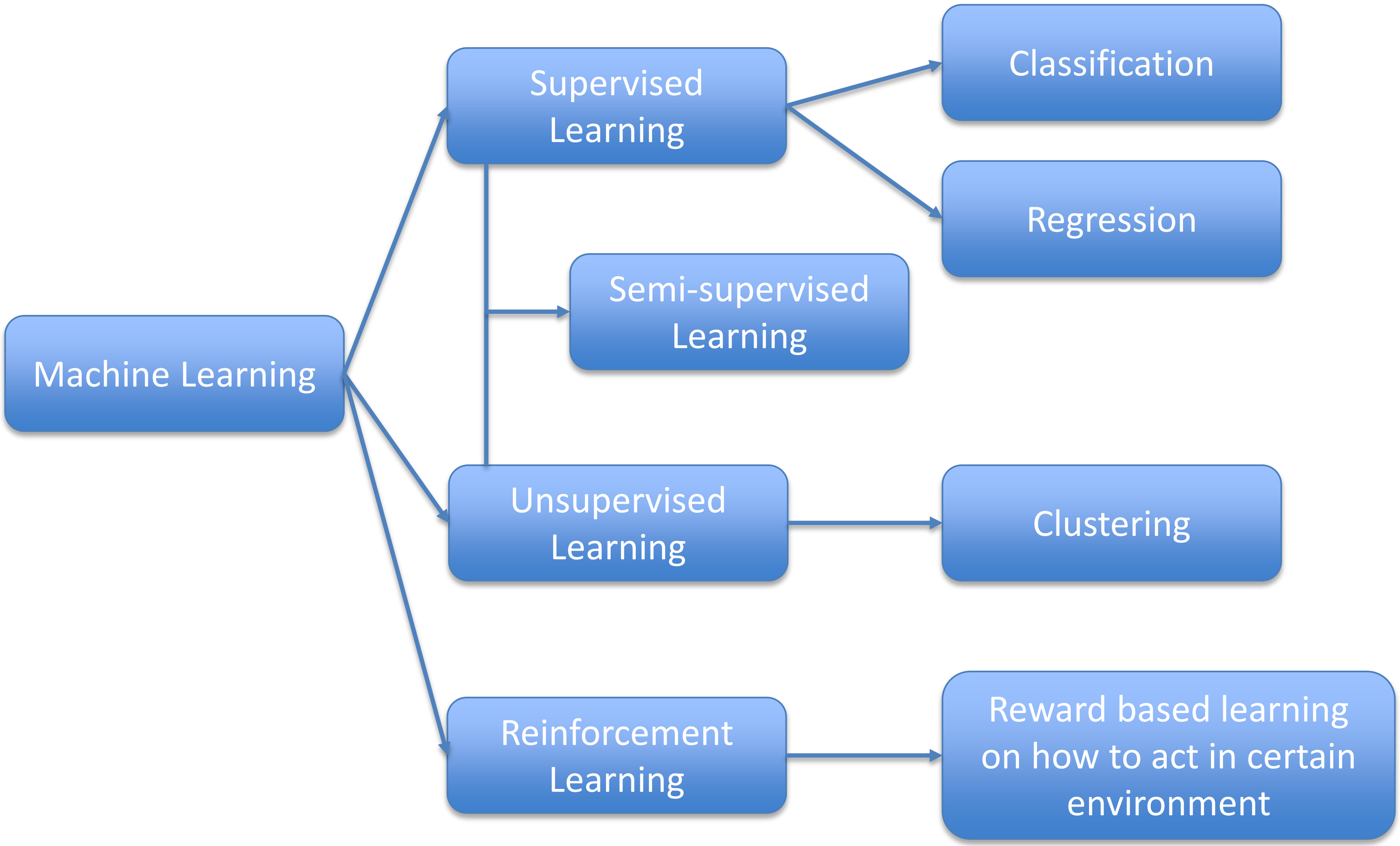


Machine Learning and Related terminology



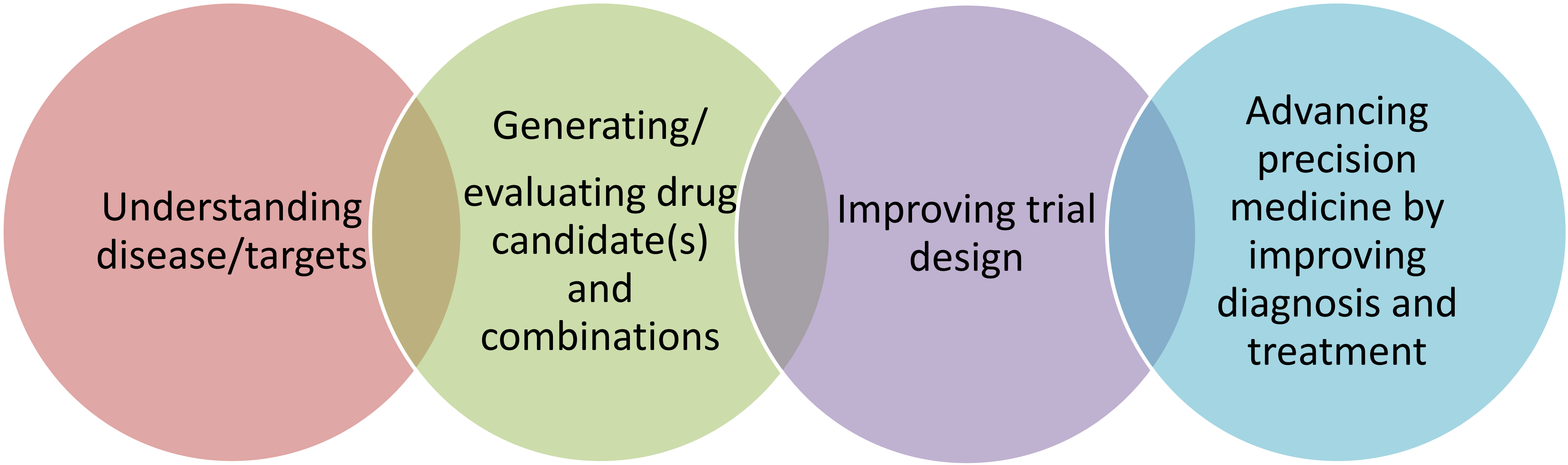


Types of Machine Learning

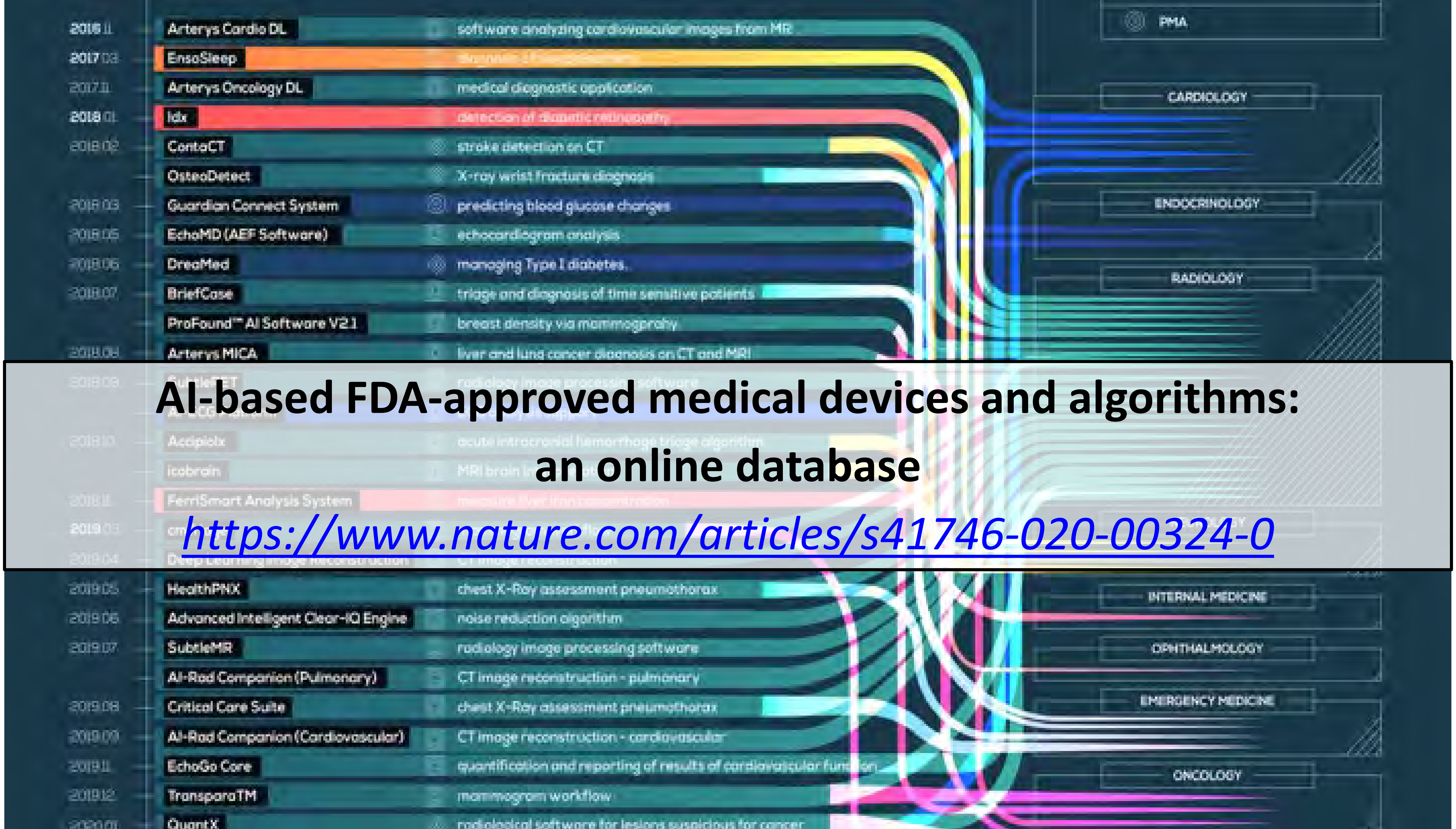


The Potential Use of Machine Leaning (ML) in Drug Development and Regulation

Aggregating data, synthesizing information, seeking patterns and optimizing decisions



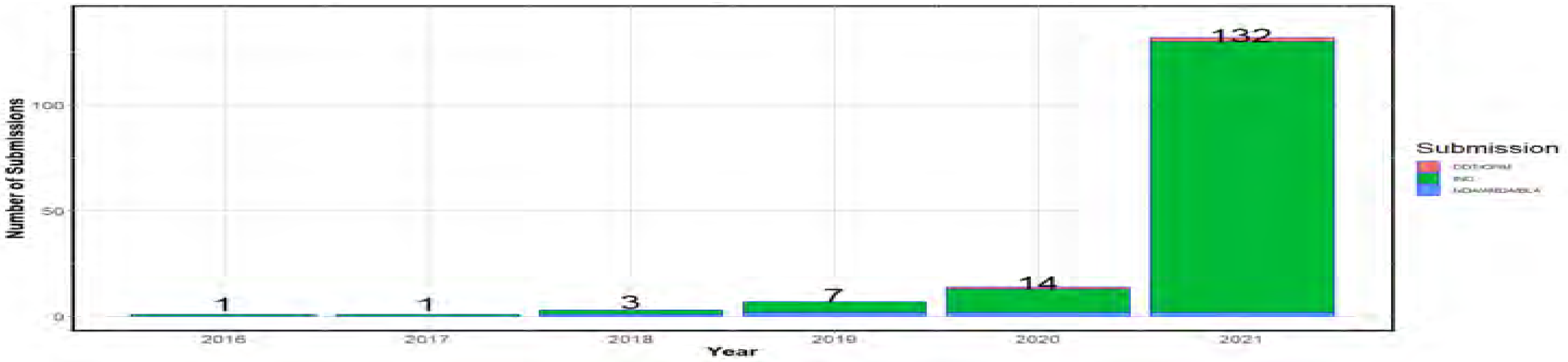
AI/ML Related Submissions to the FDA



AI-based FDA-approved medical devices and algorithms: an online database

https://www.nature.com/articles/s41746-020-00324-0

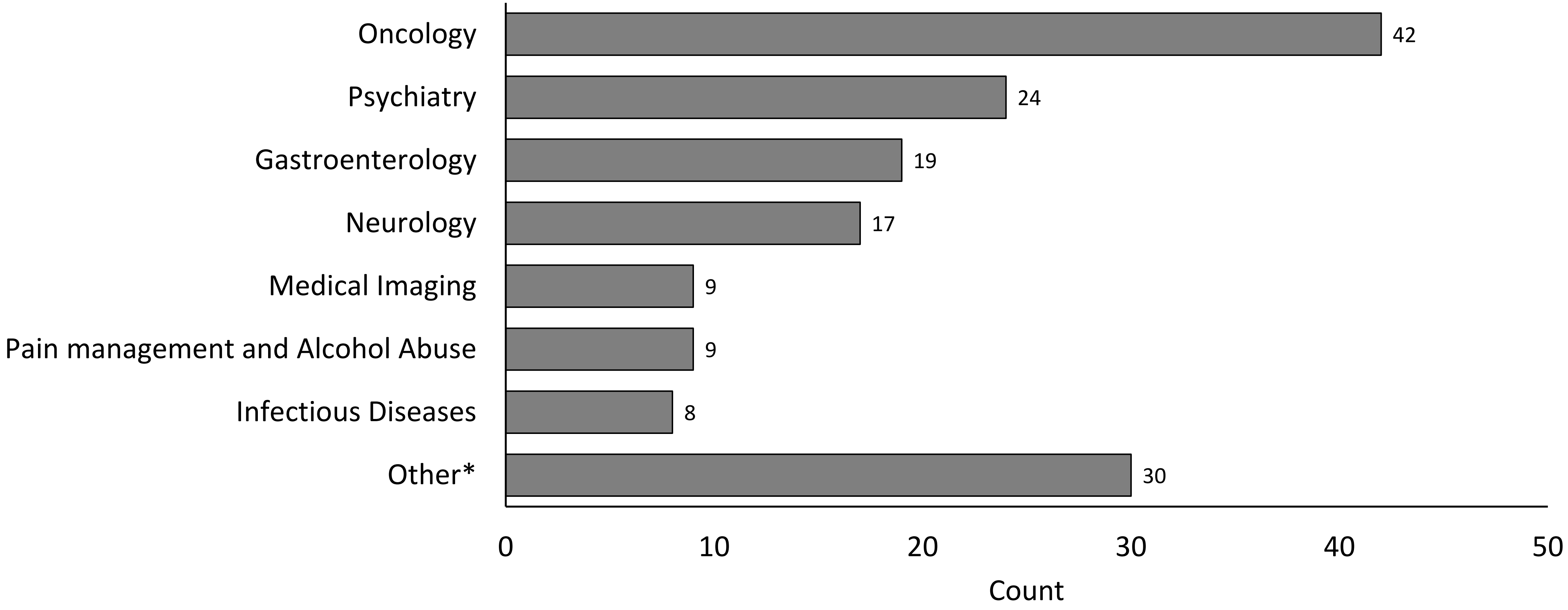
Number of AI/ML Related Submissions to CDER/FDA By Year



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

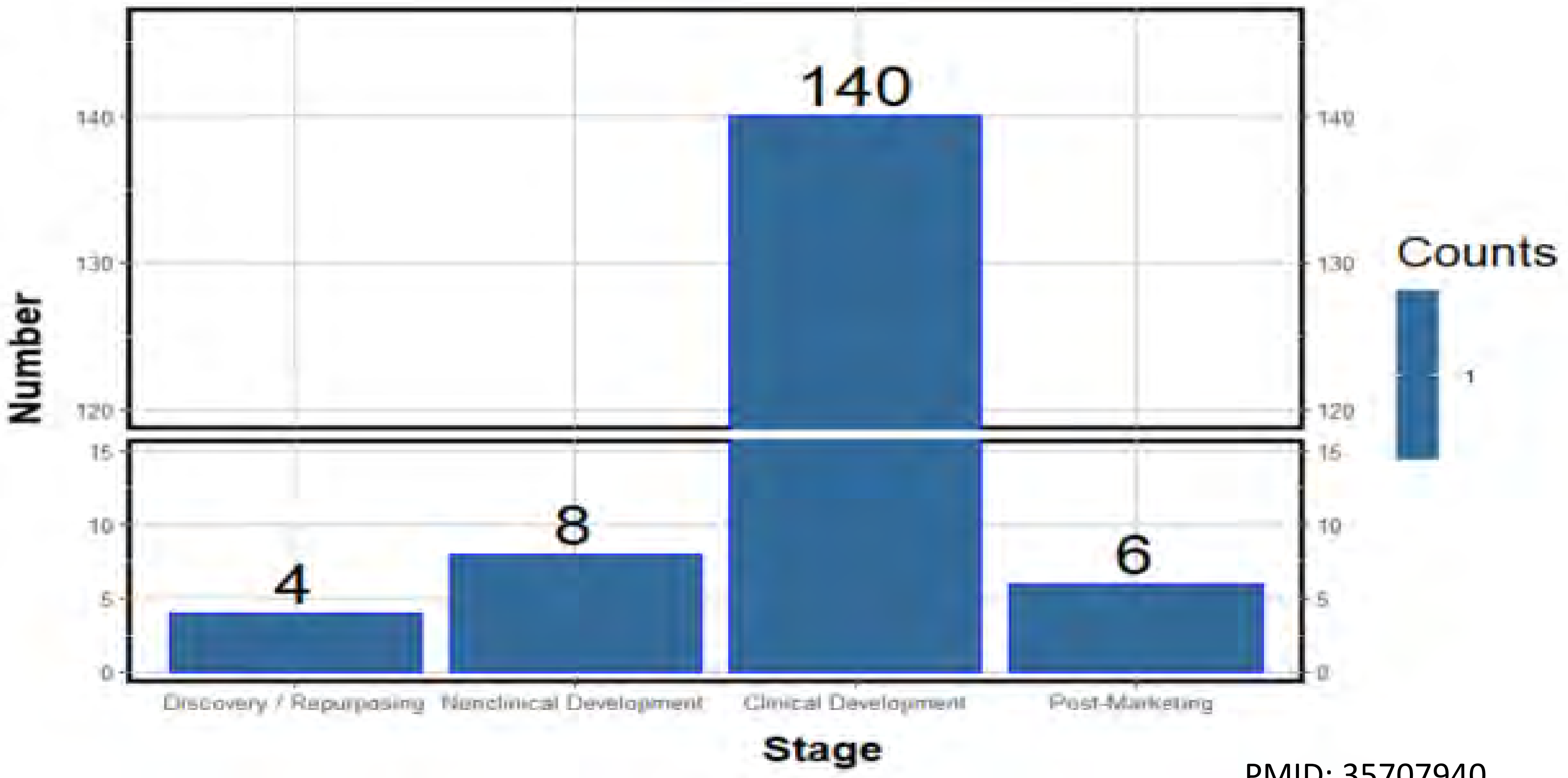
Liu Q, Huang R, Hsieh J, Zhu H, Tiwari M, Liu G, Jean D, ElZarrad MK, Fakhouri T, Berman S, Dunn B, Diamond MC, Huang SM. Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021. Clin Pharmacol Ther. 2022 Jun 16. doi: 10.1002/cpt.2668. Epub ahead of print. PMID: 35707940.

AI/ML Related Submissions to CDER/FDA By Disease Areas



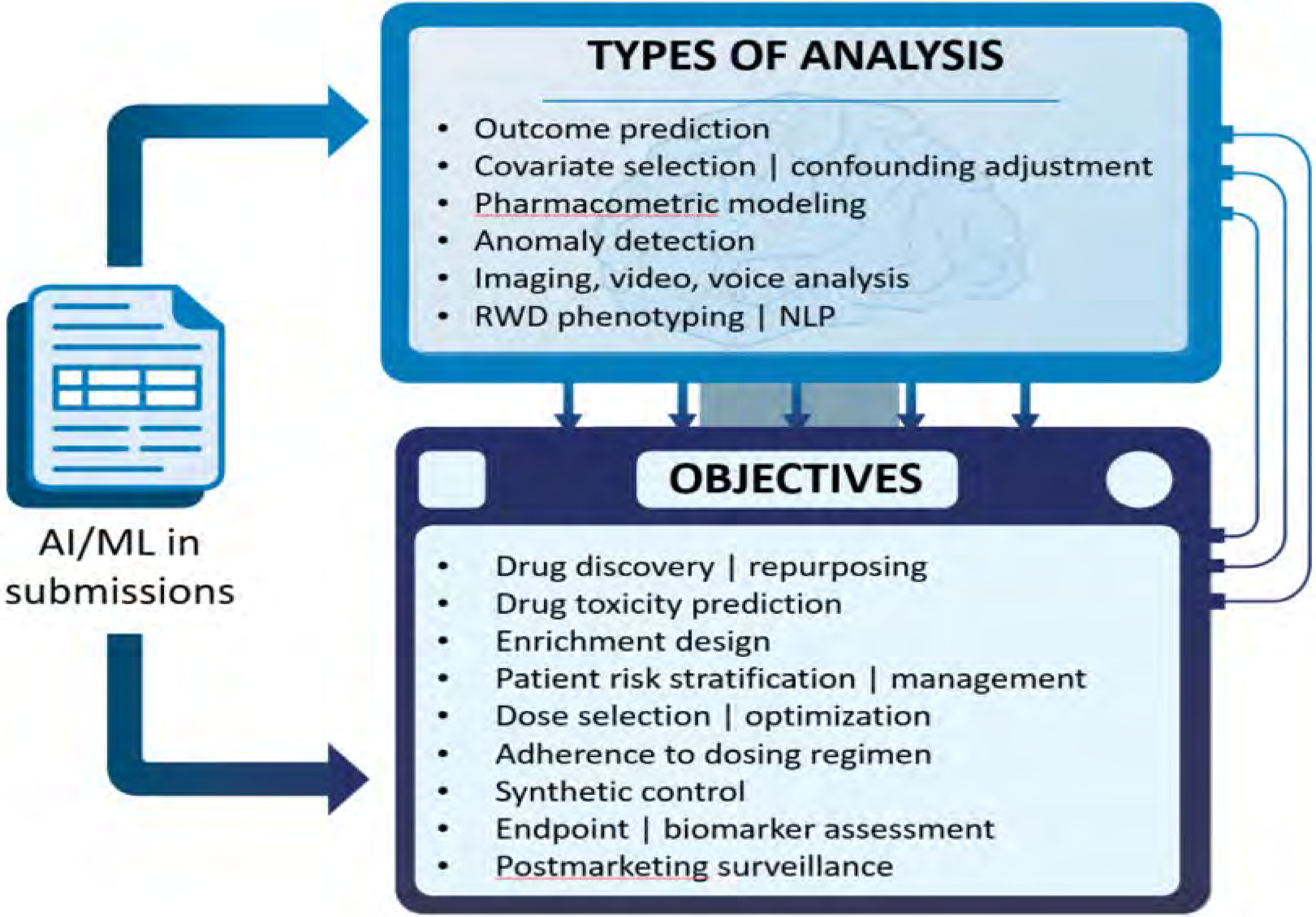
PMID: 35707940.; Figure adapted by Dr. Fakhouri

AI/ML Related Submissions to CDER/FDA By The Stage of Drug Development Lifecycle



PMID: 35707940.

AI/ML Related Submissions to CDER/FDA By Analysis Types and Objectives



PMID: 35707940.

Challenges in the application of AI/ML

- Bias
- Generalizability
- Opacity
- Privacy
- Security
- Other…

Disparity/Fairness

Trustworthiness issues

Bias

REUTERS

World Business Markets Breakingviews Video More

RETAIL OCTOBER 10, 2018 / 7:04 PM / UPDATED 3 YEARS AGO

Amazon scraps secret AI recruiting tool that showed bias against women

By Jeffrey Dastin

8 MIN READ

SAN FRANCISCO (Reuters) - Amazon.com Inc's AMZN.O machine-learning specialists uncovered a big problem: their new recruiting engine did not like women.

Bias

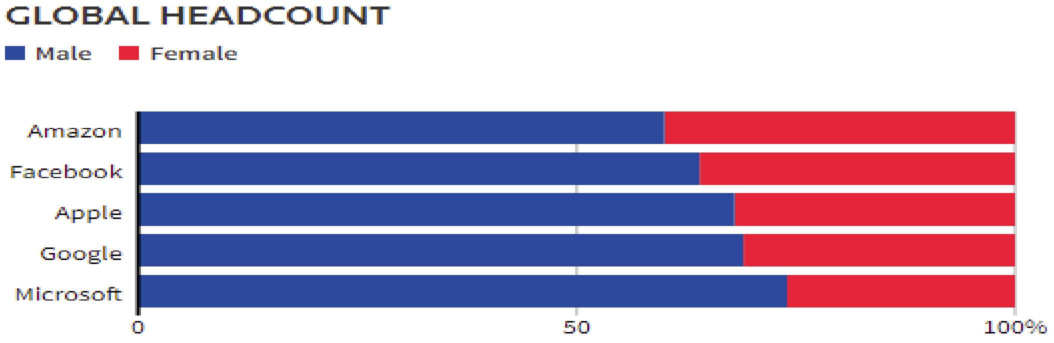
REUTERS

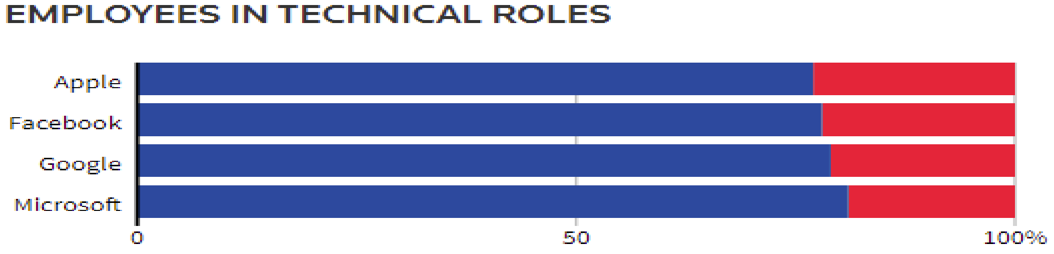
World Business Markets Breakingviews Video More

RETAIL OCTOBER 10, 2018 / 7:04 PM / UPDATED 3 YEARS AGO

Amazon scraps secret AI recruiting tool that showed bias against women

Problem: AI was learning from biased data.

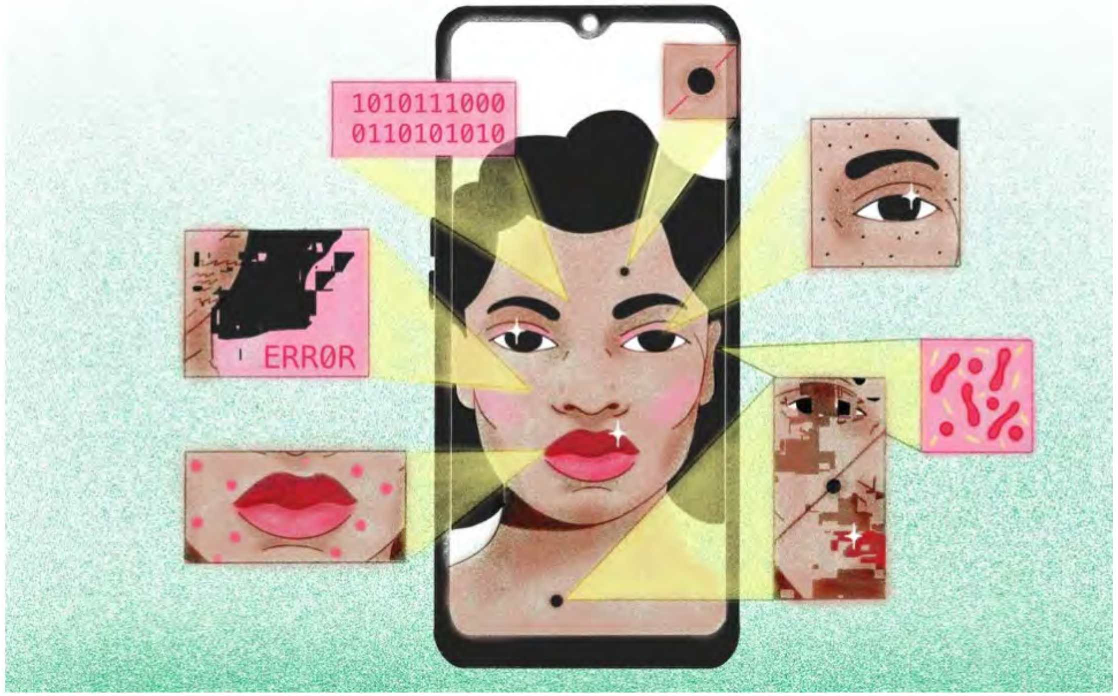




This is one of the most common causes for bias, although there are other ways that bias can be introduced.

Generalizability

These apps say they can detect cancer. But are they only for white people?



The problems arise, in part, because of how algorithms learn to recognize patterns in pictures, says Stanford University researcher James Zou. A tool developed on images from a population of older, white male patients might pick up on cues unique to that cohort rather than the disease itself. Then, if those cues are absent in a younger Black woman, it may misdiagnose her symptoms.

Another fundamental flaw lies in databases that algorithms study - particularly for skin conditions. Common databases of skin images rarely capture the myriad variations in skin tones and textures from around the world. That's in part because compared with white patients, only half as many Black or Hispanic people see dermatologists. Patients with less education or lower socioeconomic status are also far less likely to be represented in these image libraries.

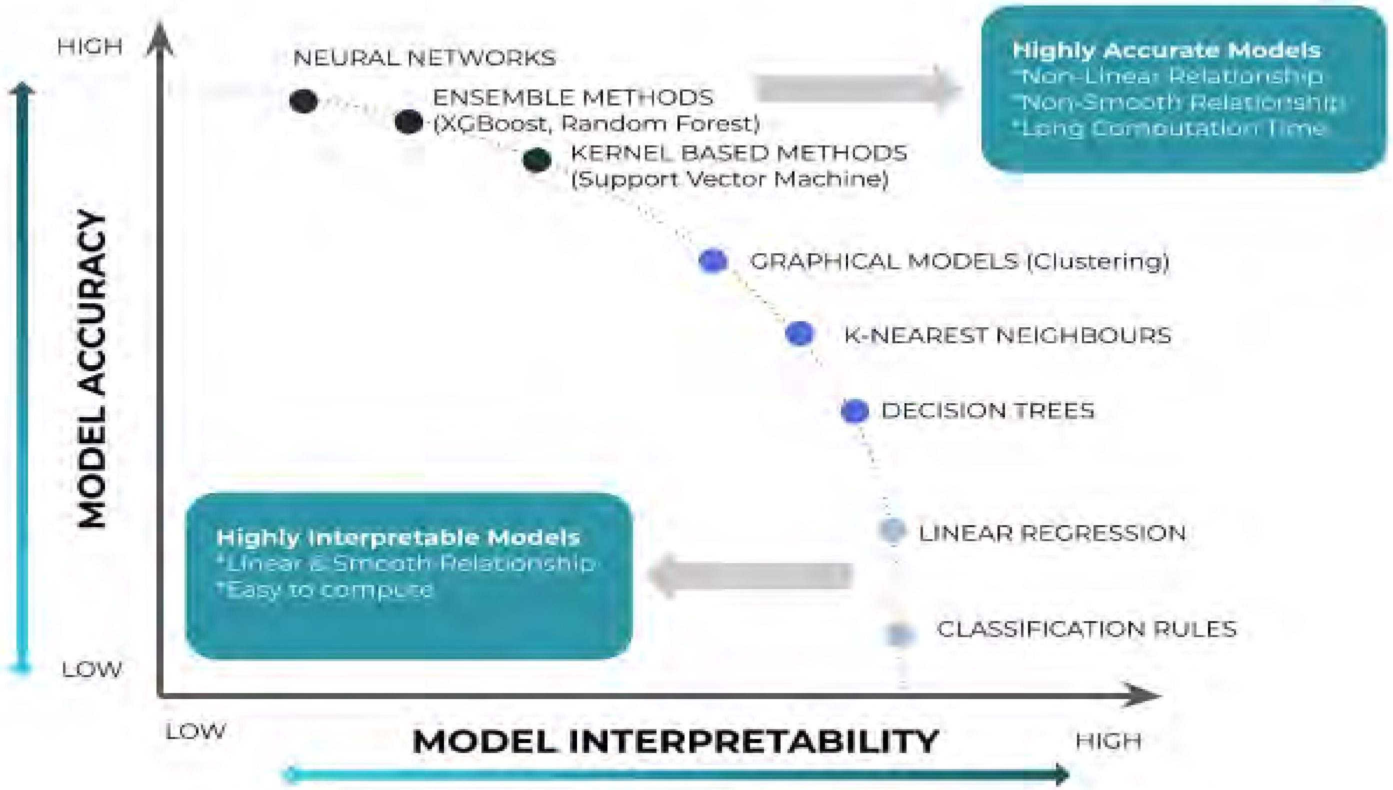
https://www.theguardian.com/us-news/2021/aug/28/ai-apps-skin-cancer-algorithms-darker

Generalizability

- Many AI/ML models were built with data from a single institution, and may not be generalizeble to other institutions
  - Differences in patient populations
  - Differences in data collection
  - Differences in medical practices

- Data sharing and collaborations are critical but can be challenging

Opacity



[How to think about explainability in your machine learning models? | by Raheel Ahmad | Towards Data Science]

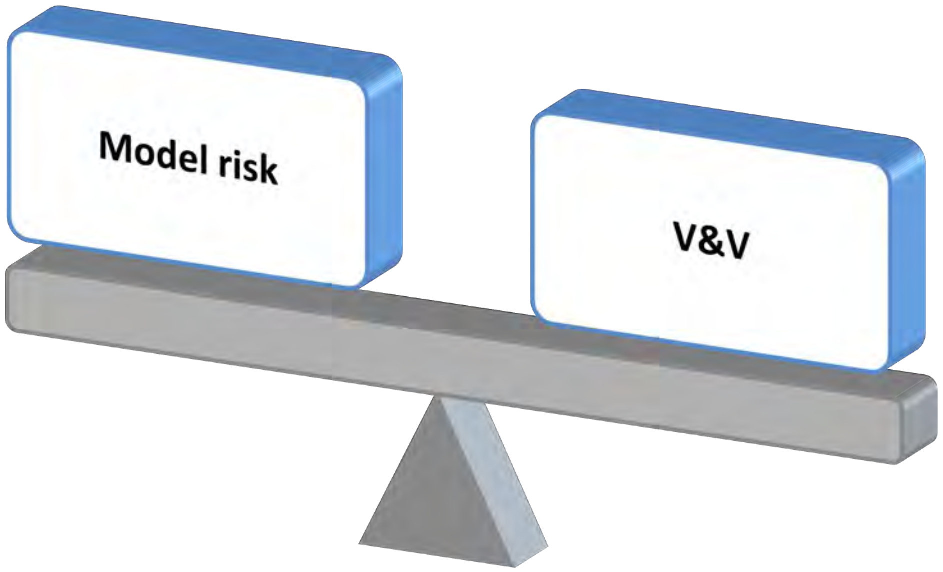
Regulatory Considerations for AI/ML in Drug Development (Personal opinion, Still Evolving)

- The context of use (COU) needs to be clearly defined
- Fit-for-purpose and risk-based validation
- Generalizability
  - Training data should be unbiased and diverse/inclusive
  - Methods need to be developed for performance guarantee
- Transparency/interpretability/explainability
  - Methods are being developed to improve interpretability/explainability
- We need to develop best practice for AI/machine learning

Borrowing Concepts from Computational Modeling Credibility Assessment Framework

- Credibility refers to trust in the predictive capability of a computational model for a particular context of use (COU).

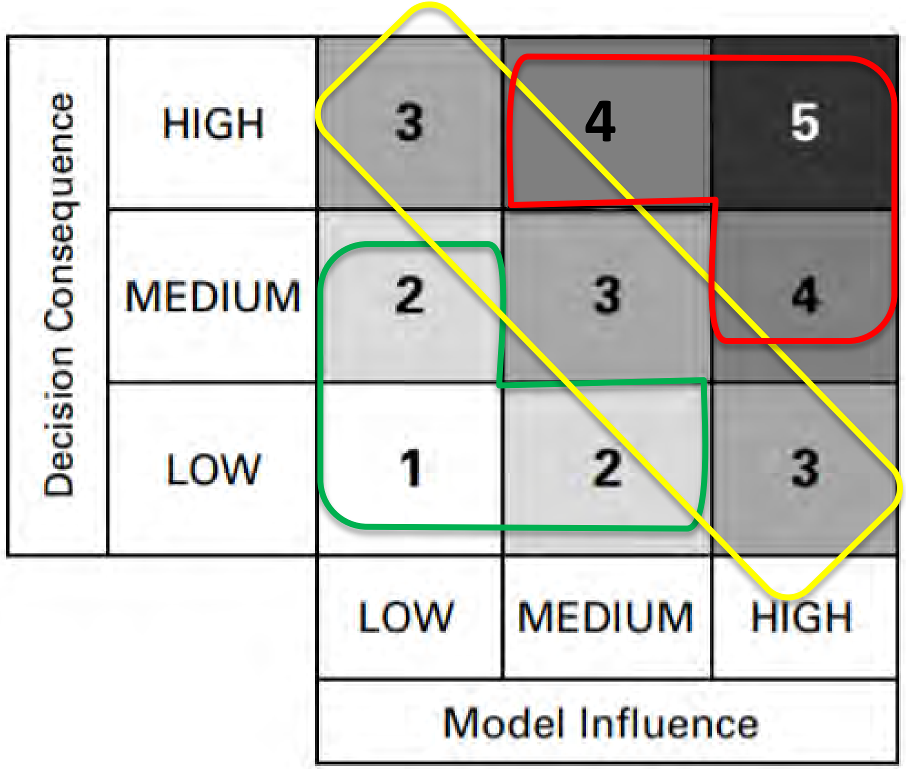
- Model risk guides the level of credibility evidence needed



Assessment of Model Risk

Model Risk is determined by model influence and decision consequence.

- **Model influence**: weight of the model in totality of evidence on a decision
- **Decision consequence**: potential consequences of a wrong decision
- An increase in either factor may lead to an increase in overall model risk



Example 1: ML for Patients Risk Stratification/Management

- **COU:** In previous trials of Drug A, all patients went through inpatient monitoring after dosing due to concern of a potentially life-threatening AE. The sponsor proposed to use a ML model to predict a patient's risk for this AE based on baseline characteristics and lab values. If predicted to be low risk, the patient will have outpatient monitoring instead of inpatient monitoring.

  The sponsor was not clear on some components of COU (e.g., in clinical trials only or in both trials and real-world application? Will this approach be used to determine the monitoring after the first dose of drug Z?). FDA sent them relevant comments.

  The sponsor also mentioned that this model could also be used for dosing regimen optimization. If so, it will need a different model risk analysis.

Example 1: ML for Patients Risk Stratification (continued)

FDA's model risk analysis:

- **Model influence: High.** The model prediction will be the sole factor to determine whether a patient will go through inpatient or outpatient monitoring after dosing.
- **Decision risk: Medium/High.** The model prediction will determine whether a patient will go through inpatient or outpatient monitoring after dosing
  - If the model erroneously predicts a low risk patient to be moderate or high risk, it may not be of major concern, as this patient will go through inpatient monitoring even though it might be unnecessary.
  - If the model erroneously predicts a moderate/high risk patient to be low risk, it will be a major concern, as this patient will not have the necessary inpatient monitoring for the potentially life-threatening AE.

Negative predictive value, i.e. probability (No AE/Negative Model prediction), will be the major performance metric to determine the acceptance of the model from a regulatory perspective.

Example 2: ML-based Enrichment Trial Design

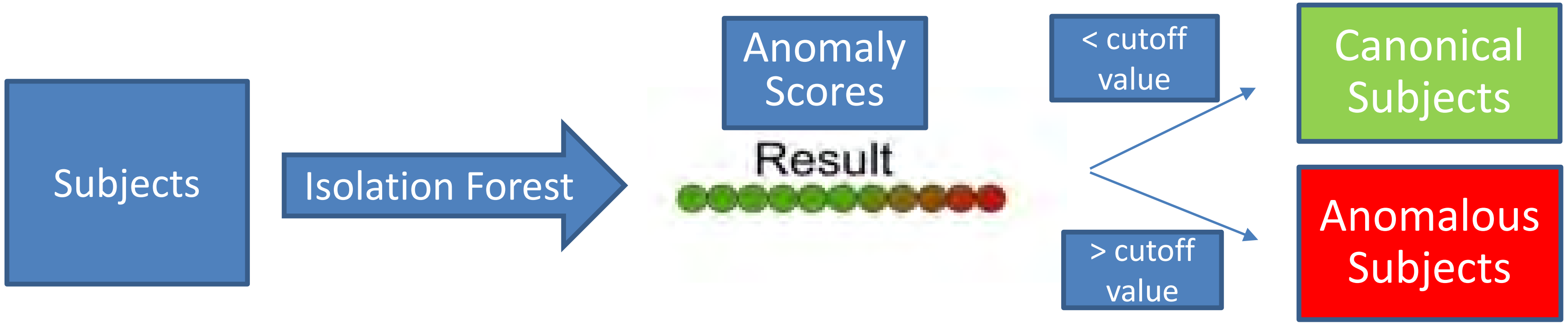
COU:

- Drug B failed to reach statistical significance in prespecified primary efficacy analysis for the phase 2 trial.
  - Unexpectedly large improvement in the primary efficacy endpoint from baseline for the placebo-treated cohort.
    - This primary efficacy endpoint was a composite endpoint with many items.
  - Motivation to explore ML method to identify patients with abnormal patterns.

- The sponsor is proposing an ML-based enrichment strategy for two planned Phase 3 studies
  - Decrease inter-subject variability prior to randomization:
    - Select canonical subjects whose symptoms are characterized by greater similarity to the typical patient in the target population.

Example 2: ML-based Enrichment Trial Design (continued)

- The dataset for ML development includes:
  - The phase II trial of Drug B
  - Multiple trials of Drug C for the same indication
- The anomaly score is calculated by applying a trained isolation forest model on the components of the efficacy endpoint at screening and baseline.
  - The anomaly score for a given subject indicates how easily this subject can be isolated from the rest of the subjects.



Slide courtesy: Ruihao Huang

Example 2: ML-based Enrichment Trial Design (continued)

- Encouraging trend was observed when ML-based inclusion criterion was applied retrospectively to the phase II data of drug B
  - Larger effect size

- In general, similar trends were observed when it was applied to trials of drug C

Example 2: ML-based Enrichment Trial Design (continued)

- FDA’s major comment to sponsor

  The sponsor proposed to use the ML-based inclusion criterion in two phase III adequate and well-controlled studies.

  FDA:

  Suggest using the ML-based inclusion criterion in only one of the two planned adequate and well-controlled studies.

  Due to the potential challenges related to the **explainability** of the model and the **generalizability** of the results, it would be helpful to include the “anomalous” patients in at least one of the adequate and well-controlled studies.

AI/ML Activities in Office of Clinical Pharmacology (OCP)/FDA

Innovative Data Analytics (IDA) Program

- EDUCATION
- RESEARCH
- COLLABORATION
- FELLOWSHIP

AI/MACHINE LEARNING

DIGITAL HEALTH TOOLS

REAL WORLD EVIDENCE

OTHER

For FDA Clinical Pharmacology Machine Learning Fellowship, check out
https://www.zintellect.com/

AI/ML Research in Office of Clinical Pharmacology

Landscape analyses

- Application of Machine Learning in Drug Development and Regulation: Current Status and Future Potential. (PMID: 31925955)

Methodology Exploration

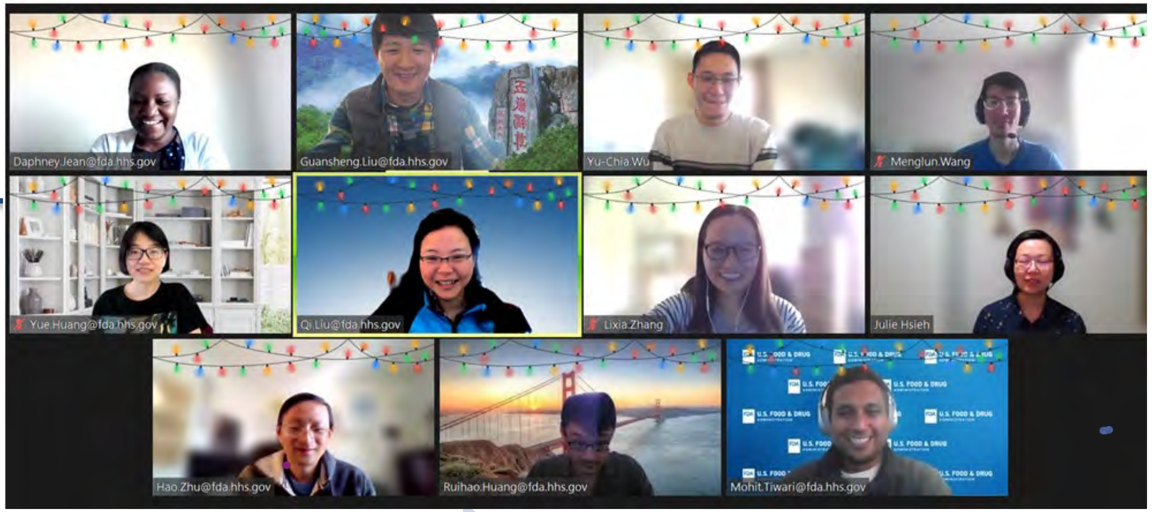
- Long short-term memory recurrent neural network for pharmacokinetic-pharmacodynamic modeling. (PMID: 33210994)
- A novel approach for personalized response model: deep learning with individual dropout feature ranking. (PMID: 33104924)
- Application of machine learning based methods in exposure-response analysis.. (PMID: 35275315)

Application for Therapeutic Optimization/Individuation

- Ongoing research: Use ML to predict the treatment outcome (both efficacy and toxicity)
- Medical Imaging data for precision medicine (in collaboration with CDRH, CBER and OCE)

- *Published*
- *Ongoing*

How Did We Make It Happen?



Grassroot Interest

Office Strategic Initiative

Business as Usual

Take-Home Messages

- AI/ML are playing an increasingly impactful role in drug development.
  - improve the efficiency of drug development
  - advance precision medicine
- Both opportunities and challenges lie ahead.
- More education, research, and collaboration are needed to move the filed forward.

Acknowledgement

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- Tala Fakhouri
- Scott Steele
- Steven Berman
- Matthew Diamond
- Shiew-Mei Huang
- Issam Zineh

Questions?

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