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

Development of Biomarkers to Assist New Drug Development for CNS Disorders

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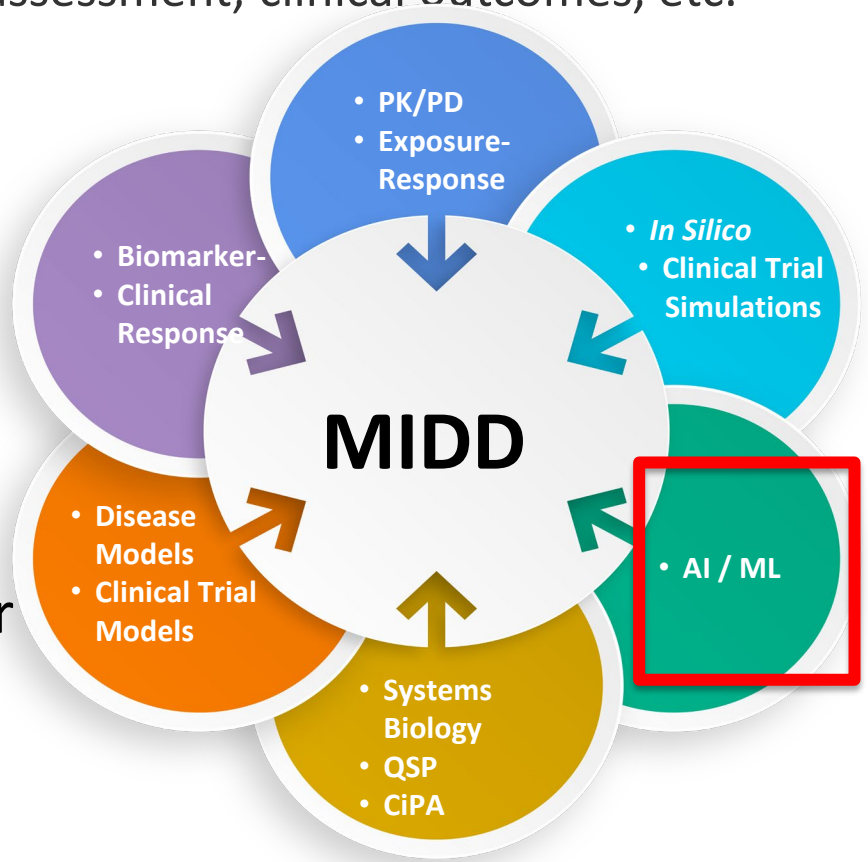
Outline

- Introduction
  - Biomarkers in new drug development
  - Biomarkers for new drug development in patients with CNS disorder
- Case Examples
  - Review example
  - Research example
- General Considerations
- Take Home Messages

Biomarkers in New Drug Development

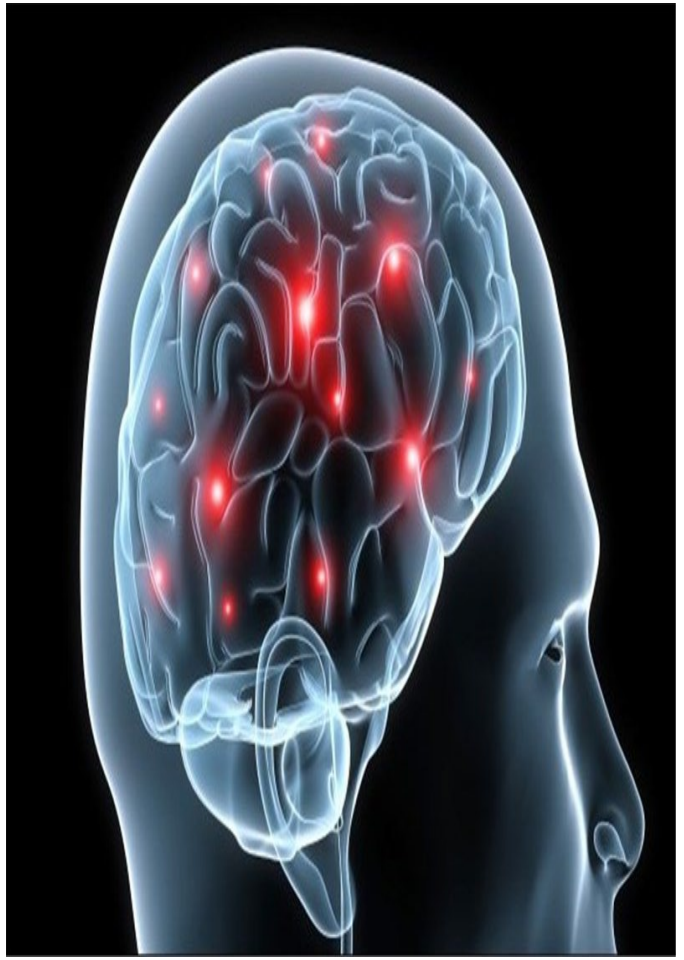
- Biomarkers are a key medical product development tool capable of facilitating development of medical products and spurring innovation.
  - Lab values, medical imagines, pharmacodynamic assessment, clinical outcomes, etc.
- Examples of usage in drug development:
  - Patient enrichment:
  - Patient selection:
  - Bridging biomarkers:
  - Surrogate endpoint:
    - Reasonably likely surrogate endpoint
    - Validated surrogate endpoint
- Quantitative/data science tools for biomarker selection



Source: Biomarkers at FDA | FDA

Biomarkers for Drug Development in Patients with CNS Disorder

- Various biomarkers are evaluated in drug development programs for patients with CNS disorders.
- Most biomarkers have been used to inform target engagement, upstream/downstream changes, proof of efficacy, dose selection, and patient selection.
- Limited examples for CNS biomarkers being considered as surrogate endpoints that can be used to support accelerated approval/approval.
- Given the complexity of CNS disorders, use of multimodal biomarkers may provide better assistance for future new drug development.



Review Example: Drug B

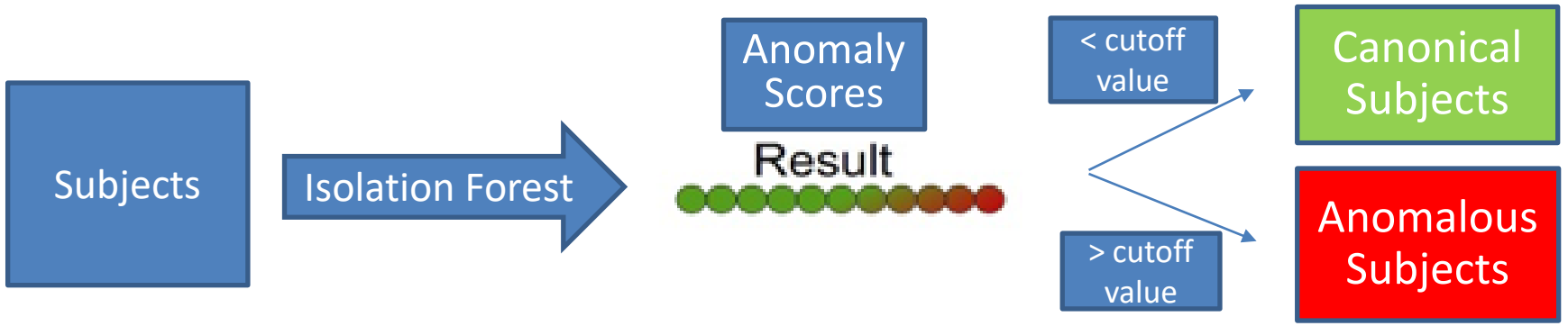
Context of Use:

- Drug B failed to reach statistical significance in prespecified primary efficacy analysis for the Phase 2 trial in patients with bipolar depression.
  - 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.

Review Example: Drug B (continued)

- The dataset for machine learning (ML) development includes:
  - The Phase 2 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.
  - Patient characteristics include
  - 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

Review Example: Drug B (continued)

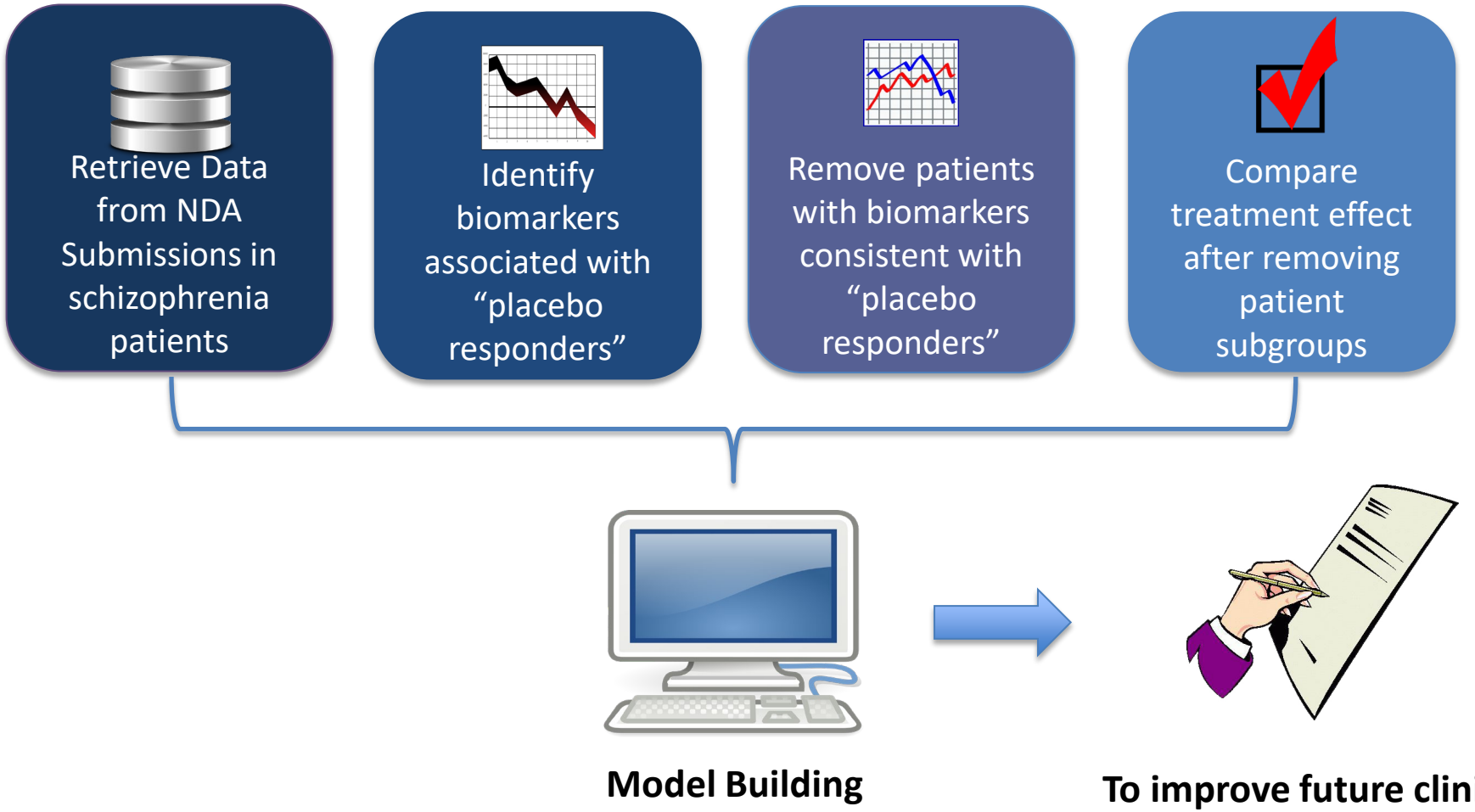
- Encouraging trend was observed when ML-based inclusion criterion was applied retrospectively to the phase II data of drug B
  - Larger effect size
- In general, similar trends were observed when it was applied to trials of drug C
- Conclusion:

  FDA:

  Suggest using the selected 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.

Research Example: Enrichment Strategy

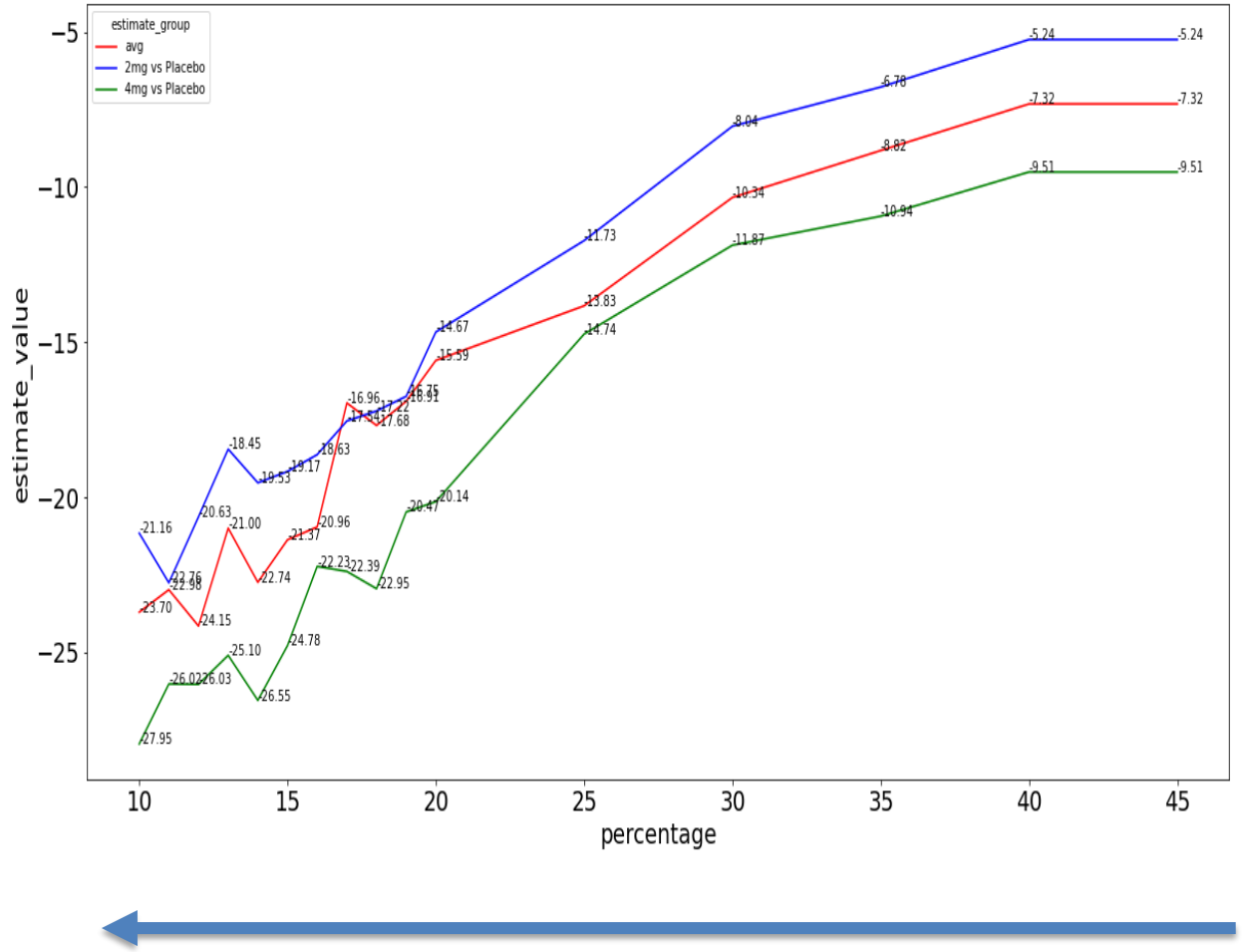


Placebo responder: patients receiving placebo showing improvement in clinical symptoms at different defined range (% improvement)

Research Example: Improved treatment effect

Treatment Effect:

Lower is better



This trend appears to be consistent for all pivotal clinical trials (Phase 3 trials) from NDAs in schizophrenia patients.

Defined Threshold for "Responders"

General Considerations (Personal Opinion, Still Evolving)

- Data Source:
  - Meta analysis: (e.g., endpoints, lab values, patients, biomarker measurement, clinical outcome assessment, standard of care, etc)
  - Data standard (e.g., variables, format, etc), data transformation, handling of missing data and outliers…
- Model Development:
  - model or covariate (patient feature) selection
  - Model validation
  - Assumption check
- Model Interpretation:
  - Generalizability (critical for AI/ML Models)
    - Training data should be unbiased and diverse/inclusive
    - Methods need to be developed for performance guarantee
  - Transparency/interpretability/explainability (Important for empirical models)
    - Methods are being developed to improve interpretability/explainability

- We need to develop best practice

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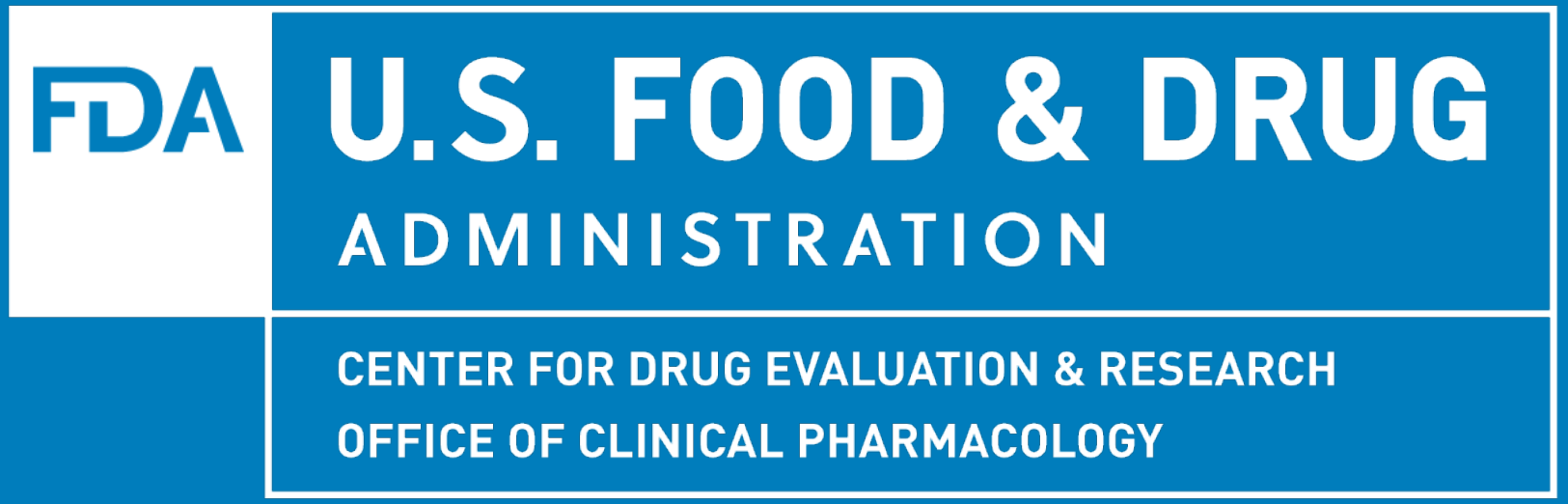

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