U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

The Application of Artificial Intelligence/Machine Learning in Drug Development and Regulation

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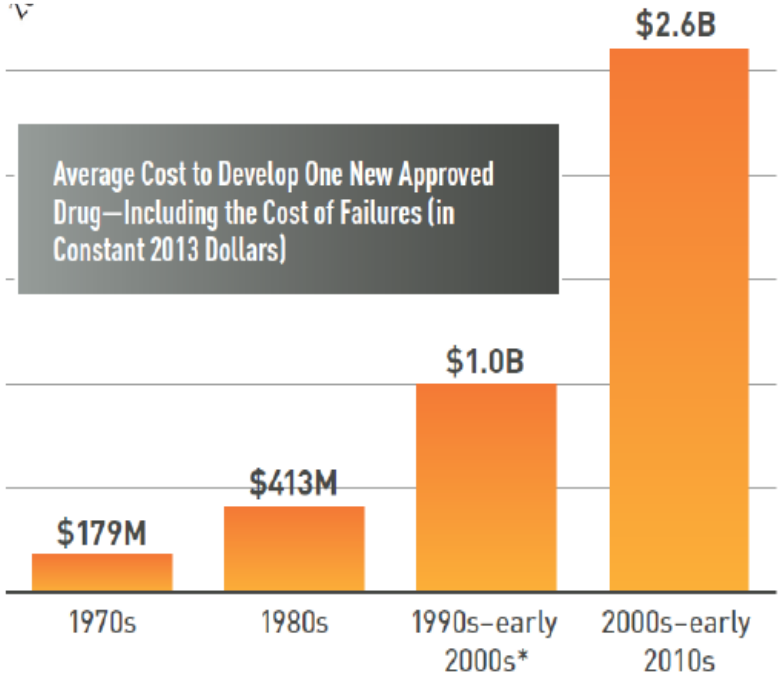
Disclaimer: This presentation reflects the views of the presenter and should not be construed to represent those of the FDA or the United States Government.

Outline

- Introduction
  - Landscape Analysis for AI/ML Related Submissions at the FDA
  - Considerations for AI/ML in Regulatory Decision Making
  - Risk-based Credibility Assessment Framework

- Case Examples
  - ML-based Enrichment Trial Design

Why are we talking about AI/ML today?



Tufts Center for the Study of Drug Development (CSDD) (2014).

Challenges in new drug development:

- **Decreasing productivity**
- **Increasing development cost**
- **High late phase attrition**

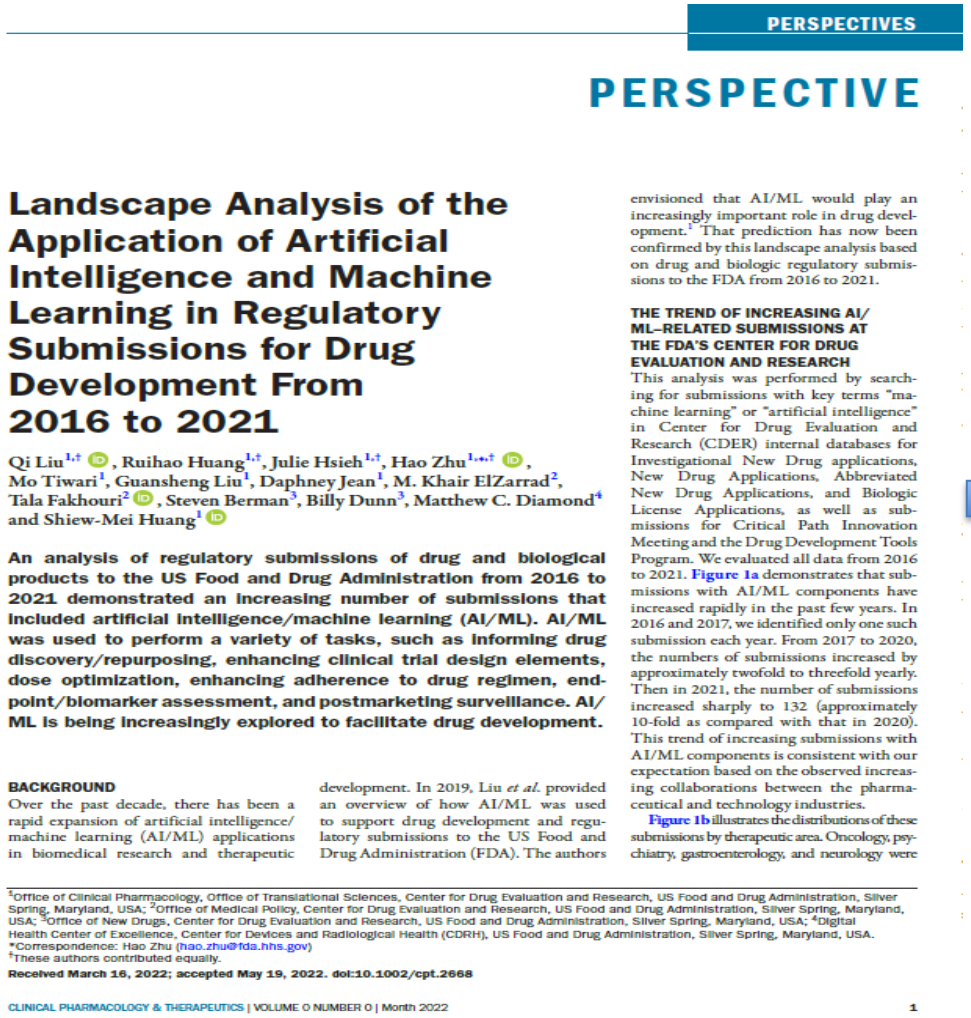
- The application of AI/ML in drug development is expanding rapidly.
- AI/ML have the potential to improve the efficiency of drug development and advance precision medicine, but they also have unique challenges.

FDA Experience with AI/ML for Drug Development

FDA recognizes the increased use of AI/ML throughout the drug development life cycle and its potential to accelerate the development of safe and effective drugs. AI/ML is increasingly integrated in areas where FDA is actively engaged, including clinical trial design, DHTs, and RWD analytics. Over the last few years, FDA has seen a rapid growth in the number of submissions that reference AI/ML. Submissions across drug and biological product applications that include AI/ML have increased over the last few years to more than 100 submissions in 2021 (Q. Liu et al., 2022). These submissions cut across a range of therapeutic areas, and the uses of AI/ML within the submissions cover the many different areas of the drug development process highlighted in this section, from drug discovery and clinical trial enrichment to endpoint assessment and postmarket safety surveillance. Inclusion of AI/ML in the clinical development/research phase represents the most common stage for AI/ML uses in submissions.

FDA Discussion paper: Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products (2025)

Landscape Analysis for AI/ML Related Submissions



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

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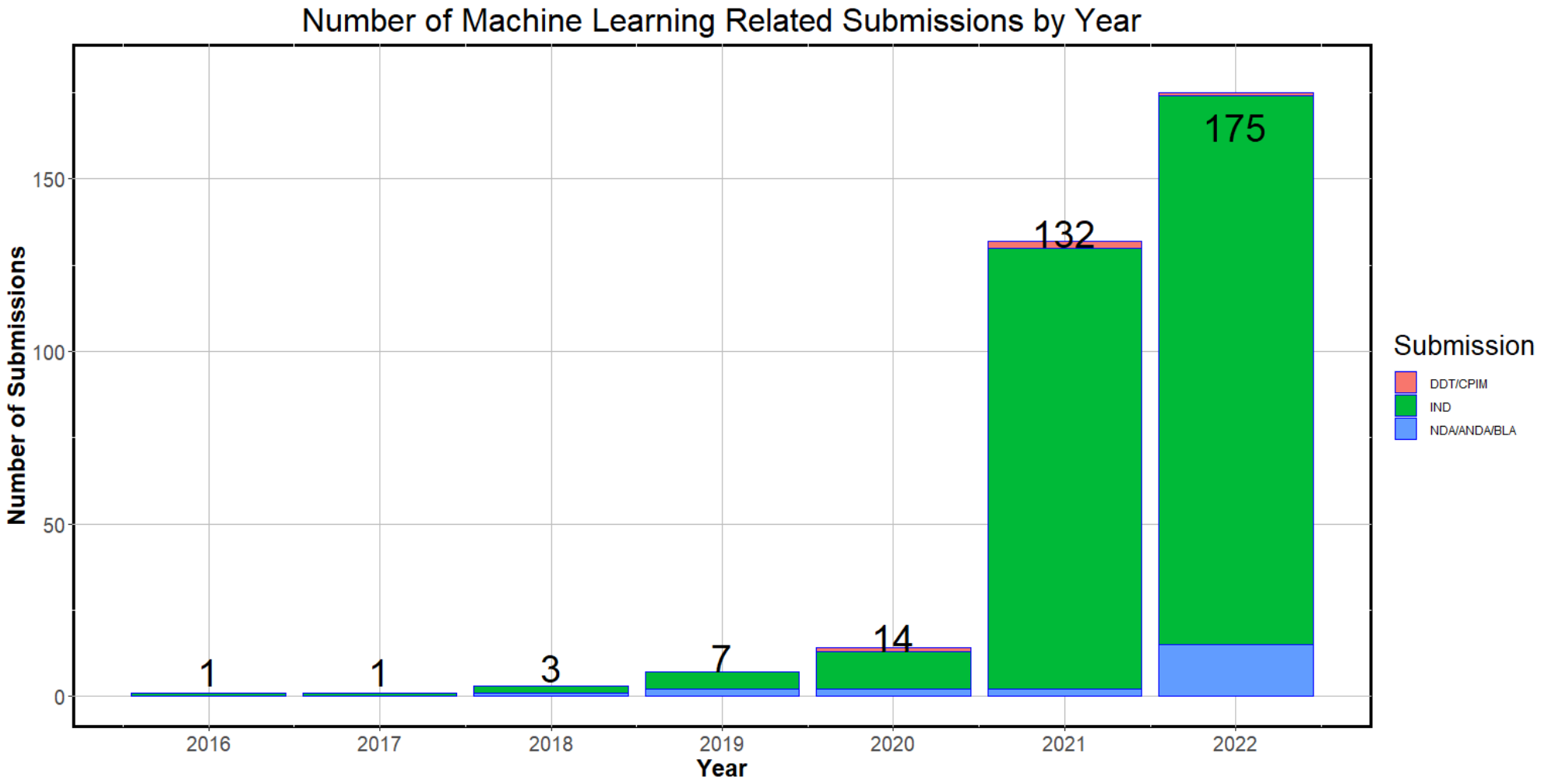
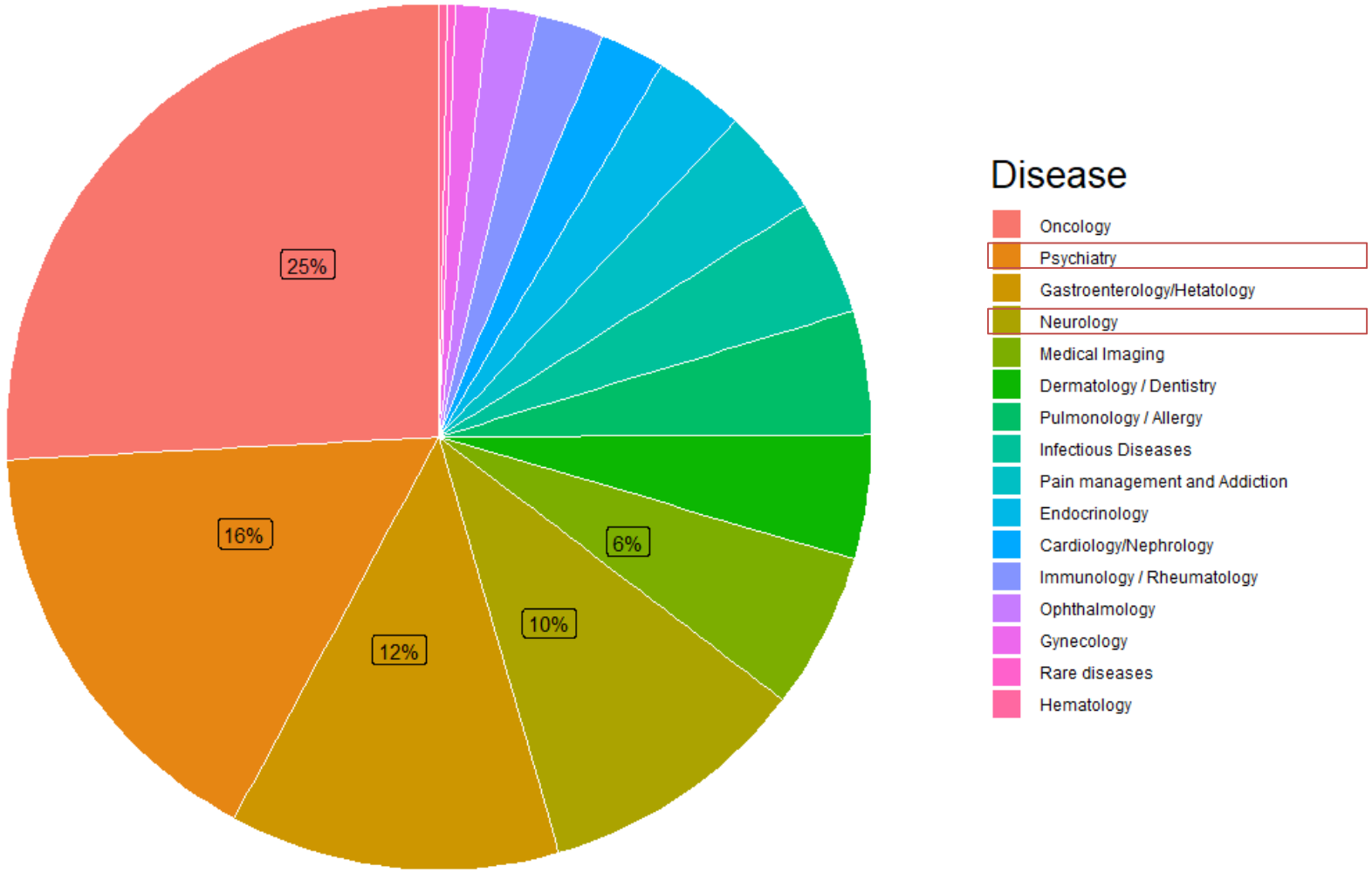
- Update the analysis by including the submissions in year 2022
- Summarize the submissions by submission type (IND, NDA/BLA etc), development stage, and disease areas over the year from 2016 to 2022

AI/ML Submissions over Time



2016 - 2022

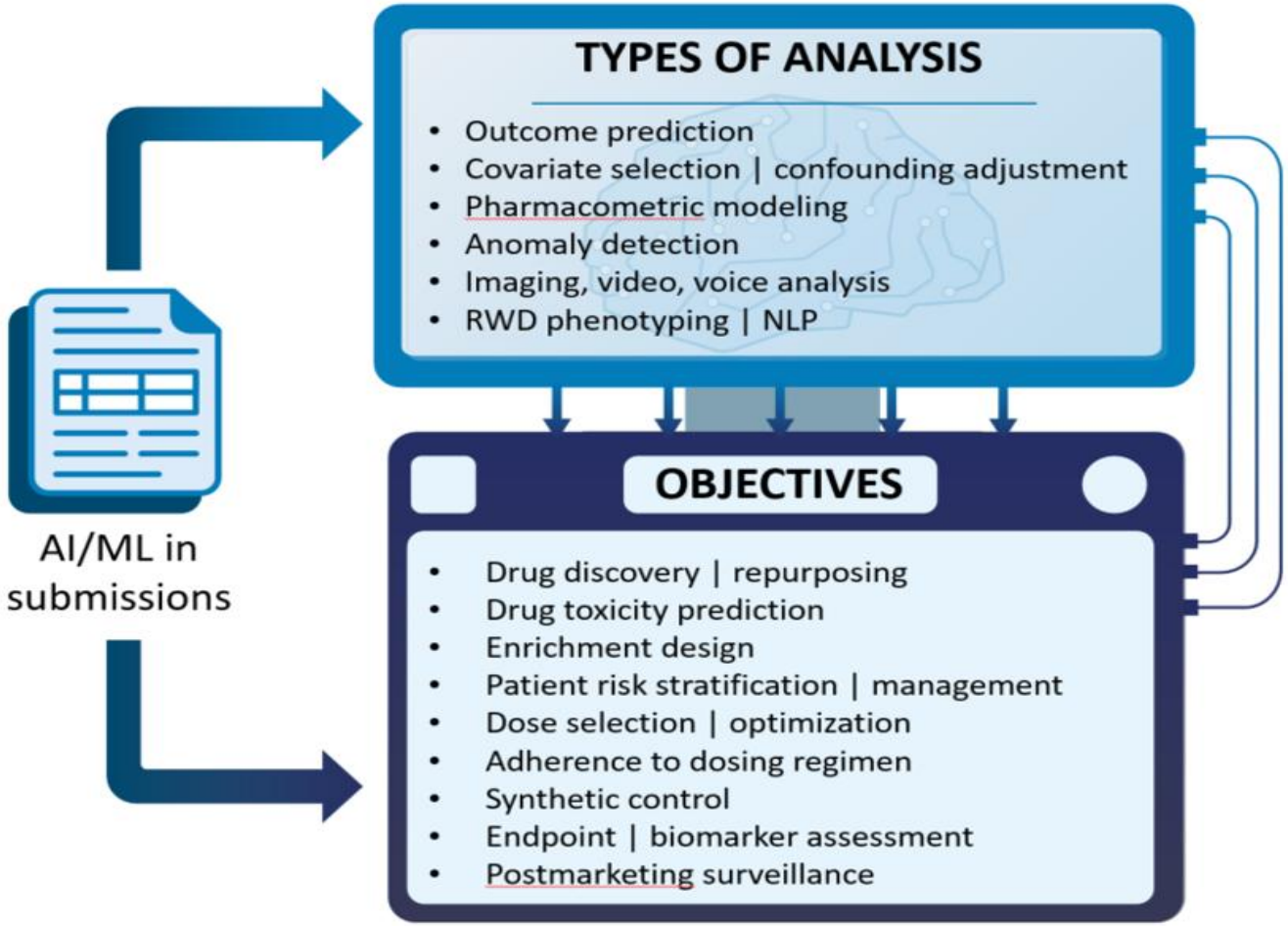
AI/ML Submissions by Therapeutic Areas



2016 - 2022

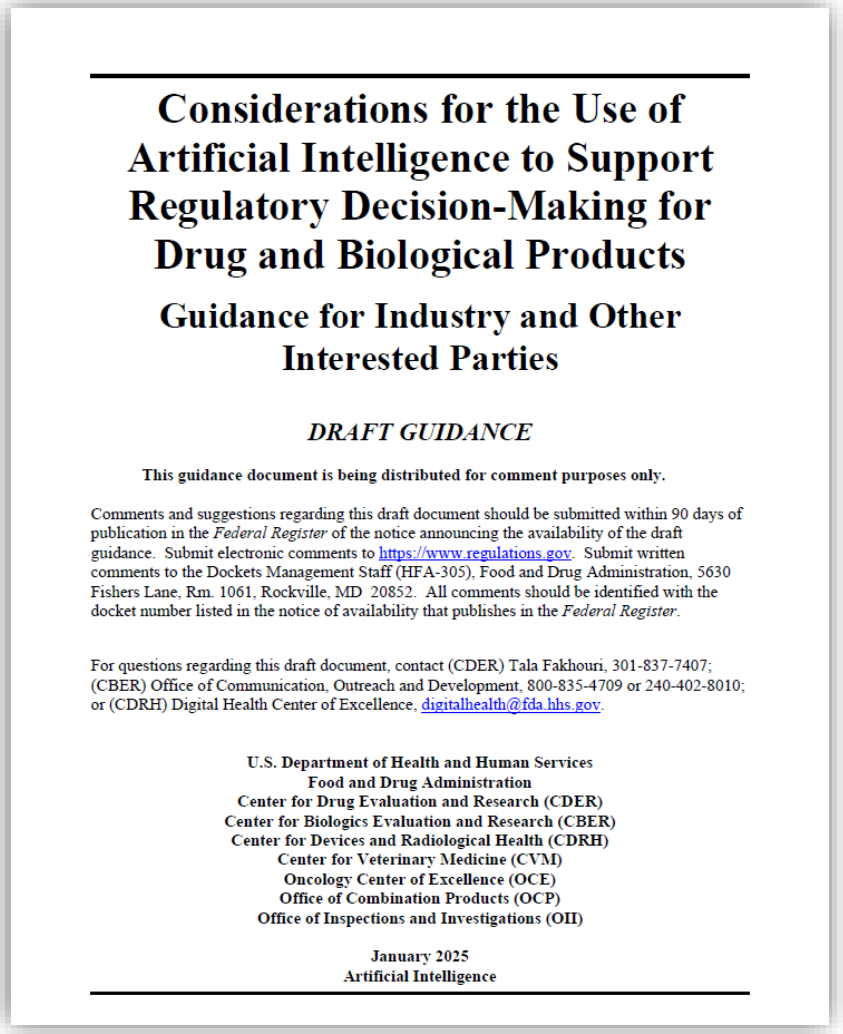
Types of AI/ML Related Analyses & Objectives

- A wide range of AI/ML algorithms
  - Neural network, LASSO, Elastic network, XGBoost, Random forest



Considerations for AI Use in Regulatory Decision Making

- Draft Guidance published in Jan 2025
- AI used to produce data or information to support regulatory decision making
- Informed by:
  - FDA's experience with reviewing over 300 submissions with AI
  - Over 800 comments received on the 2023 and 2024 discussion papers
  - Current regulatory science research
- Provides a risk-based framework for establishing and evaluating the credibility of AI use in regulatory decision making
- Help ensure that AI models used to answer regulatory questions are credible for a particular context of use and are supported with the appropriate level of evidence



Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry and Other Interested Parties

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Digital Health Center of Excellence, digitalhealth@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
Oncology Center of Excellence (OCE)
Office of Combination Products (OCP)
Office of Inspections and Investigations (OII)

January 2025
Artificial Intelligence

Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-artificial-intelligence-support-regulatory-decision-making-drug-and-biological

Considerations for AI Use in Regulatory Decision Making

- **Step 1:** State the question of interest that will be informed addressed by the AI model
- **Step 2:** Define the context of use for the AI model
- **Step 3:** Assess the AI model risk
  - Model influence:
    - The contribution of the evidence derived from the AI model relative to other contributing evidence used to inform the question of interest
  - Decision Consequence:
    - Describes the significance of an adverse outcome resulting from an incorrect decision concerning the question of interest
- **Step 4:** Develop a plan to establish AI model credibility within the context of use
- **Step 5:** Execute the plan
- **Step 6:** Document the results of the credibility assessment and discuss deviations from the plan
- **Step 7:** Determine the adequacy of the credibility assessment

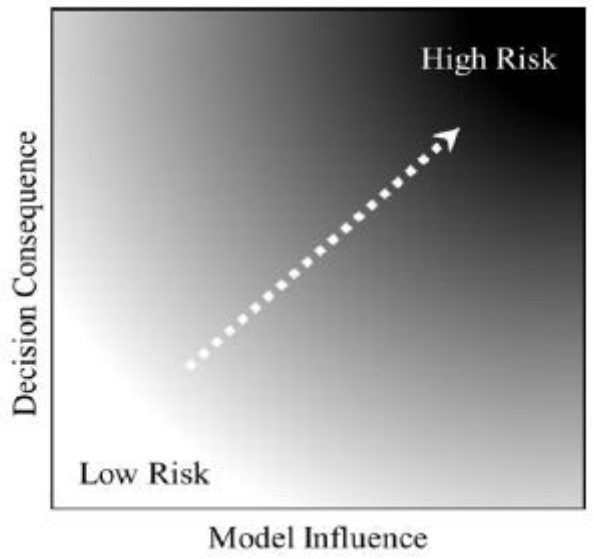


Figure 1. Model risk matrix. The model risk moves from low to high as decision consequence or model influence increases. The ratings for decision consequence and model influence are independently determined.

The credibility assessment activities used to establish the credibility of AI model outputs should be commensurate with the AI model risk.

Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-artificial-intelligence-support-regulatory-decision-making-drug-and-biological

Determine the adequacy of the credibility assessment

- If either the sponsor or FDA determine that *model credibility is not sufficiently established for the model risk*, several outcomes are possible:
  - The sponsor *may downgrade the model influence by incorporating additional types of evidence* in conjunction with the evidence from the AI model to answer the question of interest;
  - The sponsor *may increase the rigor of the credibility assessment activities* or augment the model's output by adding additional development data;
  - The sponsor *may establish appropriate controls to mitigate risk*;
  - The sponsor may consider the credibility of the AI model's output inadequate for the COU; therefore, *the model's COU would be rejected or revised in an iterative fashion*.

Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-artificial-intelligence-support-regulatory-decision-making-drug-and-biological

Example: ML-based Enrichment Trial Design

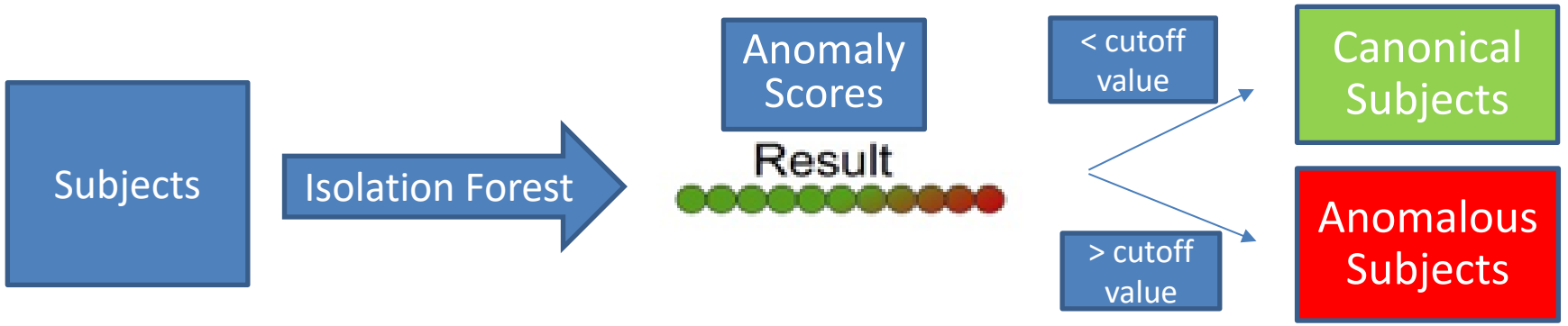
COU:

- Drug X 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 2 trial of Drug X
  - 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.



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

- Encouraging trend was observed when ML-based inclusion criterion was applied retrospectively to the phase 2 data of Drug X
  - 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.

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Thank You!