Artificial Intelligence/Machine Learning: The New Frontier of Drug Development & Regulation

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Why are we talking about AI/ML today?

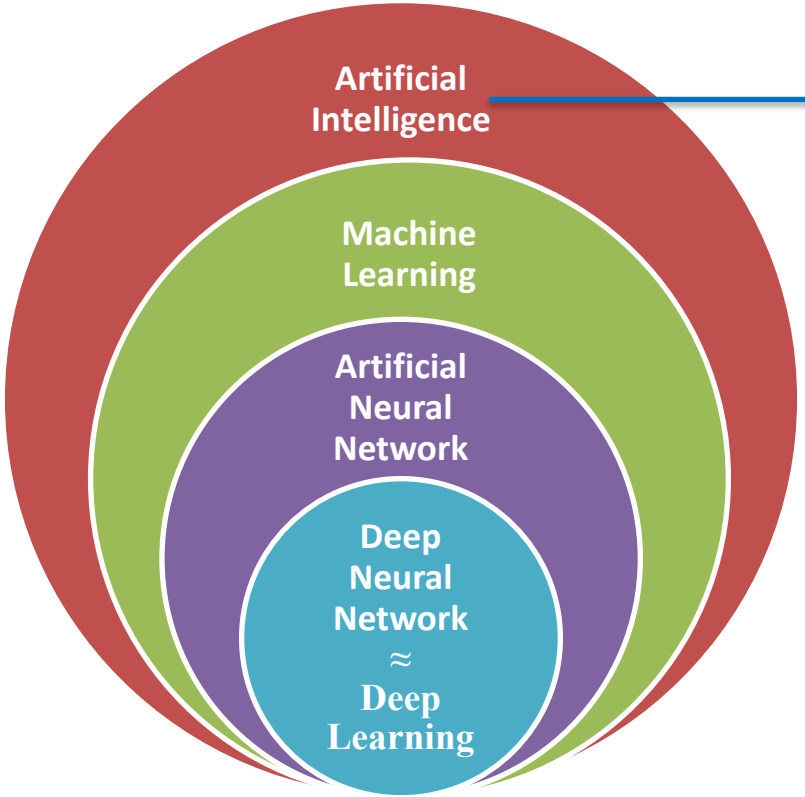
- Their application in drug development is expanding rapidly
- Powerful tools
  - — to improve the efficiency and probability of success of drug development
  - — To advance precision medicine
- Unique challenges

* Figure generated by Qi Liu using AI – Midjourney

Learning Objectives

- Introduction of background information of AI/ML
- Describe the landscape of AI/ML-related submissions/review at CDER
- List challenges related to the applications of AI/ML
- Discuss regulatory considerations (still evolving)
- List AI/ML related activities in the Office of Clinical Pharmacology

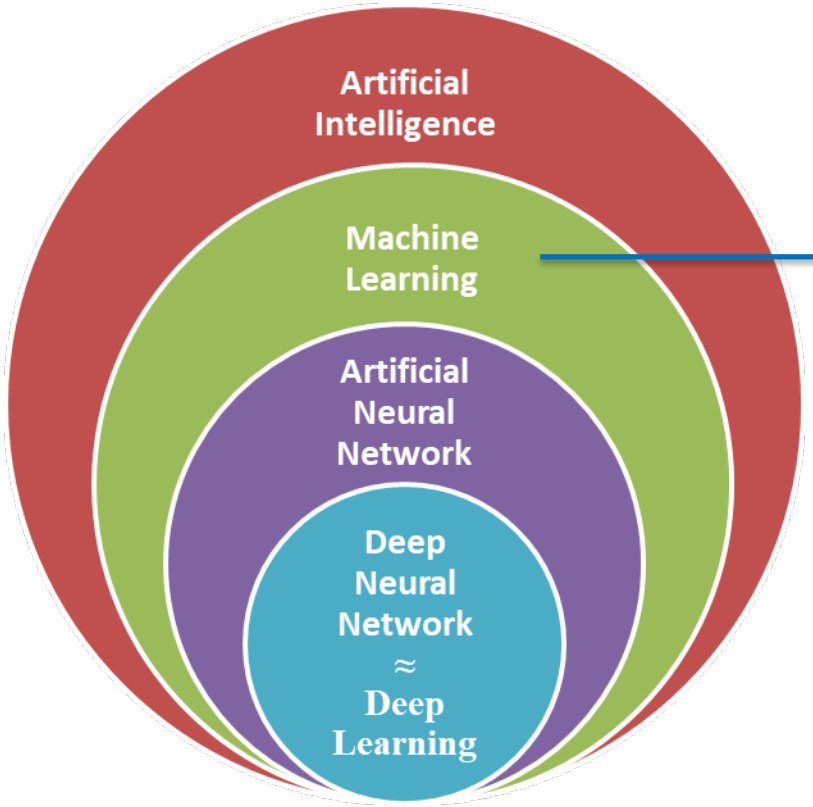
AI/ML and Related terminology



The science and engineering of making intelligent machines -John McCarthy

Artificial intelligence (AI) enables computer systems to perform tasks normally requiring human intelligence.
Artificial Intelligence (AI) | HHS.gov

Definition of Machine Learning (ML)

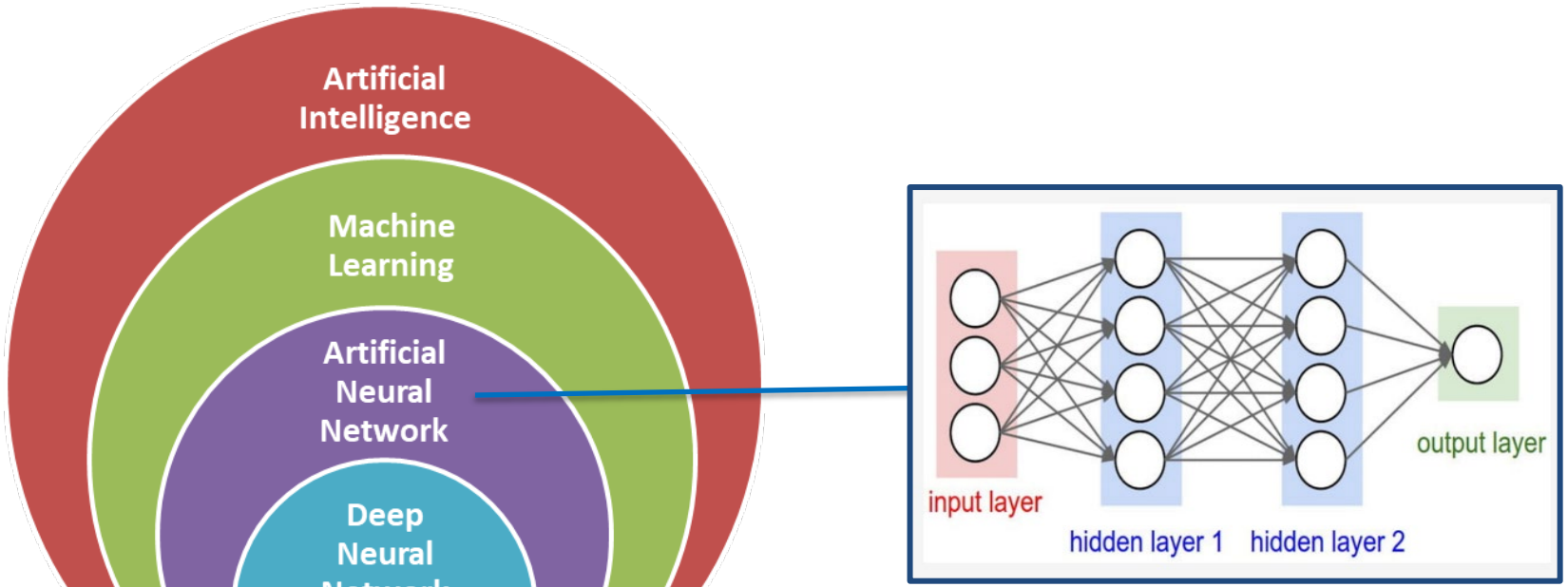


The field of study that gives computers the ability to learn without being explicitly programed - Arthur Samuel

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

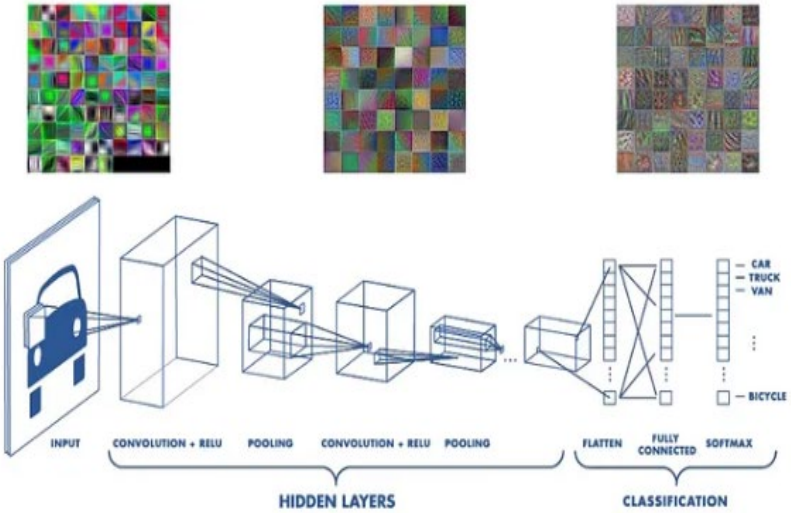
The algorithm's performance improves with accumulating data.
ML has a lot of overlap with statistical and pharmacometric modeling.

AI/ML and Related terminology



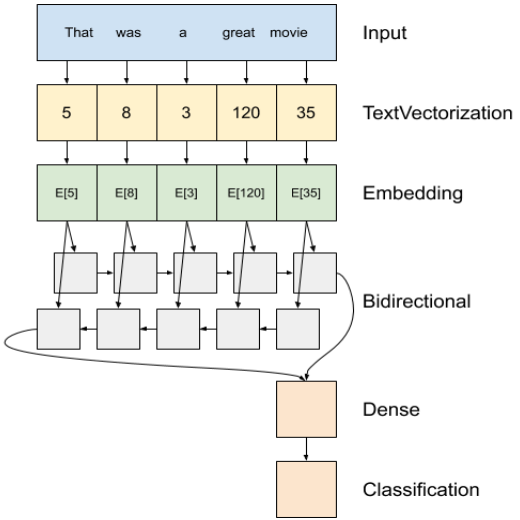
Important Types of Neural Networks

Convolutional Neural Network (CNN)



[Convolutional Neural Network (CNN) In Deep Learning | by Chetan Yeola | Python in Plain English]

Recurrent Neural Network (RNN)

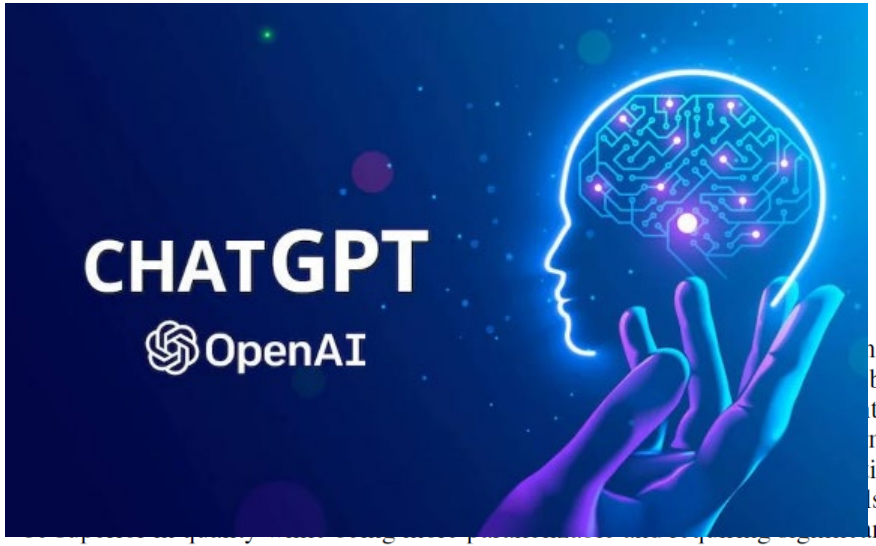


[Text classification with an RNN | TensorFlow]

Important Types of Neural Networks (Continued)

Transformer Neural Network

Attention Is All You Need



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less time to train. Our model achieves 28.4 BLEU on the WMT 2014 English-to-German translation task, improving over the existing best results, including ensembles, by over 2 BLEU. On the WMT 2014 English-to-French translation task, our model establishes a new single-model state-of-the-art BLEU score of 41.0 after training for 3.5 days on eight GPUs, a small fraction of the training costs of the best models from the literature.

31st Conference on Neural Information Processing Systems (NIPS 2017)

Opportunities for the Application of AI/ML in Drug discovery, Drug Development and Patient Care

Artificial Intelligence/Machine Learning: The New Frontier of Clinical Pharmacology and Precision Medicine by Qi Liu et al, accepted by CPT. (Disclosure: The artwork was generated using OpenAI's GPT4 model.)

Landscape Analysis for AI/ML Related Submissions at CDER/FDA

PERSPECTIVES

PERSPECTIVE

Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021

Qi Liu[1,†], Ruihao Huang[1,†], Julie Hsieh[1,†], Hao Zhu[1,*,†], Mo Tiwari[1], Guansheng Liu[1], Daphney Jean[1], M. Khair ElZarrad[2], Tala Fakhouri[2], Steven Berman[3], Billy Dunn[3], Matthew C. Diamond[4] and Shiew-Mei Huang[1]

An analysis of regulatory submissions of drug and biological products to the US Food and Drug Administration from 2016 to 2021 demonstrated an increasing number of submissions that included artificial intelligence/machine learning (AI/ML). AI/ML was used to perform a variety of tasks, such as informing drug discovery/repurposing, enhancing clinical trial design elements, dose optimization, enhancing adherence to drug regimen, endpoint/biomarker assessment, and postmarketing surveillance. AI/ML is being increasingly explored to facilitate drug development.

BACKGROUND

Over the past decade, there has been a rapid expansion of artificial intelligence/machine learning (AI/ML) applications in biomedical research and therapeutic development. In 2019, Liu *et al.* provided an overview of how AI/ML was used to support drug development and regulatory submissions to the US Food and Drug Administration (FDA). The authors envisioned that AI/ML would play an increasingly important role in drug development.[1] That prediction has now been confirmed by this landscape analysis based on drug and biologic regulatory submissions to the FDA from 2016 to 2021.

THE TREND OF INCREASING AI/ML–RELATED SUBMISSIONS AT THE FDA'S CENTER FOR DRUG EVALUATION AND RESEARCH

This analysis was performed by searching for submissions with key terms "machine learning" or "artificial intelligence" in Center for Drug Evaluation and Research (CDER) internal databases for Investigational New Drug applications, New Drug Applications, Abbreviated New Drug Applications, and Biologic License Applications, as well as submissions for Critical Path Innovation Meeting and the Drug Development Tools Program. We evaluated all data from 2016 to 2021. Figure 1a demonstrates that submissions with AI/ML components have increased rapidly in the past few years. In 2016 and 2017, we identified only one such submission each year. From 2017 to 2020, the numbers of submissions increased by approximately twofold to threefold yearly. Then in 2021, the number of submissions increased sharply to 132 (approximately 10-fold as compared with that in 2020). This trend of increasing submissions with AI/ML components is consistent with our expectation based on the observed increasing collaborations between the pharmaceutical and technology industries.

Figure 1b illustrates the distributions of these submissions by therapeutic area. Oncology, psychiatry, gastroenterology, and neurology were

[1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [2]Office of Medical Policy, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [3]Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [4]Digital Health Center of Excellence, Center for Devices and Radiological Health (CDRH), US Food and Drug Administration, Silver Spring, Maryland, USA.
*Correspondence: Hao Zhu (hao.zhu@fda.hhs.gov)
†These authors contributed equally.

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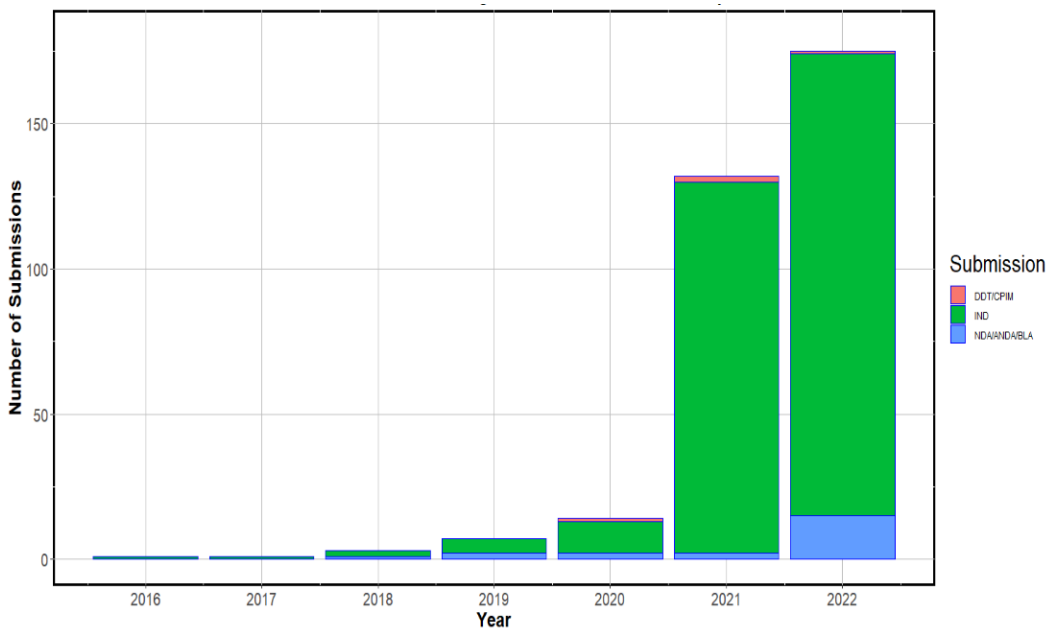
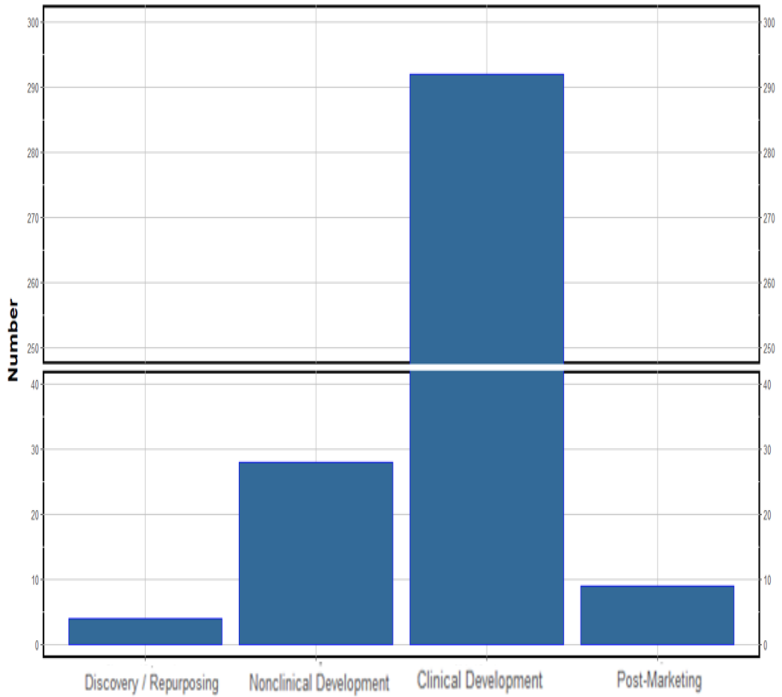
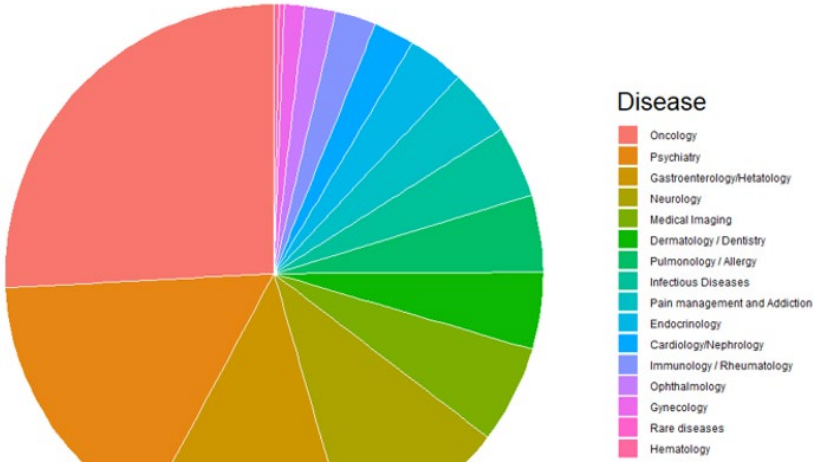
Update the analysis by including the submissions in year 2022



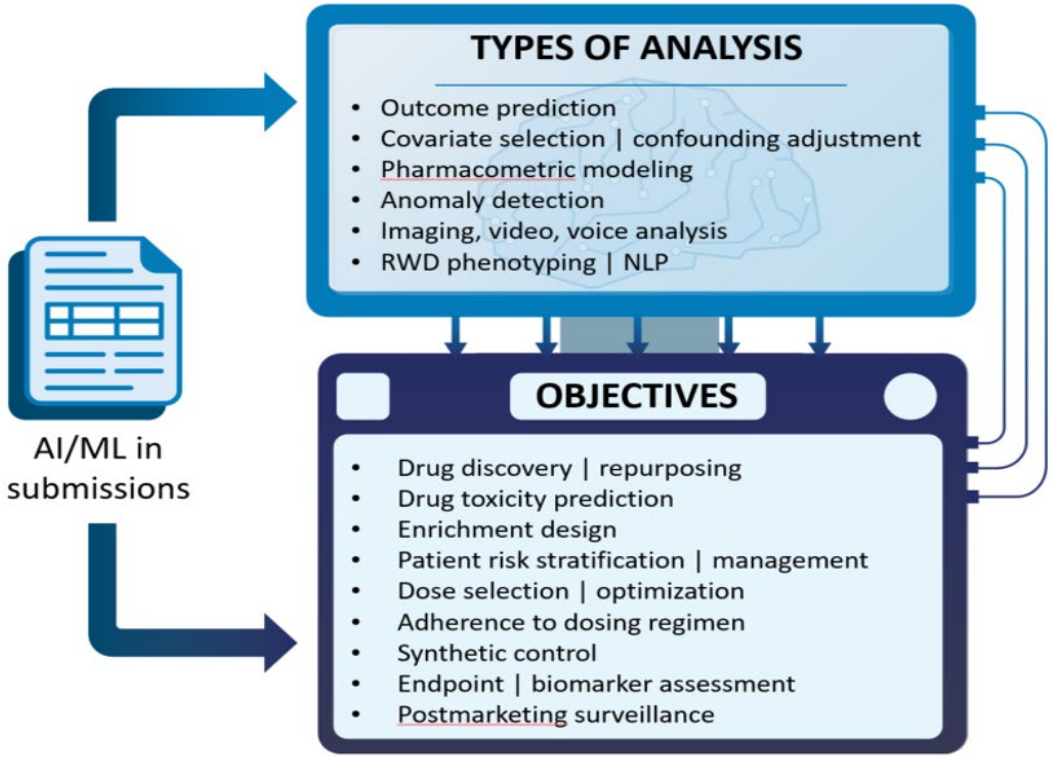
AI/ML Submissions by Development Stage and Therapeutic Area





2016 - 2022

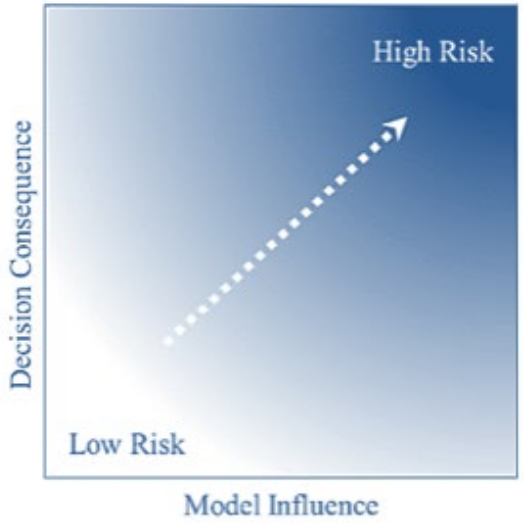
Types of AI/ML Related Analyses & Objectives



(PMID: 35707940)

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 model selection/development
- **Risk-based** credibility assessment
- Transparency/interpretability/explainability
- We need to develop best practice for AI/machine learning



Review 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.

  Initially the sponsor was not clear on some components of COU (e.g., in clinical trials only or in both trials and real-world application?). 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.

Review Example 2: 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: 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 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 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) and sensitivity, will be the major performance metrics to determine the acceptance of the model from a regulatory perspective.

Review Example 2: AI-generated digital twins and Prognostic Covariate Adjustment

- **Background:** A generative deep learning based prognostic model has been developed to produce digital twins, which are probabilistic representations of potential placebo outcomes for a specific clinical trial participant, given his/her baseline characteristics.

- **Context of Use:** Use AI-generated digital twins and covariate adjustment procedure to reduce variance of treatment effect estimate for drug B and enable reduction in placebo sample size in the Phase 2 and 3 randomized controlled clinical trials with continuous endpoints.

Figure generated by Qi Liu using AI – DALL·E 3

Review Example 2: AI-generated digital twins and Prognostic Covariate Adjustment (Continued)

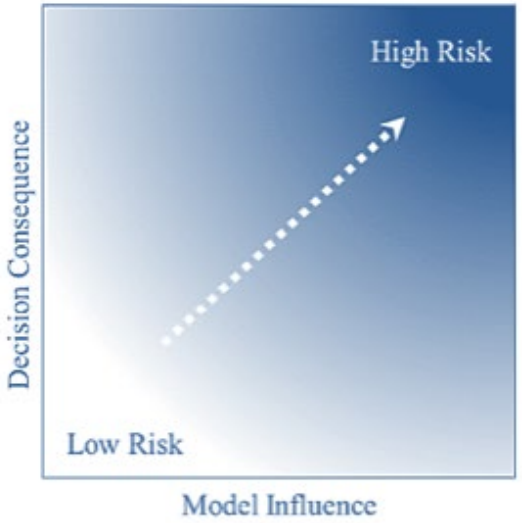
FDA's model risk analysis:

- **Model influence: High.** The AI model prediction will be the sole factor to determine the patient prognostic score based on baseline variables.

- **Decision Consequence: Low (for both Phase 2 & 3).** Covariate adjustment possesses several desirable statistical properties (minimal impact on bias or the Type I error rate when used in RCTs).

  FDA guidance document*: "Covariate adjustment can still be performed with covariates that are not prognostic, but there may not be any gain in precision (or may be a loss in precision) compared with an unadjusted analysis."

  *https://www.fda.gov/media/148910/download



Review Example 2: AI-generated digital twins and Prognostic Covariate Adjustment (Continued)

Summary of FDA's Feedback/Questions to the Sponsor:

- No objection if it is implemented in the phase 2 trial as an exploratory analysis.
- Its use as the primary analysis in the phase 3 trial may be acceptable. Provide details for the phase 3 trials including data analysis plan etc.
- Is the training dataset for the prognostic model representative of the population the sponsor plans to enroll?
- Since generative AI will be used for prognostic score generation, ensure the same patient retains the same value if the process is repeated multiple times.
- Suggestion of using explainable AI techniques to identify key contributing features for the prognostic score.

Review Example 3: ML-based Patient Population Selection

Using Machine Learning to Determine a Suitable Patient Population for Anakinra for the Treatment of COVID-19 Under the Emergency Use Authorization

Qi Liu[1,†], Raj Nair[2,*,†], Ruihao Huang[1,†], Hao Zhu[1,†], Austin Anderson[2], Ozlem Belen[2], Van Tran[3], Rebecca Chiu[3], Karen Higgins[3], Jianmeng Chen[1], Lei He[1], Suresh Doddapaneni[1], Shiew-Mei Huang[1], Nikolay P. Nikolov[2] and Issam Zineh[1]

Liu et al. CPT doi:10.1002/cpt.3191

Anakinra EUA review https://www.fda.gov/media/163546/download

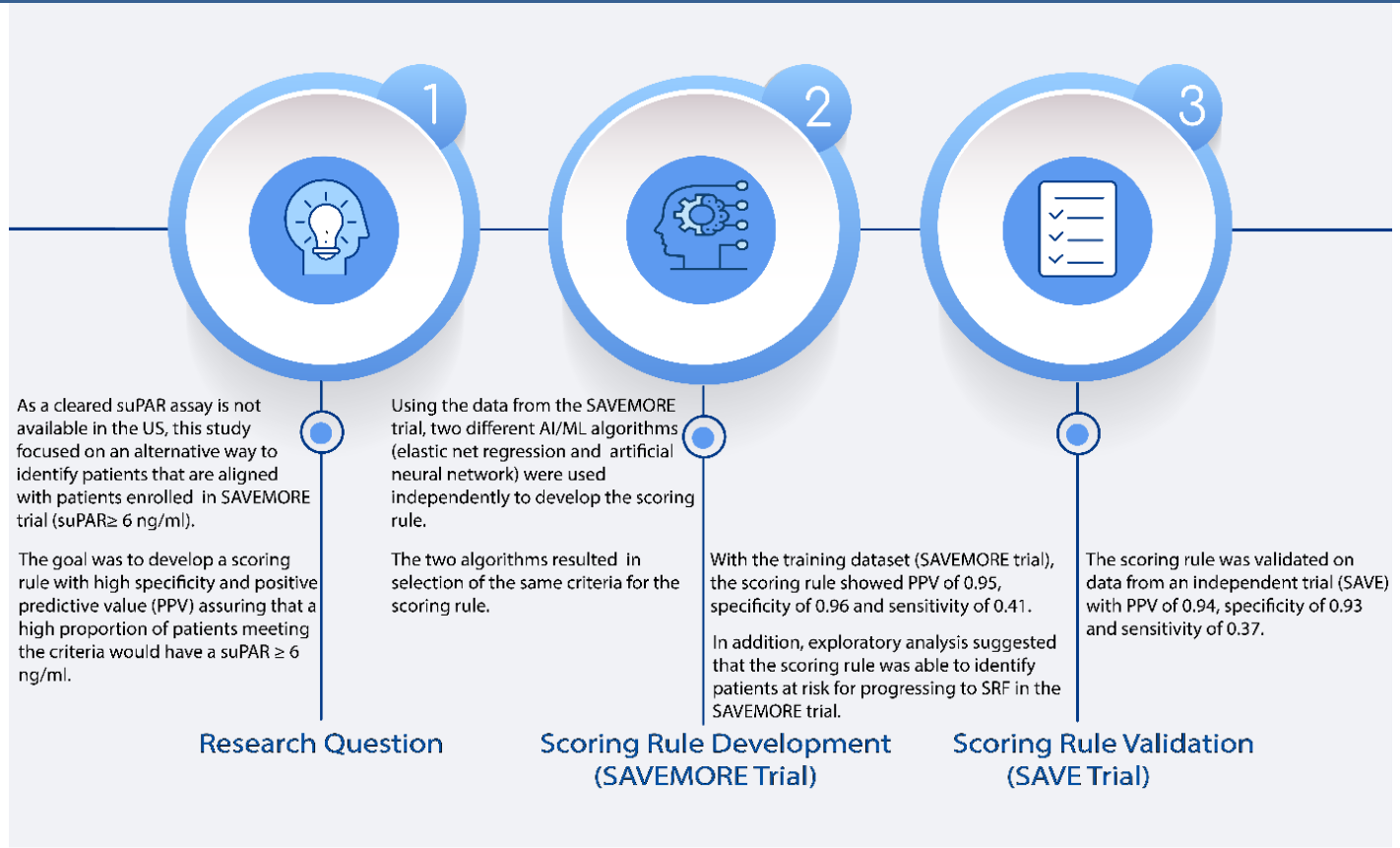
Regulatory Challenge

Patients in the Phase 3 trial (SAVE-MORE) were selected based on a biomarker cut-off, suPAR ≥ 6 ng/mL, intending to enrich the trial with patients at risk for progression to severe respiratory failure

SuPAR test is not commercially available in the United States at this time

Section 1.1 Fact Sheet of Kineret ®

Using ML to address the challenge: Is there an alternative way to identify patients that are aligned with patients enrolled in SAVE-MORE trial (suPAR-high)?



Liu et al.
CPT
doi:10.1002/cpt.3191

Selected Score (3 out of 8)
SOFA* score ≥ 3
Smoking history (active or past)
Blood hemoglobin ≤ 10.5 g/dL
Medical history of ischemic stroke
Severe disease by WHO criteria
Age ≥ 75 years
Blood Urea ≥ 50 mg/dL and/or Medical history of chronic Renal disease
Neutrophil-to-lymphocyte ratio (NLR) >=7

* SOFA: Sequential Organ Failure Assessment

Anakinra EUA Fact Sheet ***

1.1 Patient Population Identification

KINERET is authorized for emergency use for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma suPAR.

In the SAVE-MORE trial used to support the efficacy and safety of KINERET in COVID-19, key exclusion criteria were: pO2/FiO2 ratio < 150 mmHg, requirement for non-invasive ventilation (NIV), requirement for mechanical ventilation (MV), requirement for extra-corporeal membrane oxygenation (ECMO), and < 1500 neutrophils/mm^3.

All enrolled patients were required to have a plasma soluble urokinase plasminogen activator receptor (suPAR) level ≥ 6 ng/mL *[see Clinical Studies (14.1)]*. The suPAR assay is not commercially available in the United States. In order to identify a comparable population as was studied in the SAVE-MORE trial, an alternative patient identification method was developed to select patients most likely to have suPAR ≥ 6 ng/mL based on commonly measured patient characteristics. Patients meeting at least three of the following eight criteria are considered likely to have suPAR ≥ 6 ng/mL at baseline:

***: US Fact Sheet of Kineret ® <<Drugs@FDA: FDA-Approved Drugs

Challenges in the Application of AI/ML

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

Disparity/Fairness

Trustworthiness issues

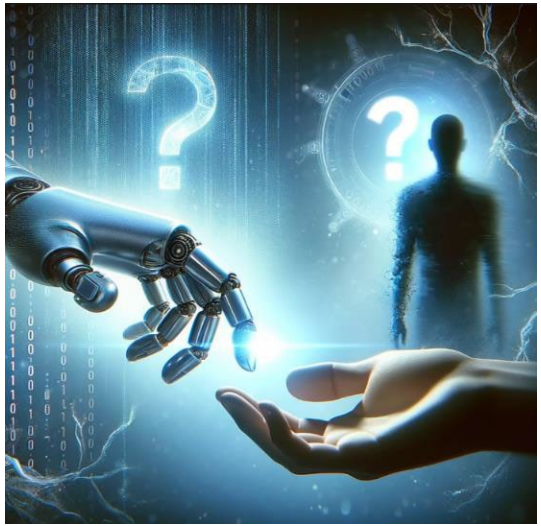


Figure generated by Qi using AI – DALL·E 3

FDA AI Discussion Paper

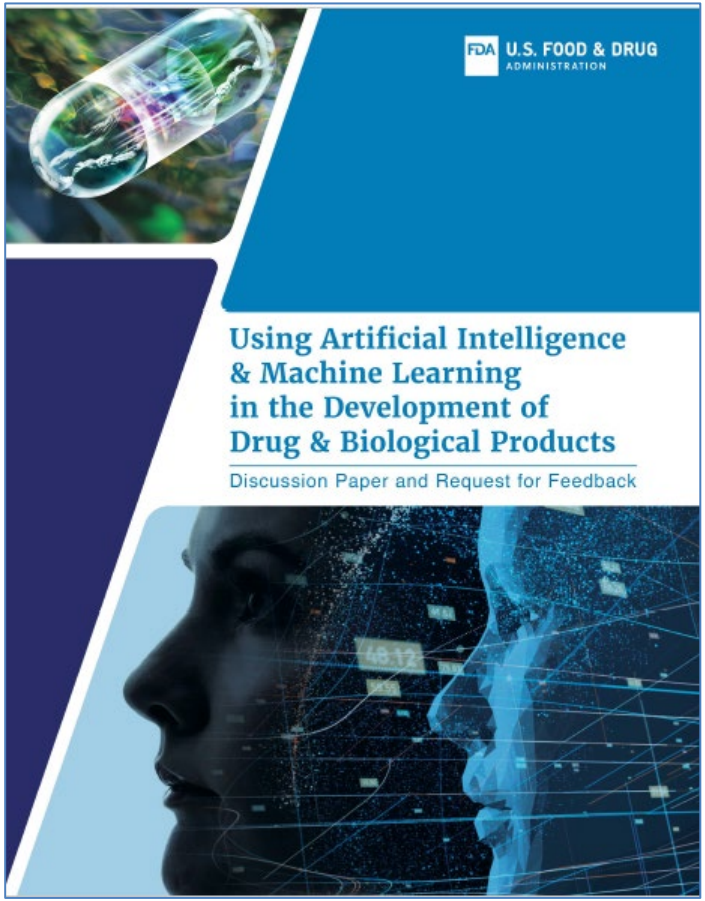


Table of Contents

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 OCP

Landscape analyses

- Application of Machine Learning in Drug Development and Regulation: Current Status and Future Potential. (PMID: 31925955)
- Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021. (PMID: 35707940)

Methodology Exploration

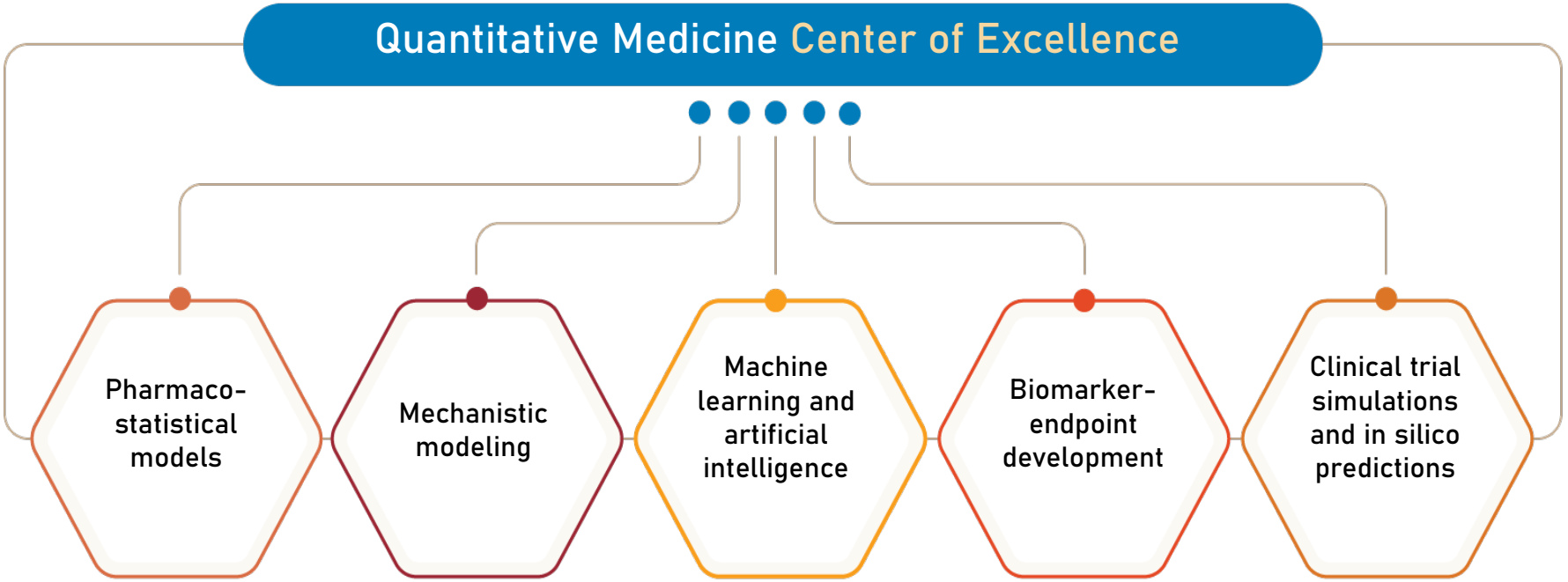
- Long short-term memory recurrent neural network for pharmacokinetic-pharmacodynamic modeling. (PMID: 33210994)
- A novel approach for personalized response model: deep learning with individual dropout feature ranking. (PMID: 33104924)
- Application of machine learning based methods in exposure-response analysis. (PMID: 35275315)
- Measurement and Mitigation of Bias in Artificial Intelligence (doi.org/10.1002/cpt.3117)
- Methods for preventing prediction for out-of-scope data
- Interpretable/Explainable ML
- Large Language Model for document editing

Application for Therapeutic Optimization/Individuation

- Ongoing research: Use ML to predict prognosis or treatment outcome (both efficacy and toxicity)
- Multi-omics data for precision medicine (PMID: 37965805)

● *Published*
●*Ongoing*

CDER QM CoE Scope



Take-Home Messages

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

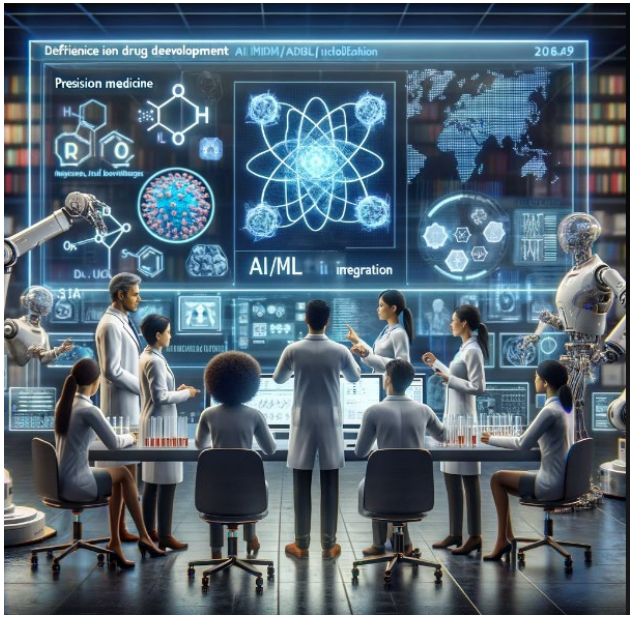


Figure generated by Qi Liu using AI – DALL·E 3

Challenge Question #1

How can artificial intelligence enhance drug development?

A. by improving the probability of success of drug development

B. by improving the efficiency of drug

C. by advancing precision medicine to tailor treatments to individuals

D. All the above

Challenge Question #2

True or False:

Machine learning is considered a subset of AI.

Acknowledgement

- Ruihao Huang
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