QUANTITATIVE MEDICINE

TRANSFORMING DRUG DISCOVERY

Technology Evaluation Consortium
Cambridge Healthtech Associates

September 6, 2013

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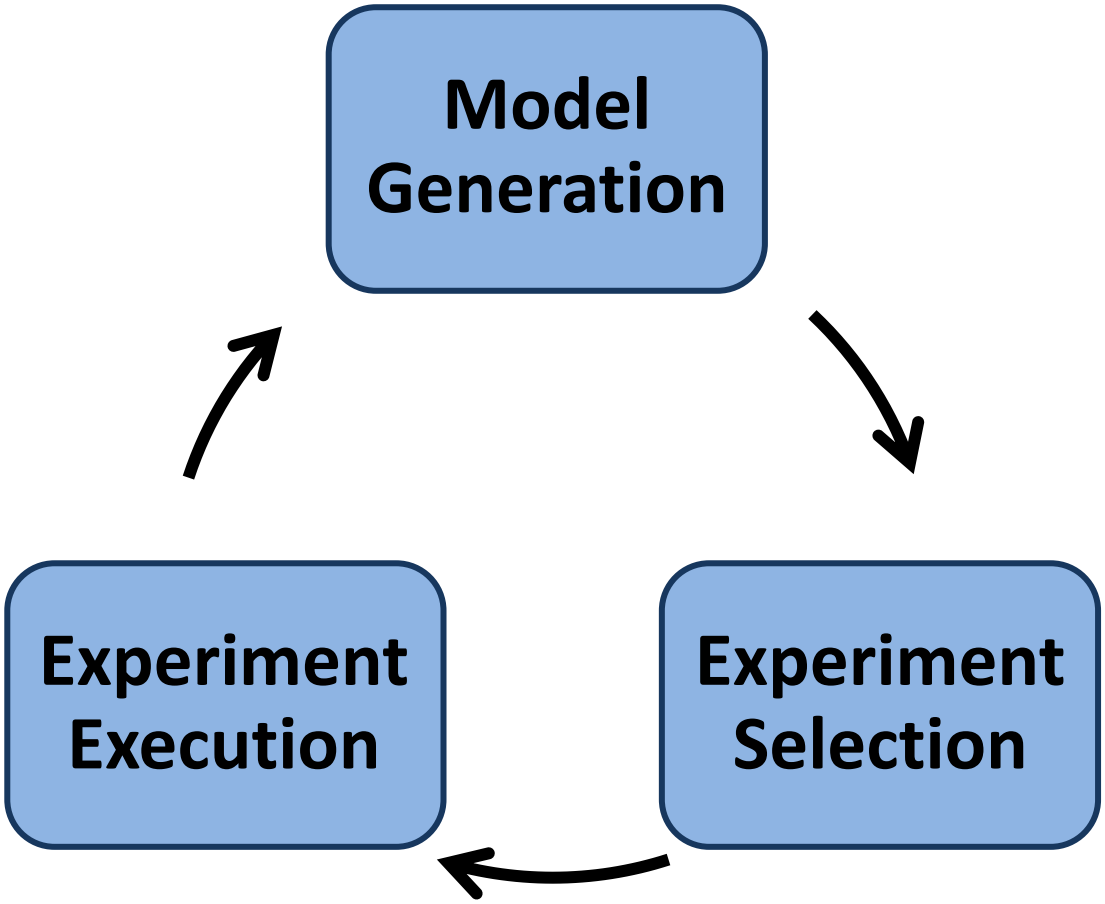
Agenda

- ToxCast Study Design
- Proposed Studies
- Next Steps

Active Learning



Potential ToxCast Studies

AFRS Directed Study Types

Retrospective

- Experiment Direction Simulated
- Show *potential* for improved **accuracy** and **efficiency**
- May discover new useful knowledge through AFRS analytics

Prospective

- Experiments Directed as Selected
- Yield *actual* improvements in accuracy and efficiency
- Likely to discover new useful knowledge through directed experimentation ***and*** AFRS analytics

Study Guidelines

- Define Relevant Use Case
- Map Use Case to ToxCast dataset
  - One ToxCast measurement -> one Toxicology Assay
- Hide ToxCast data
- Run simulations with different experiment direction methods as if ToxCast experiments were being executed as directed rather than looking at the whole dataset at once
- Measure success after each batch

ToxCast Study 1

Purpose: Develop a Model to Actively Learn and Accurately Predict All Observations in ToxCast

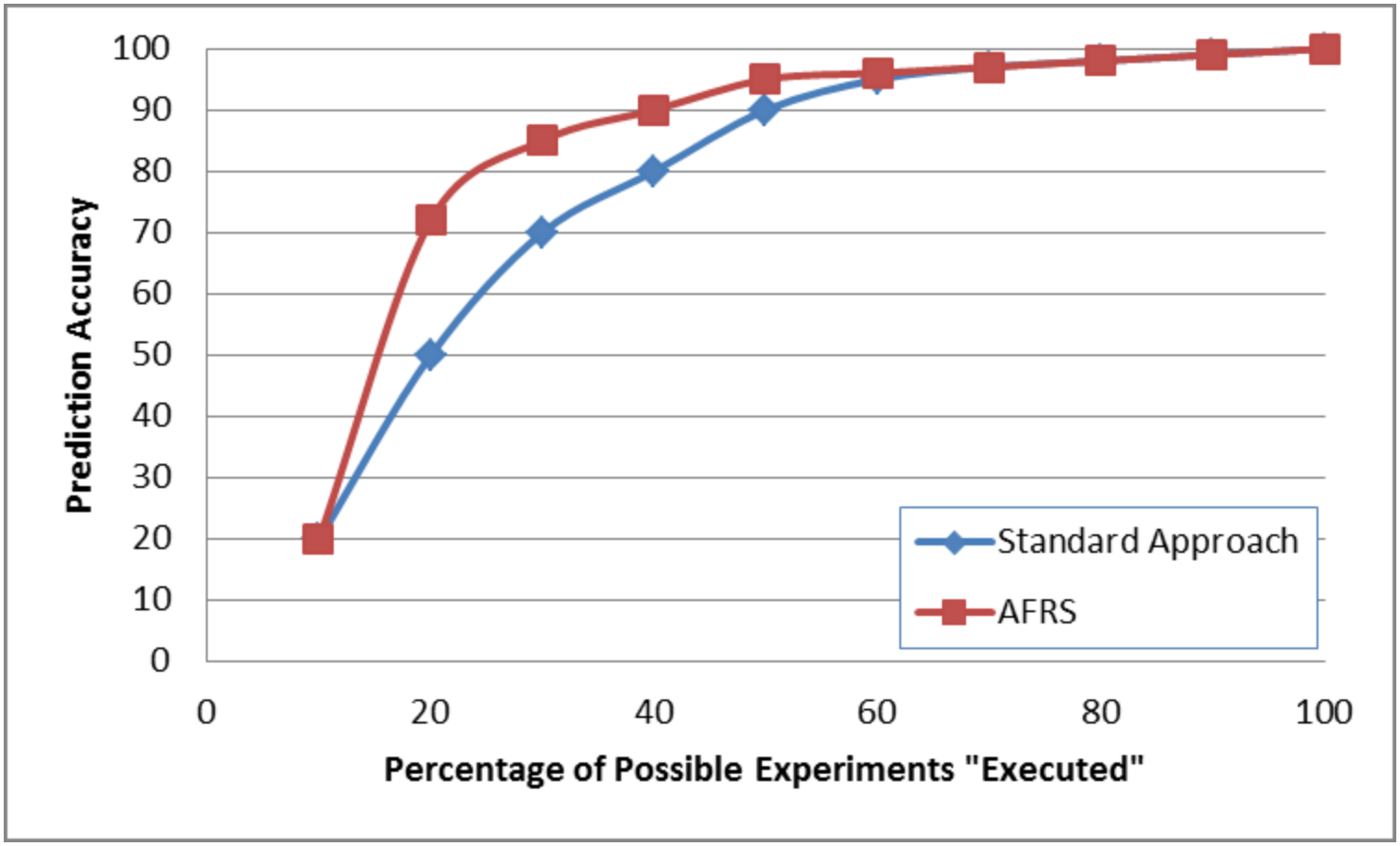
Standard Approach: Choose a single batch of compounds believed to represent sufficient structural diversity. Execute those experiments. Learn a QSAR model for each assay. Use that model to make predictions for untested experiments.

ToxCast Study 1

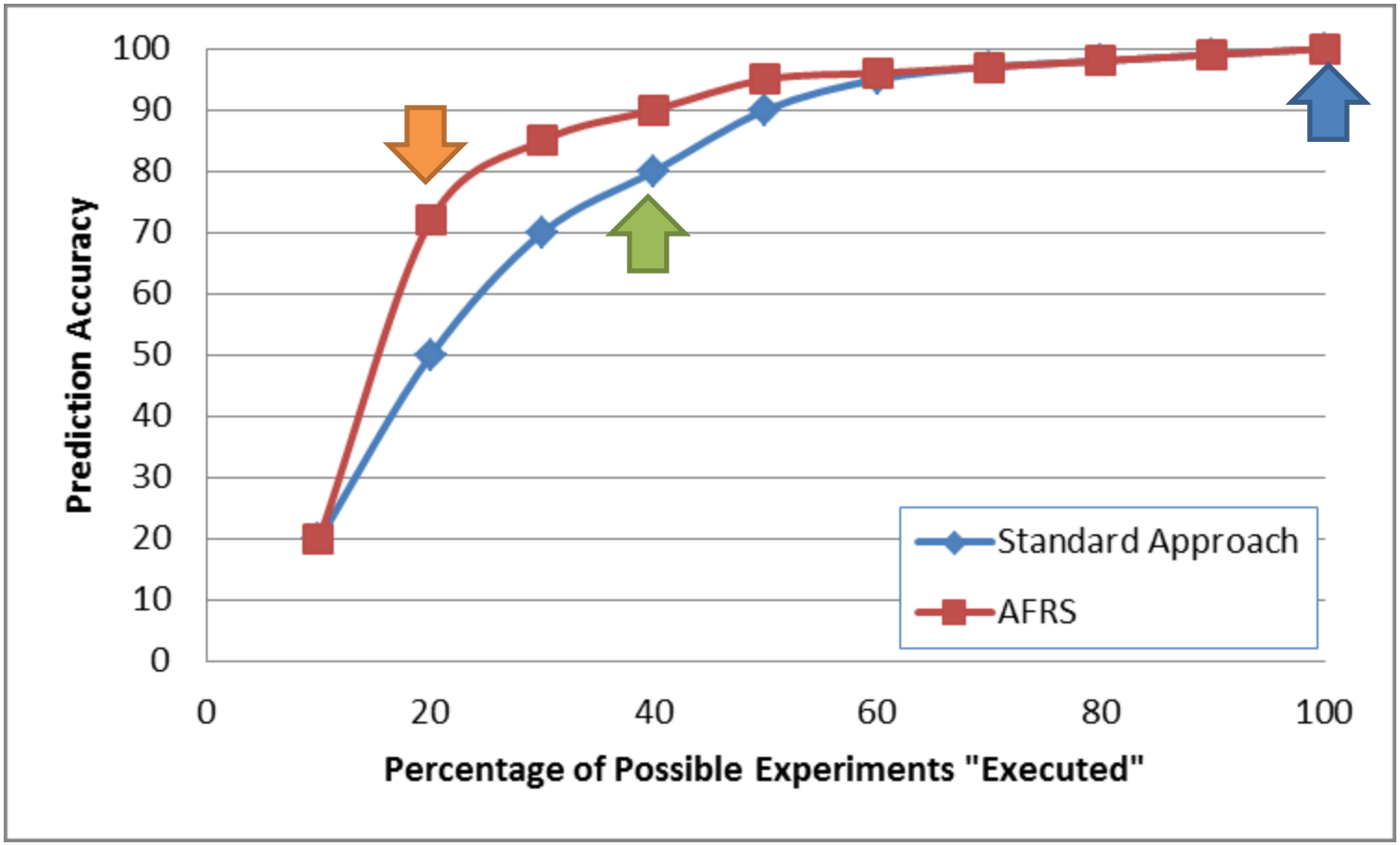
Purpose: Develop a Model to Actively Learn and Accurately Predict All Observations in ToxCast

AFRS Approach: Choose batches of experiments believed to be the most informative. “Execute” those experiments. Learn a model using the AFRS for to predict the results of all untested experiments.

ToxCast Study 1



ToxCast Study 1



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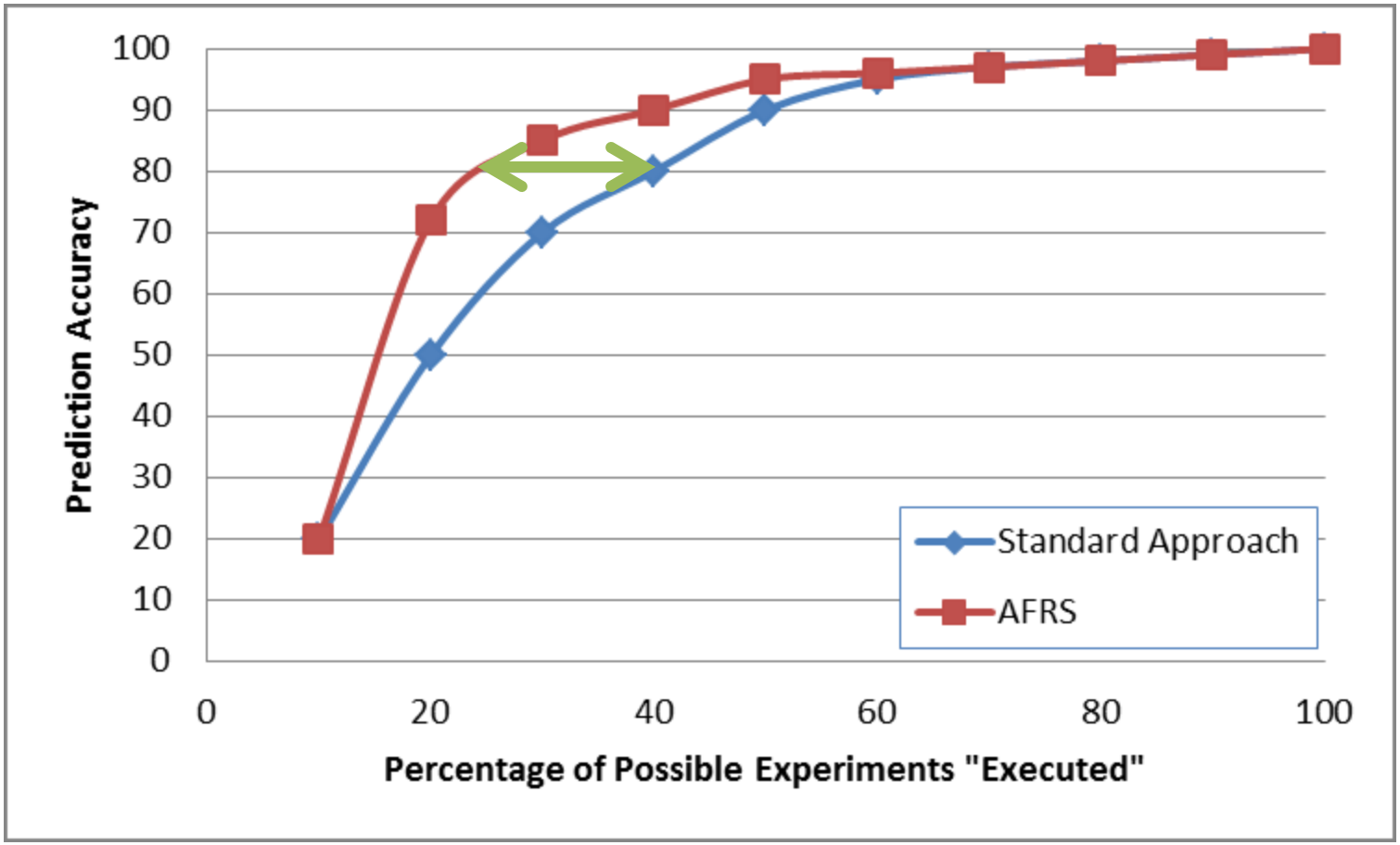

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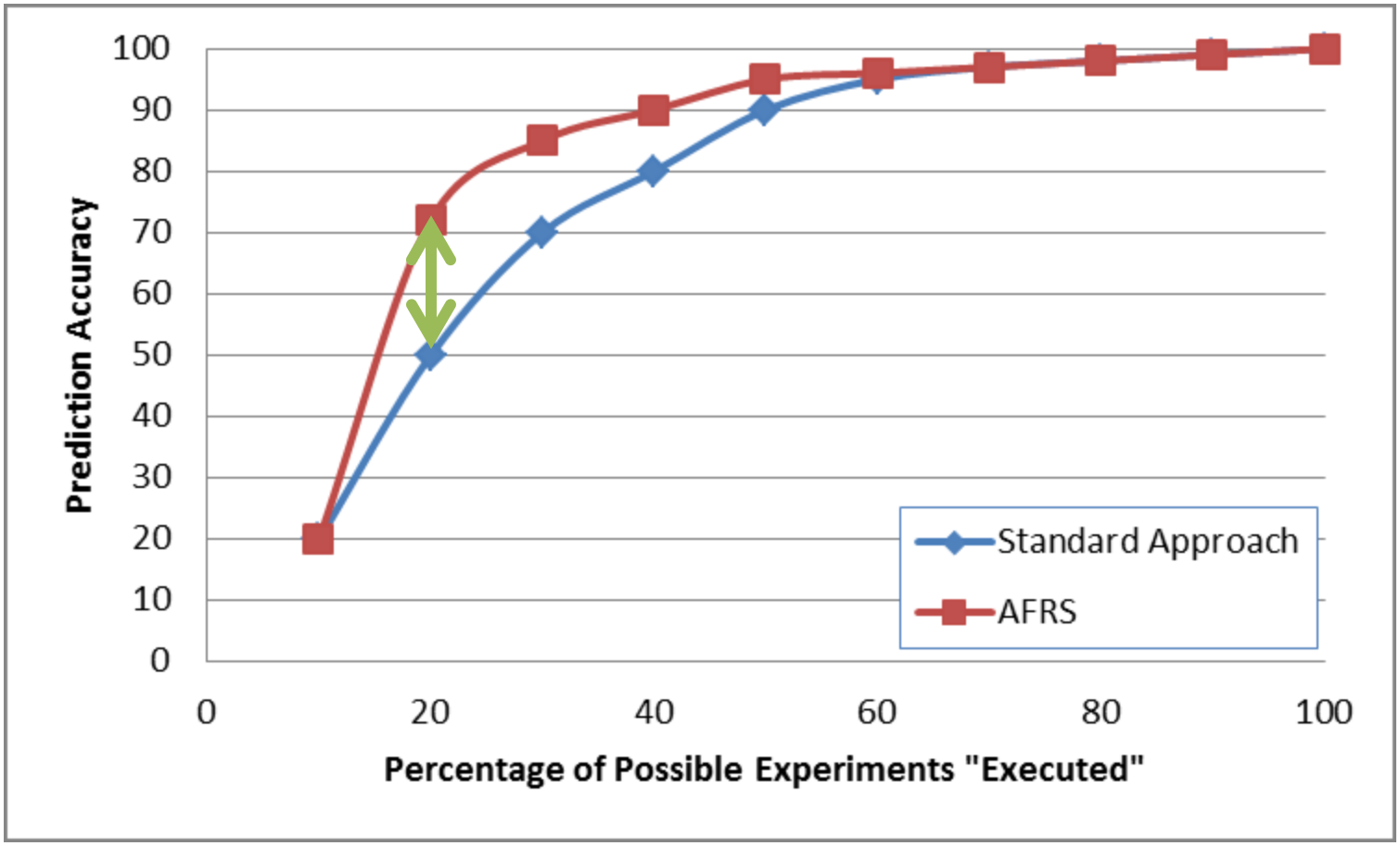


Recommendation

- Use ToxCast Study 1?
  - Allows us to dissect real world data in an informative manner
  - Most general problem
  - Most applications to other areas within your organizations

ToxCast Study 2

Purpose: Efficiently Identify All compounds with desirable profiles across ToxCast assays.

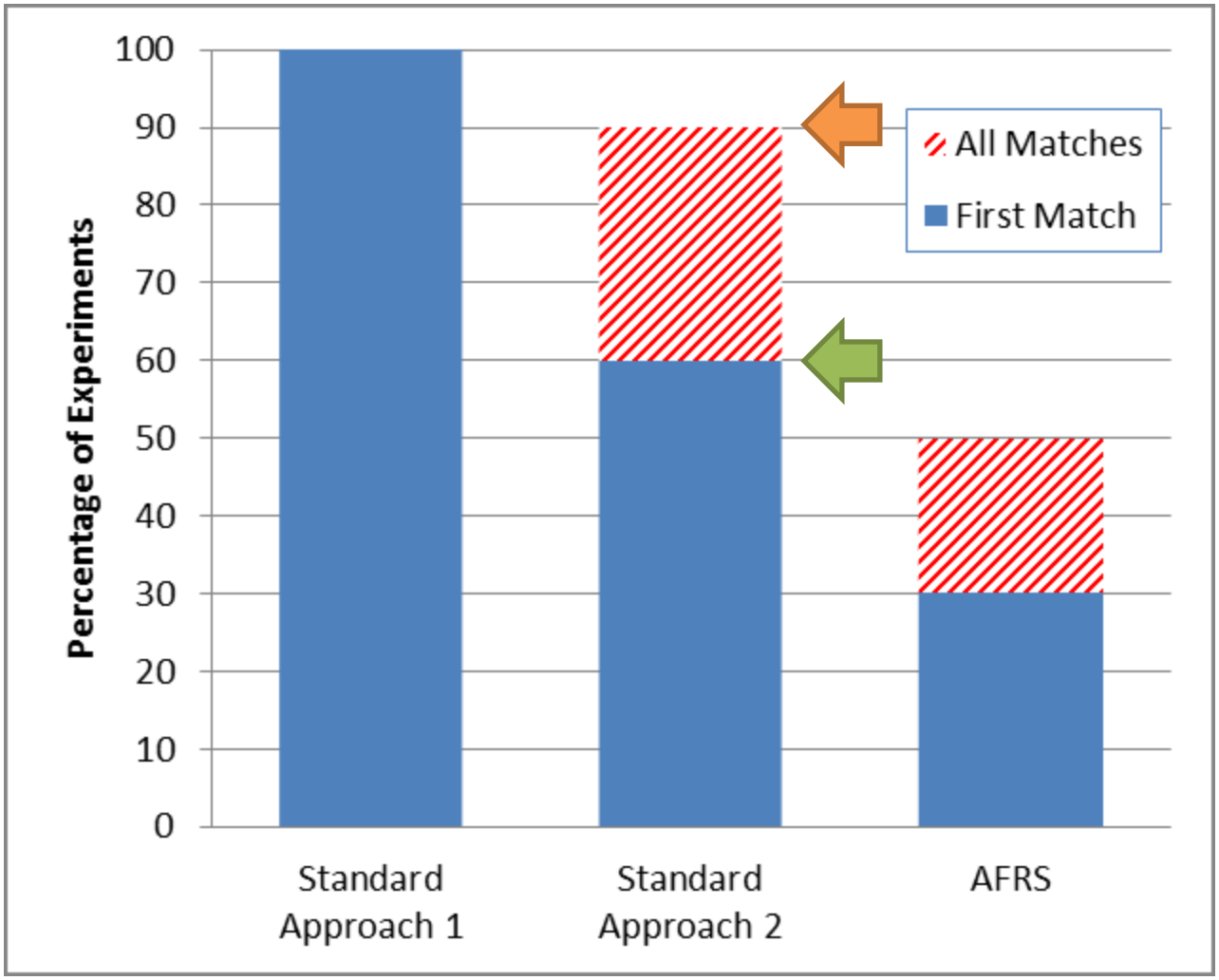
Standard Approach: “the Funnel Approach”- Order the assays. Run one assay for all compounds. Reject all compounds that don’t match the desired profile for that assay. For the next assay, run only compounds that were not rejected in the previous assays. This process will continue with remaining assays until all compounds have been characterized.

ToxCast Study 2

Purpose: Efficiently Identify All compounds with desirable profiles across ToxCast assays.

AFRS Approach: Choose batches of *n* experiments using the AFRS until compound(s) with desired profile are identified.

ToxCast Study 2



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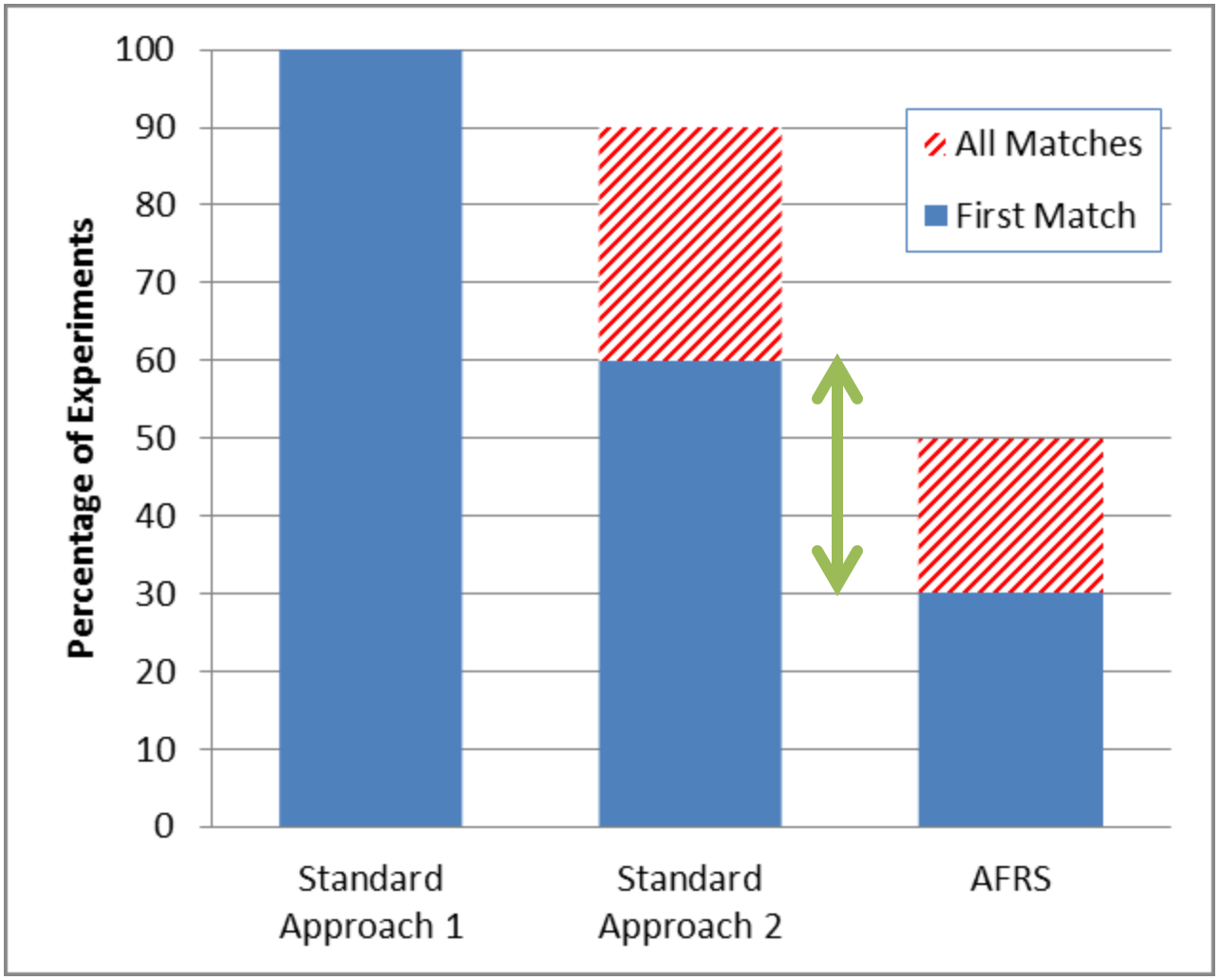

ToxCast Study 3

Purpose: Efficiently Eliminate All compounds with Undesirable toxicity.

Standard Approach: “the Funnel Approach” - Order the assays. Run one assay for all compounds. Reject all compounds that don’t match the desired profile for that assay. For the next assay, run only compounds that were not rejected in the previous assays. This process will continue with remaining assays until all compounds have been characterized.

ToxCast Study 3

Purpose: Efficiently Eliminate All compounds with Undesirable toxicity.

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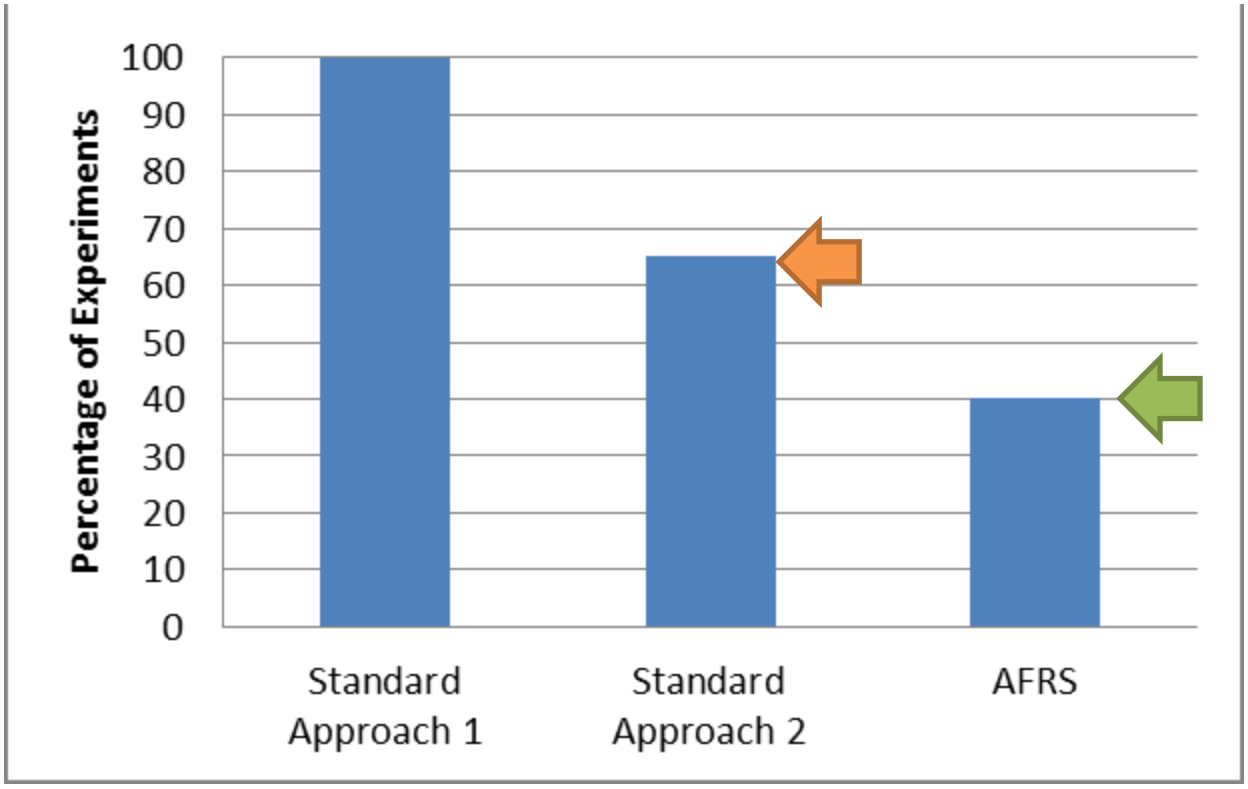
ToxCast Study 3



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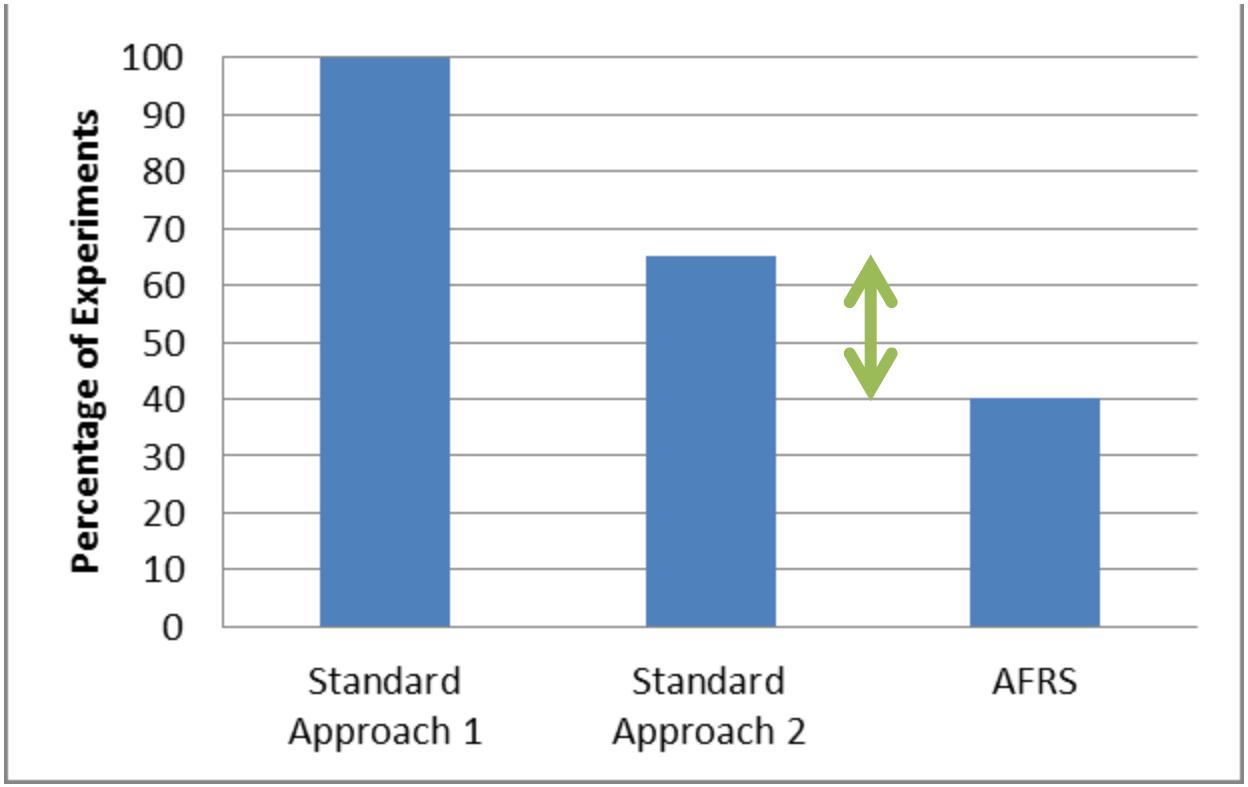

Quantitative Medicine

Transforming Drug Discovery

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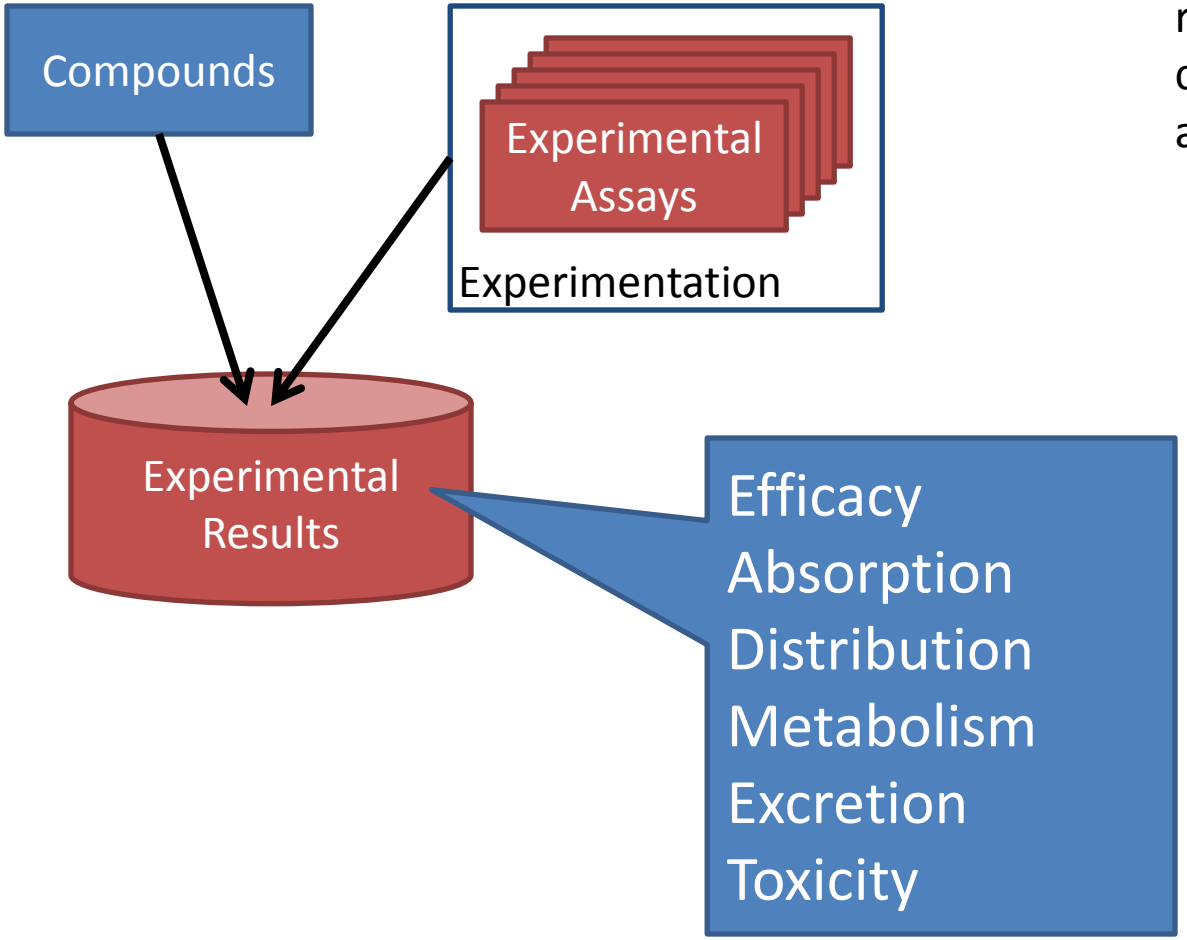
Current Experimental Approach

1. Select a set of compounds of interest (2 – 10^6 total).

Compounds

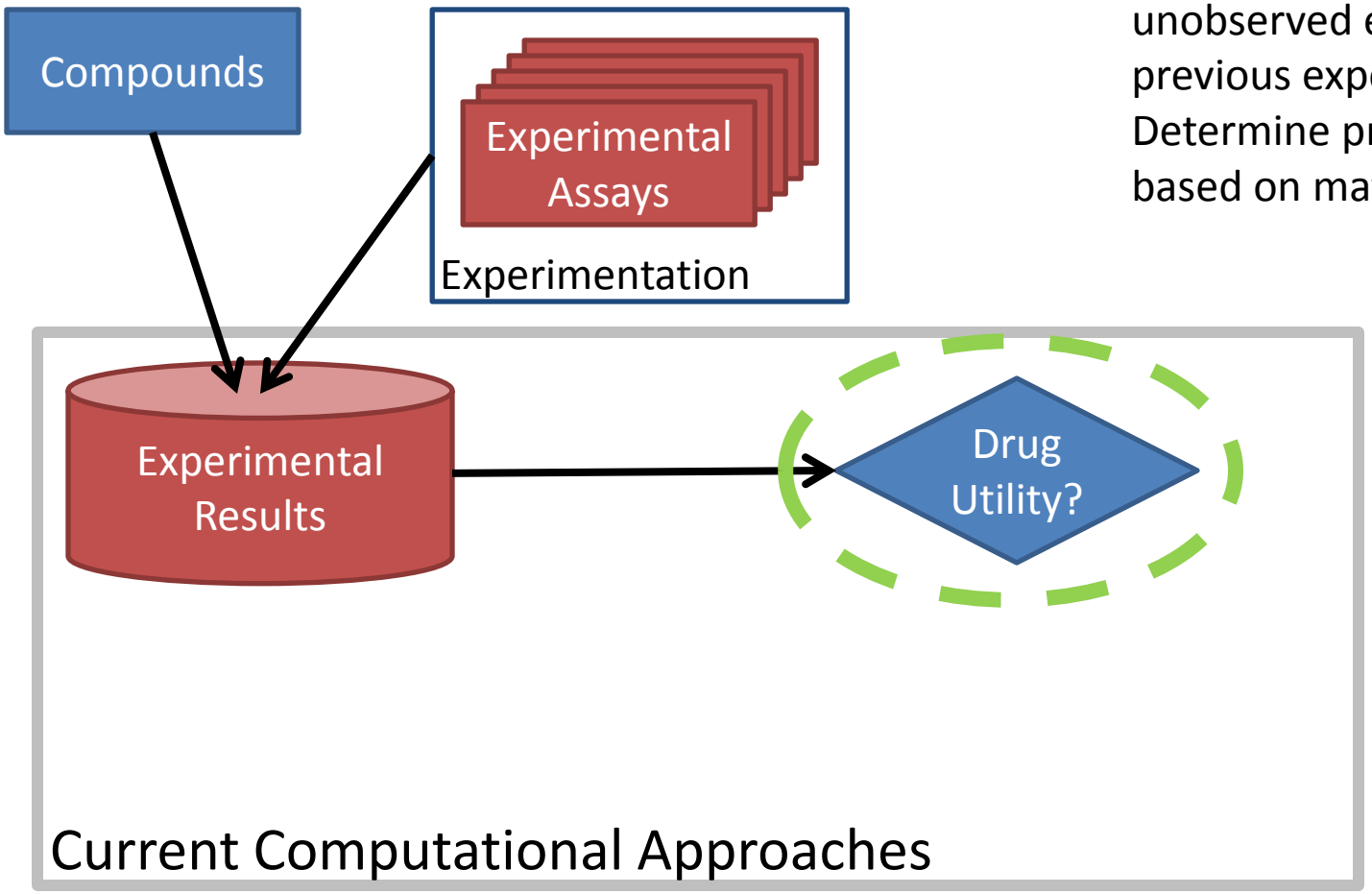
Current Computational Approach



2. For a set of relevant assays, gather all available experimental results from running those compounds against those assays (1-10^2).

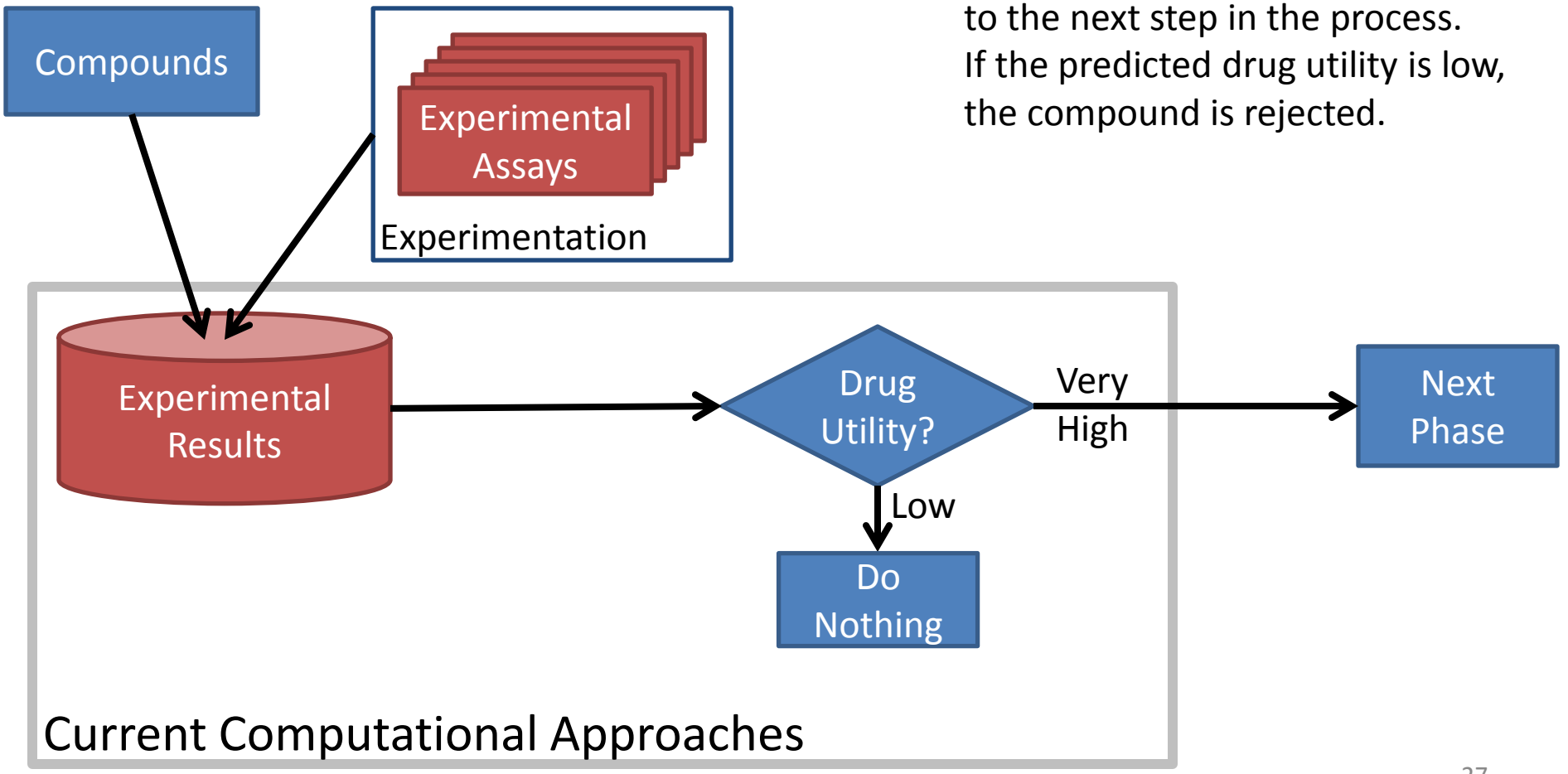
Current Computational Approach

3. Use computational methods to predict the results for all unobserved experiments based on previous experimental results. Determine predicted “drug utility” based on match to a desired profile.



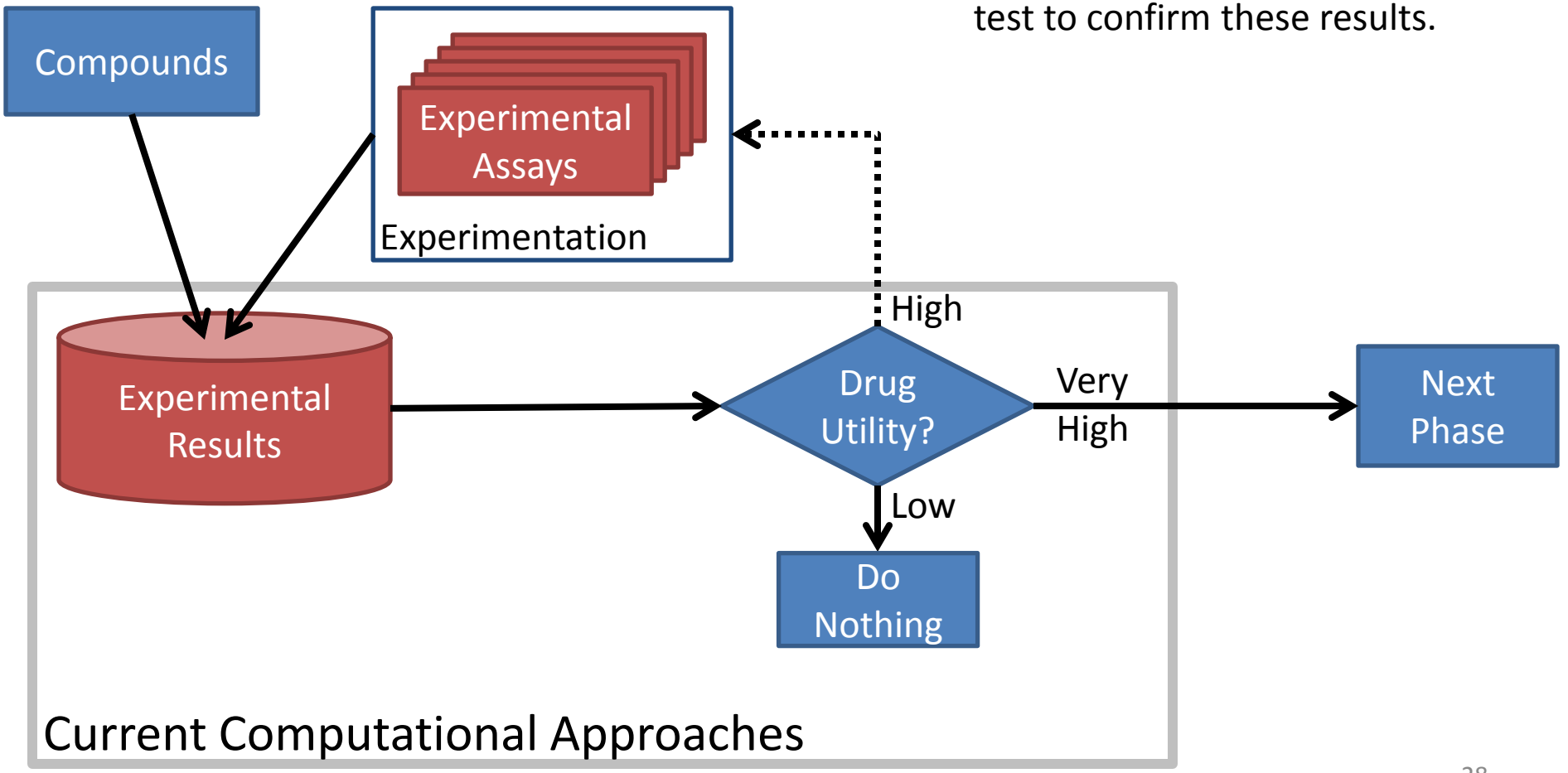
Current Computational Approach

4. If the predicted drug utility is very high, the compound can be moved to the next step in the process. If the predicted drug utility is low, the compound is rejected.

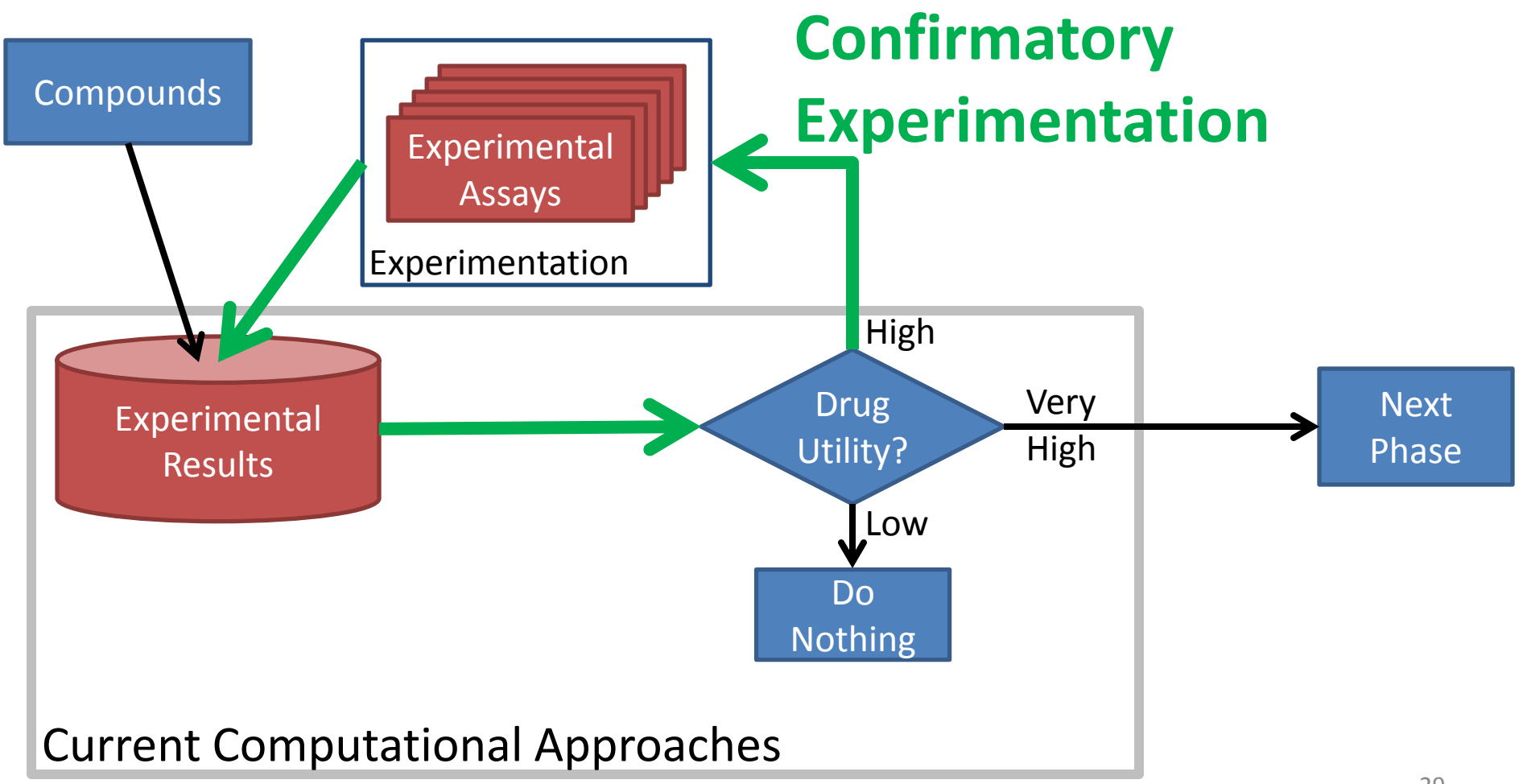


Current Computational Approach

5. If the there is a high predicted drug utility, one might run more test to confirm these results.



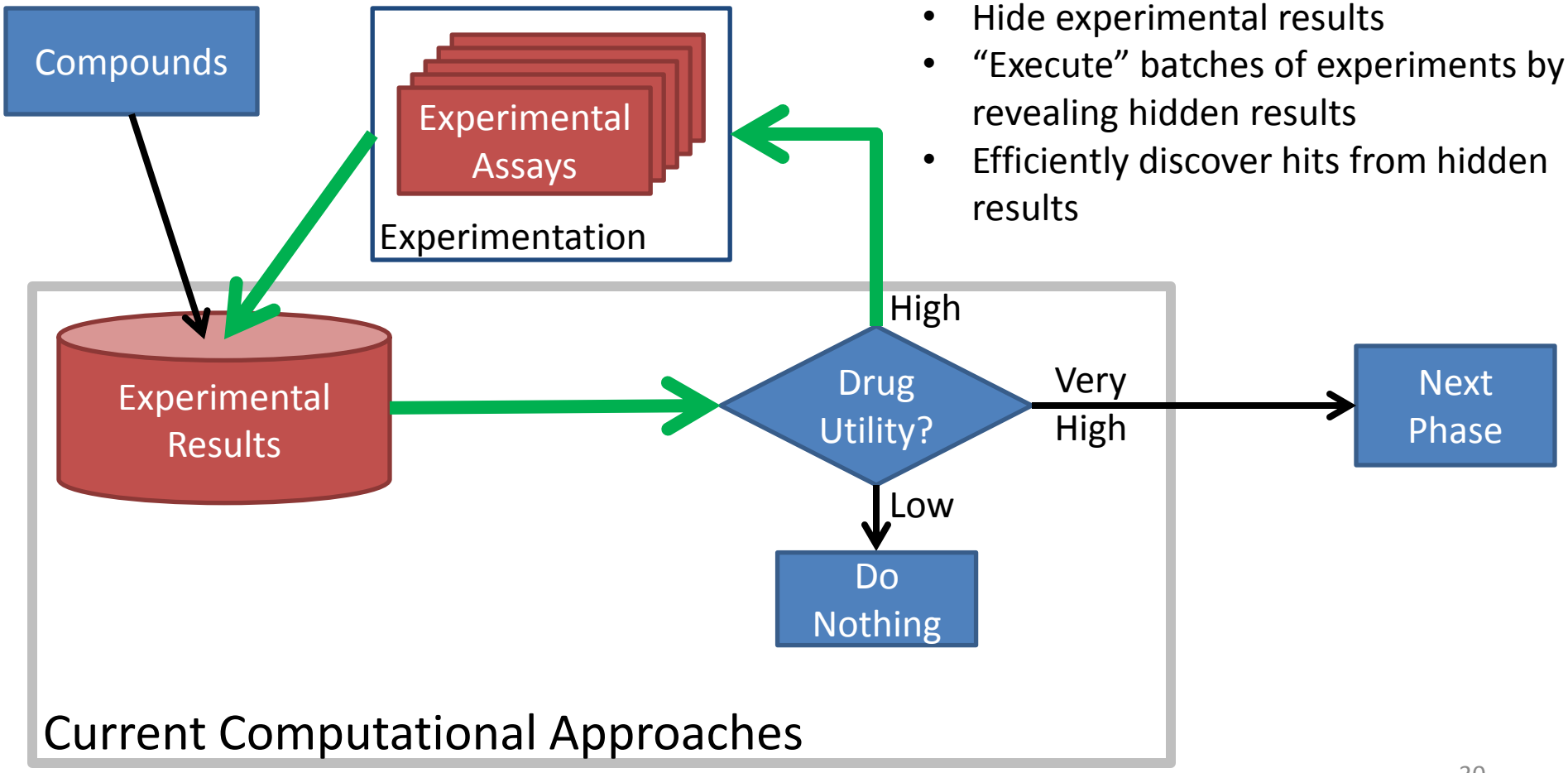
Current Computational Approach



Current Computational Approach

PubChem Simulation:

- 20,000 compounds and 177 assays
- Hide experimental results
- "Execute" batches of experiments by revealing hidden results
- Efficiently discover hits from hidden results



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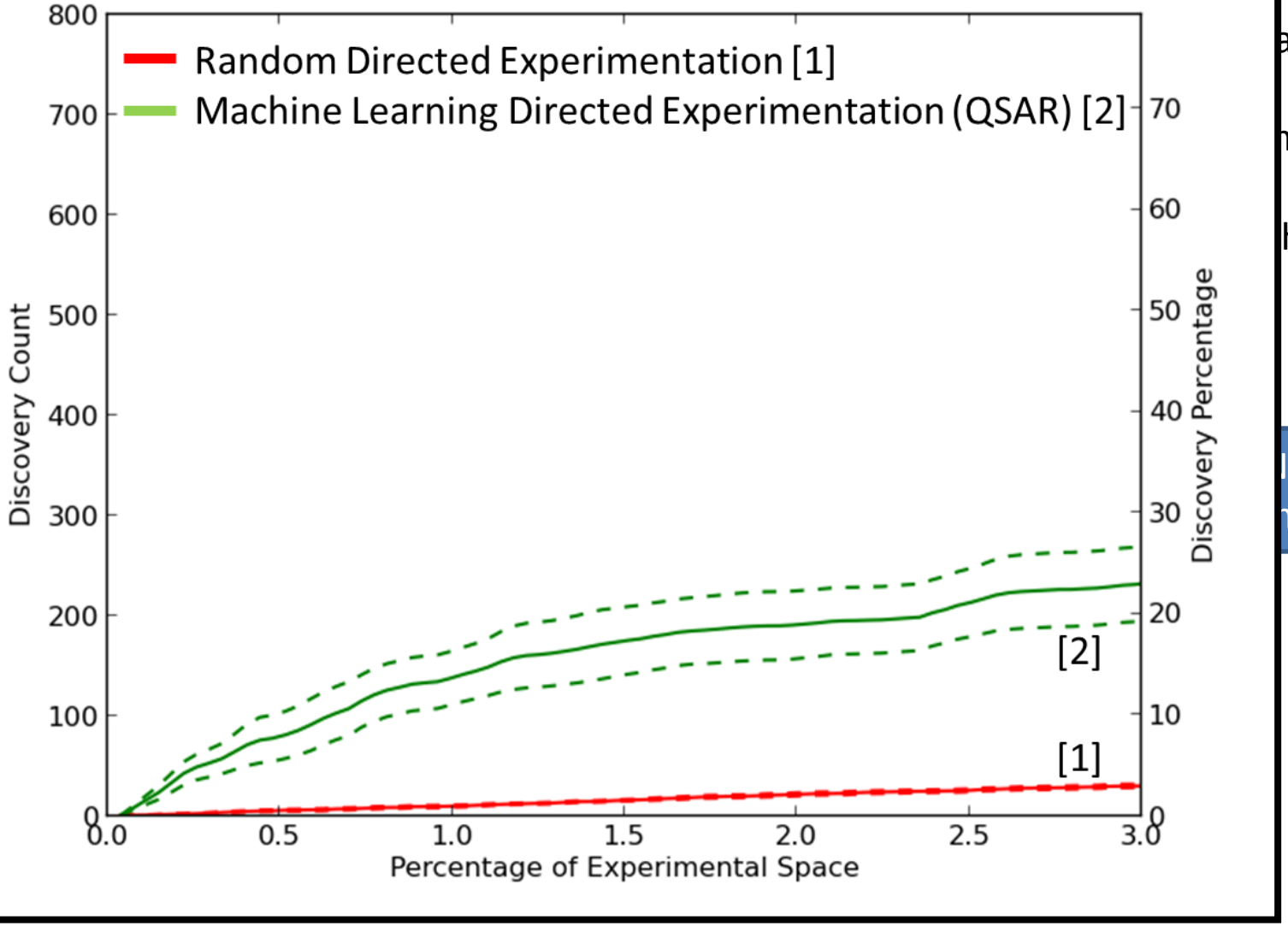
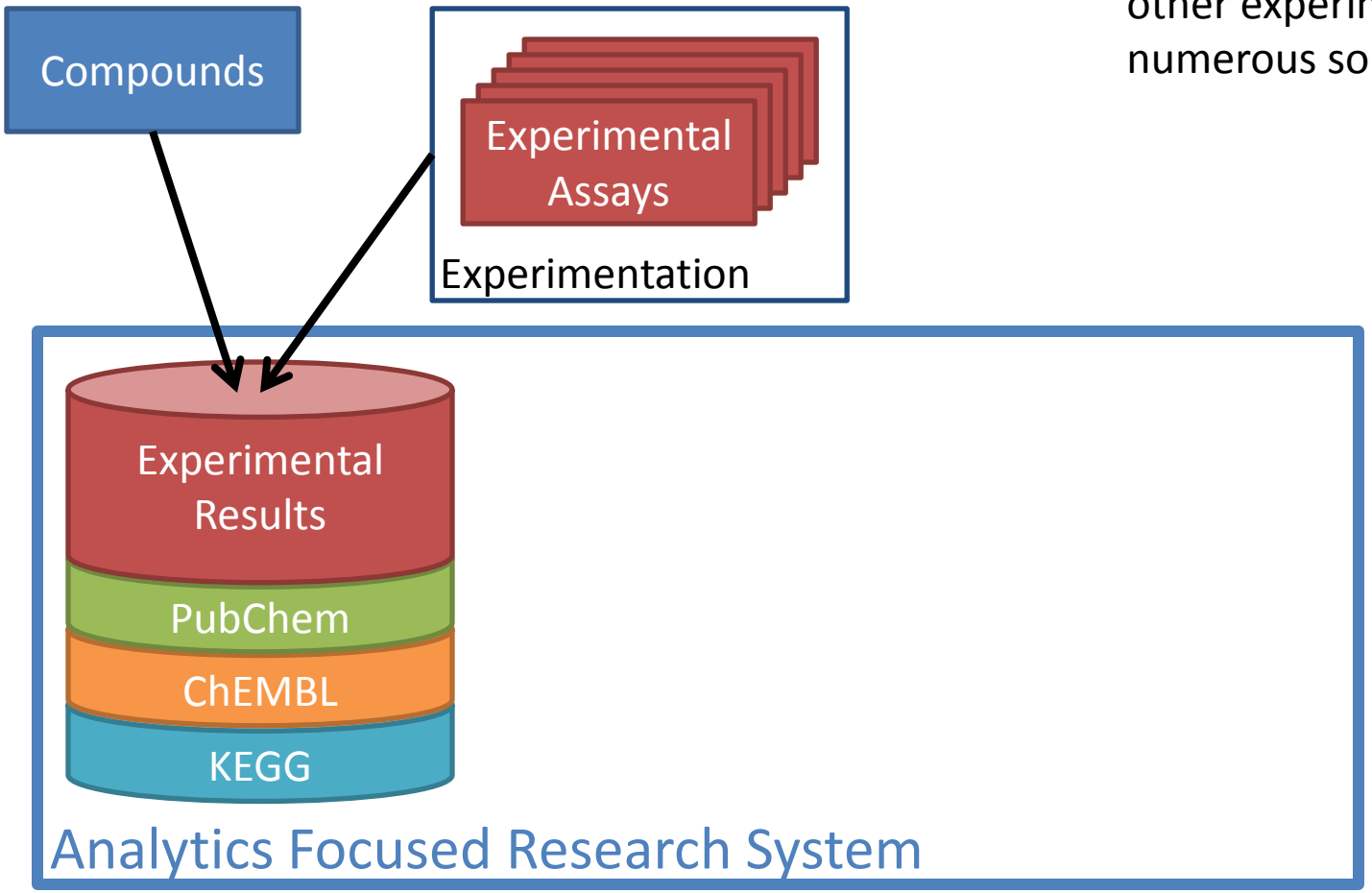


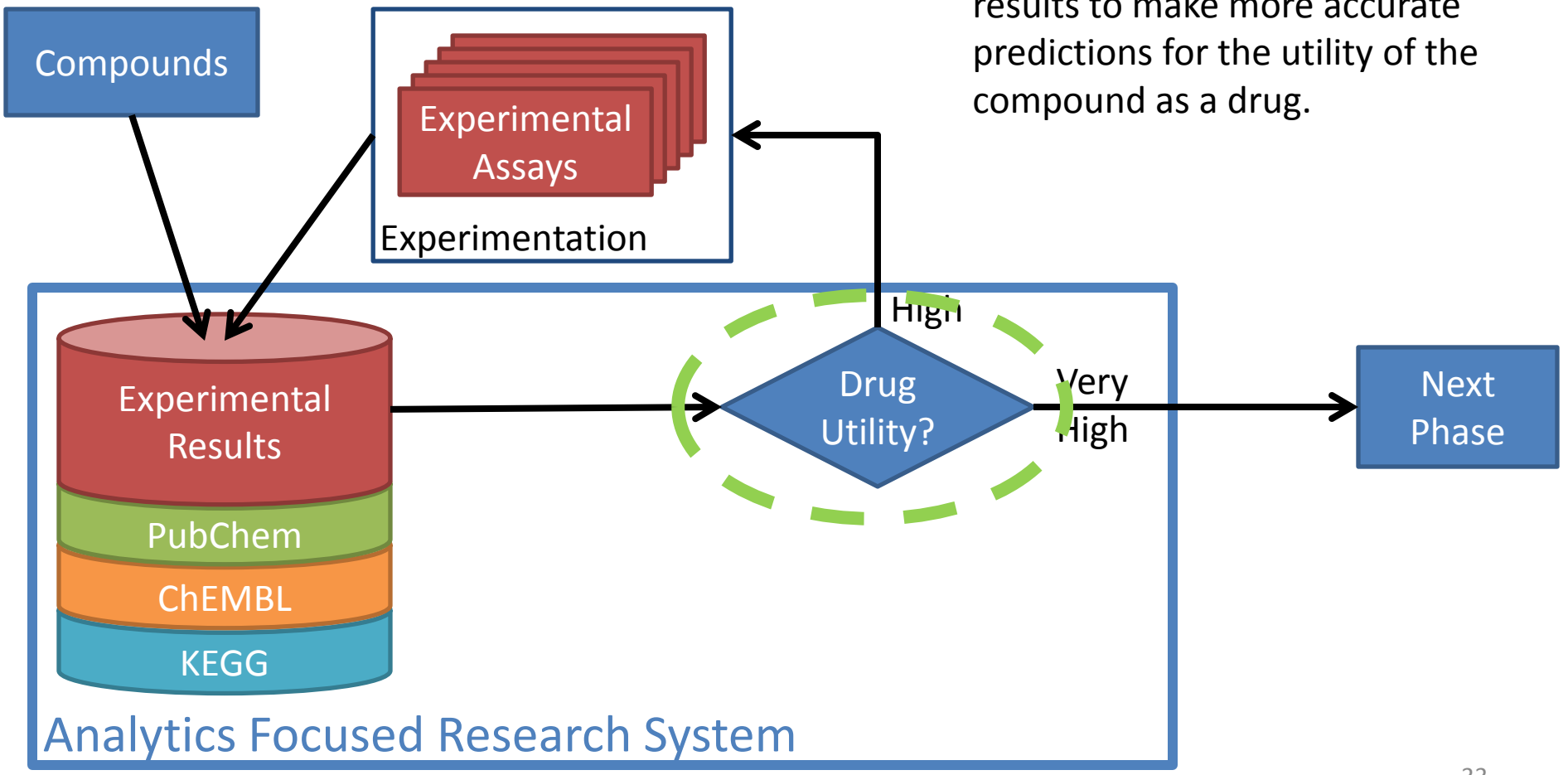
AFRS Approach For Efficient Experimentation

1. We combine experimental results with a large knowledge base of other experimental results from numerous sources.



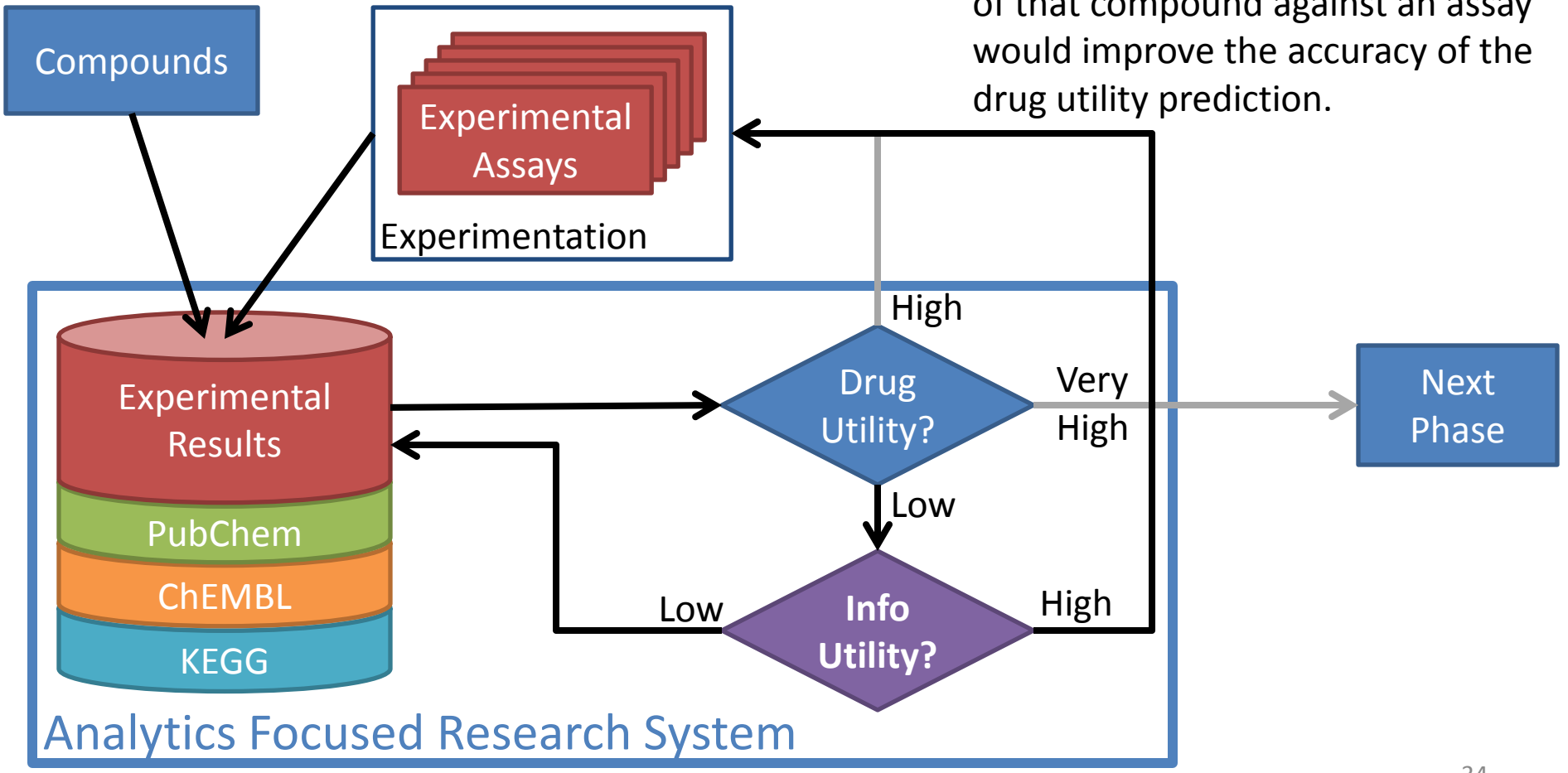
AFRS Approach For Efficient Experimentation

2. We use our vast sources of information as well as experimental results to make more accurate predictions for the utility of the compound as a drug.



AFRS Approach For Efficient Experimentation

3. If a compound has low predicted drug utility, we predict if the results of that compound against an assay would improve the accuracy of the drug utility prediction.



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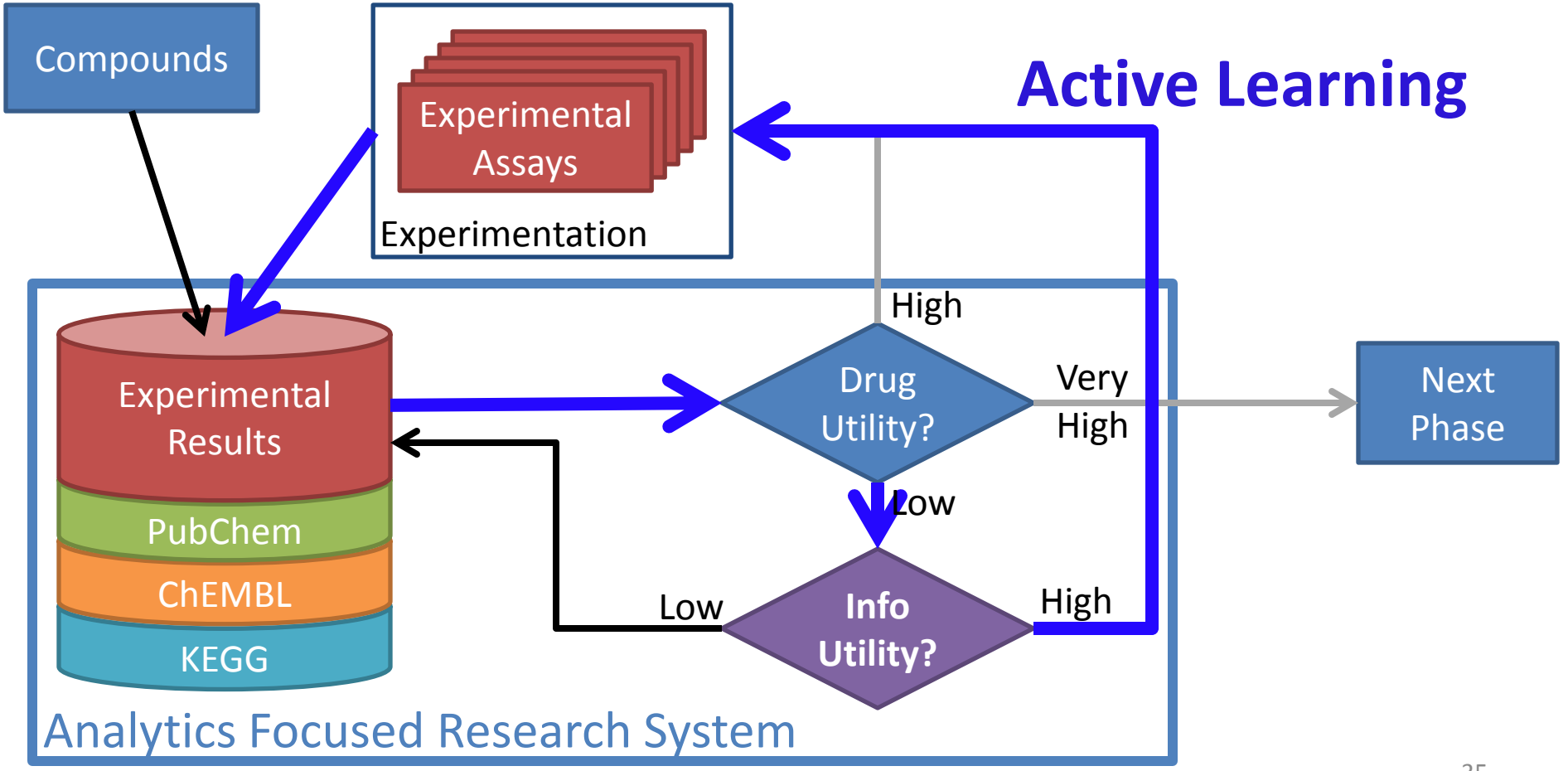

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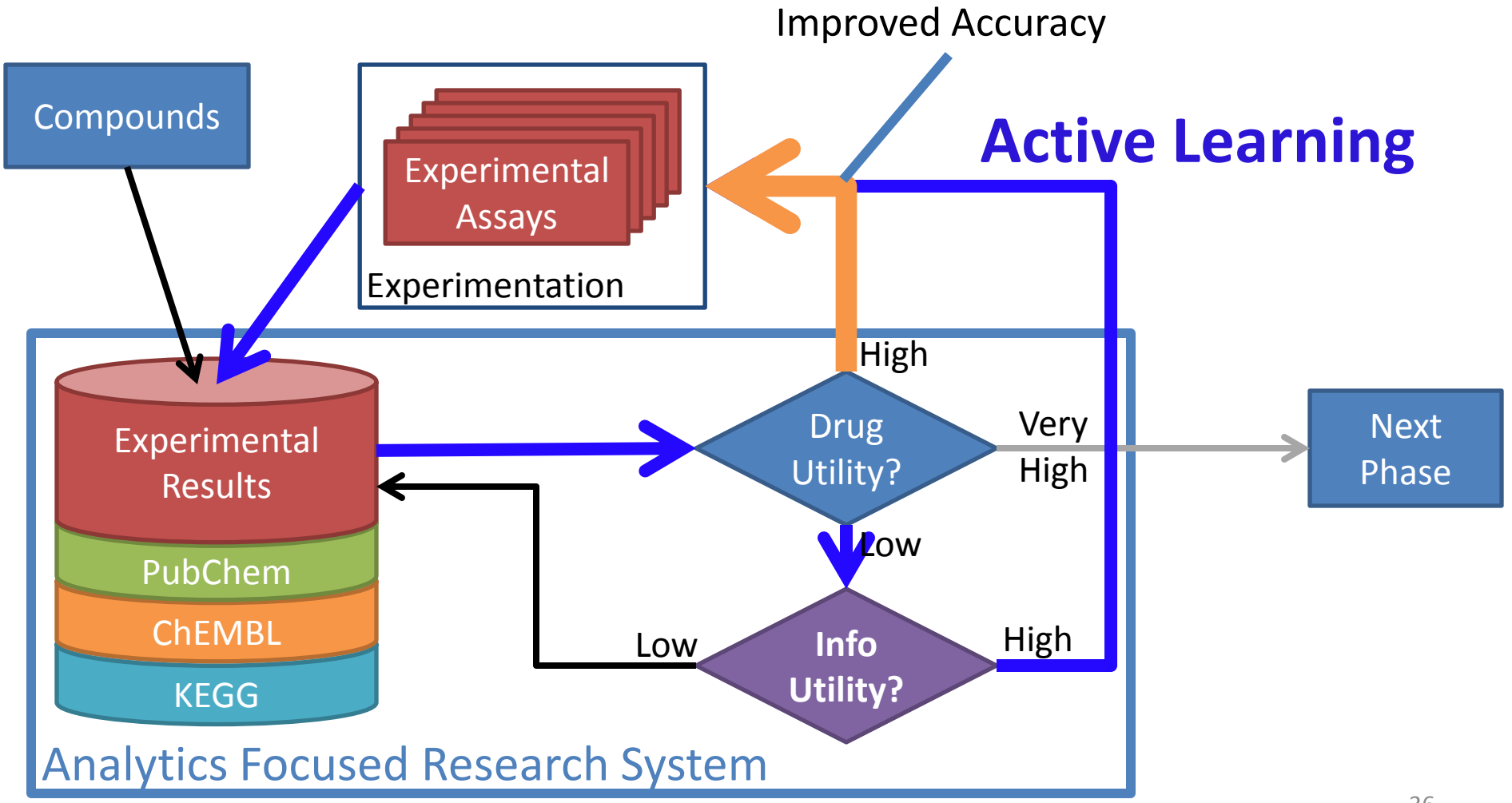
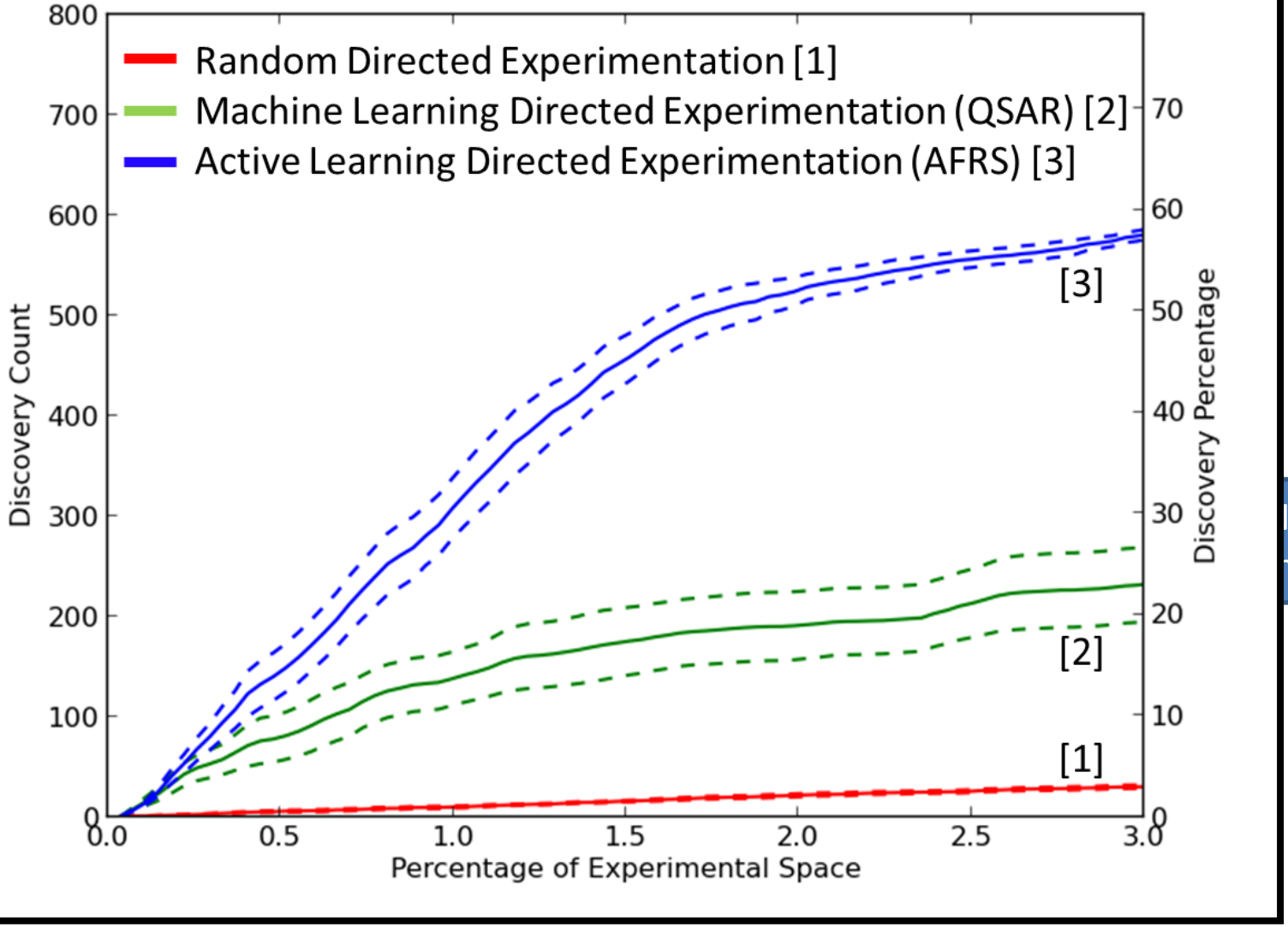


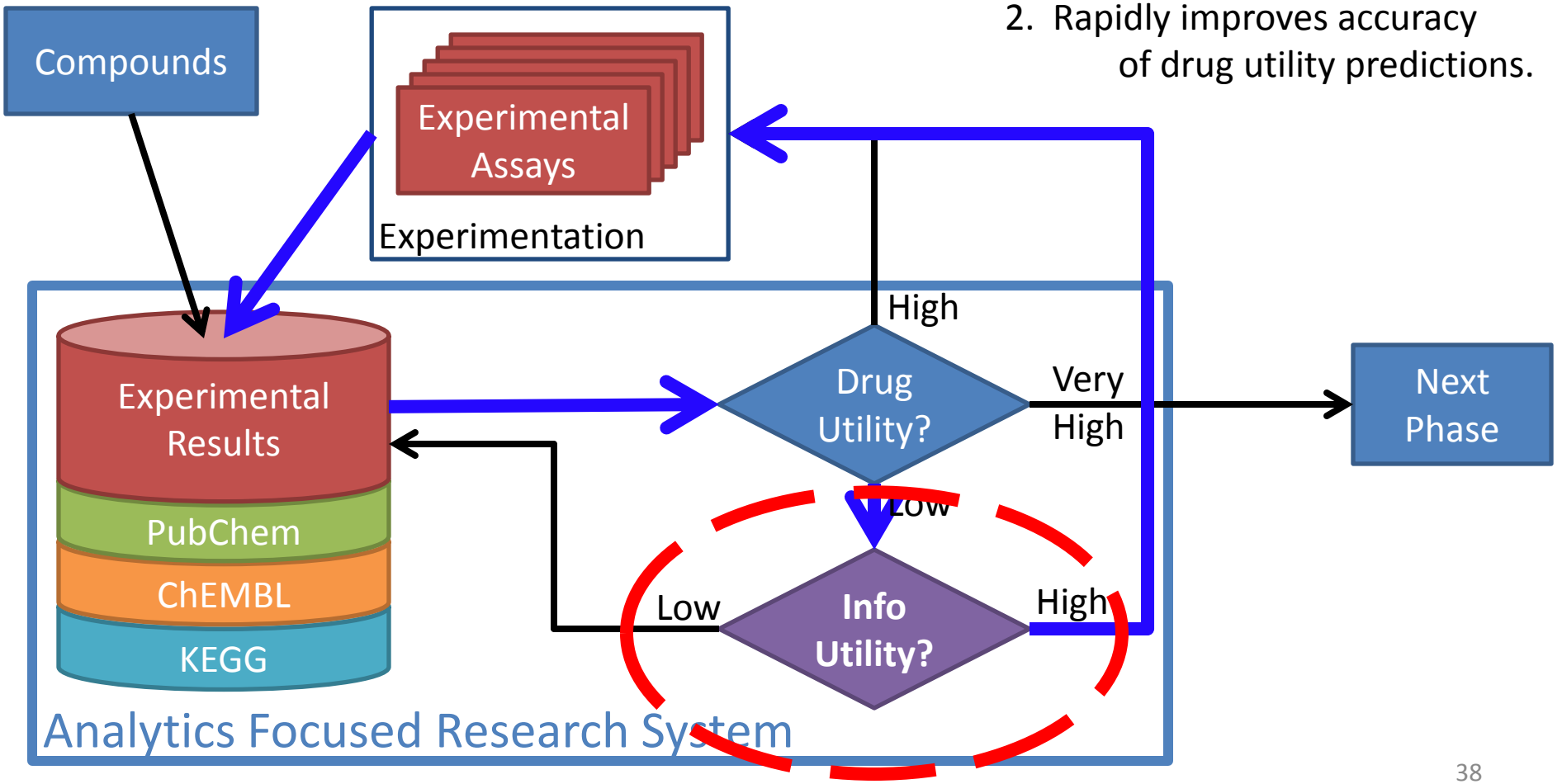
AFRS Approach For Efficient



AFRS Approach For Efficient Experimentation

Running this path:

1. Reduces experimentation
2. Rapidly improves accuracy of drug utility predictions.



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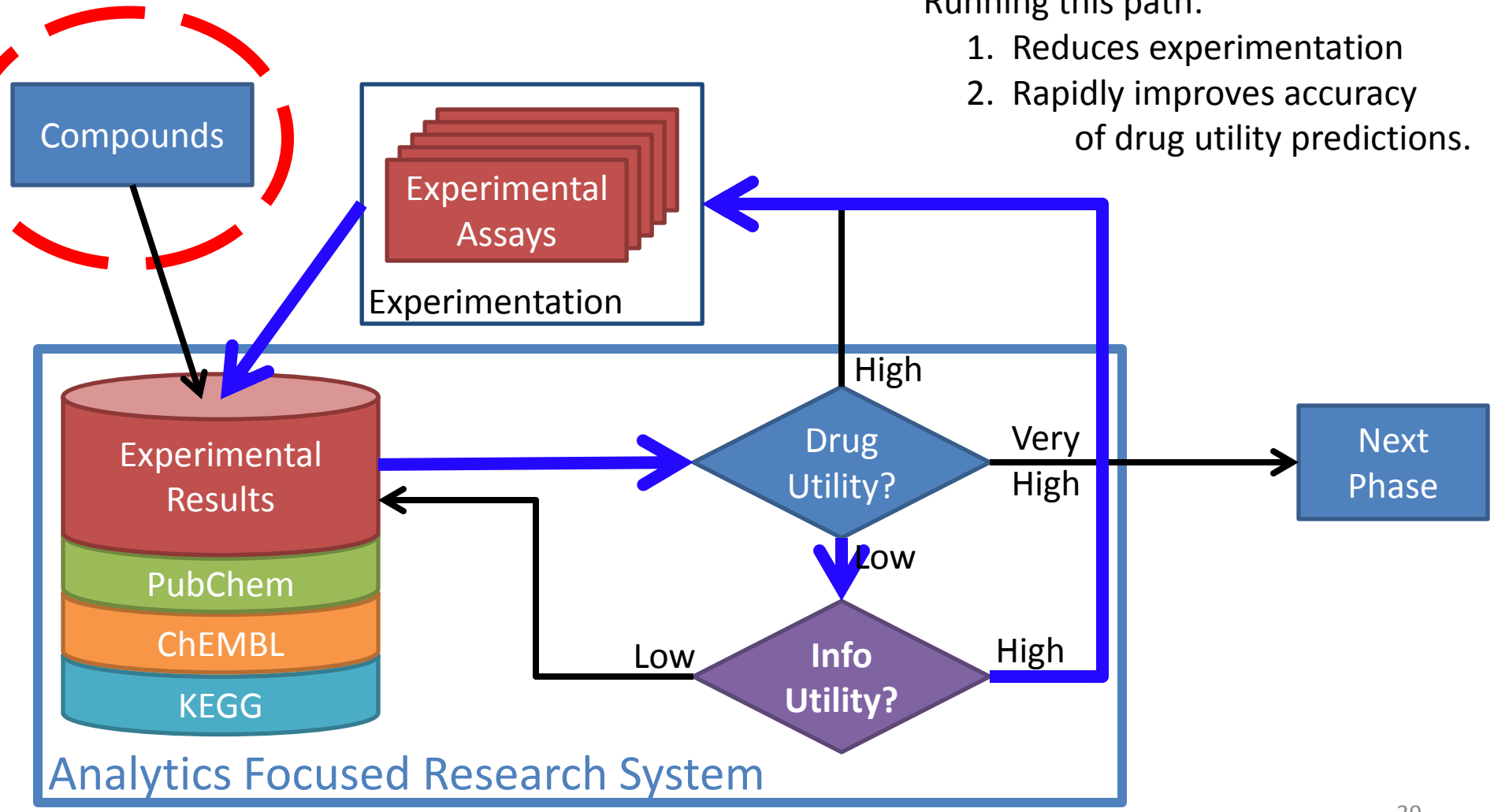

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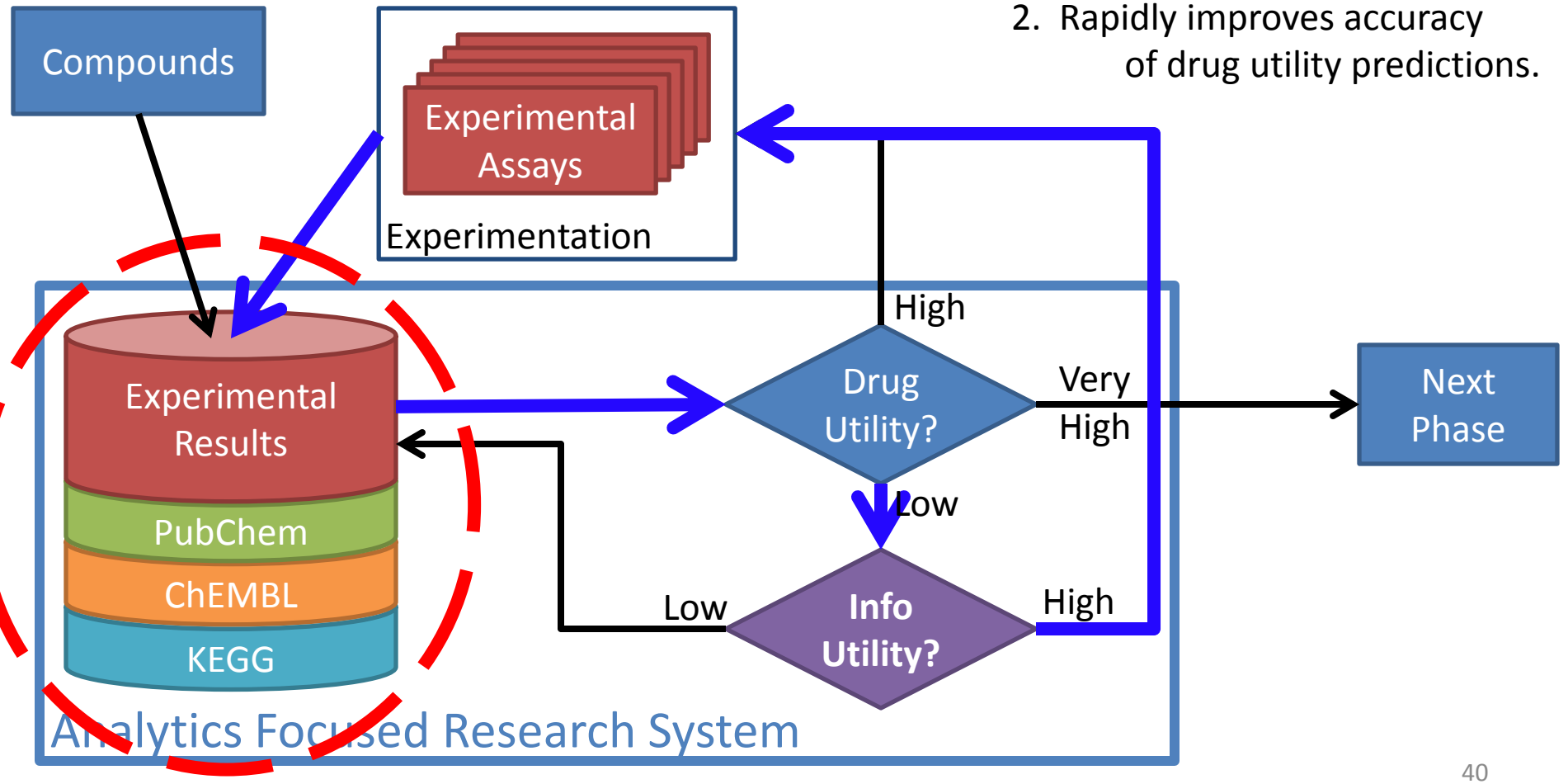

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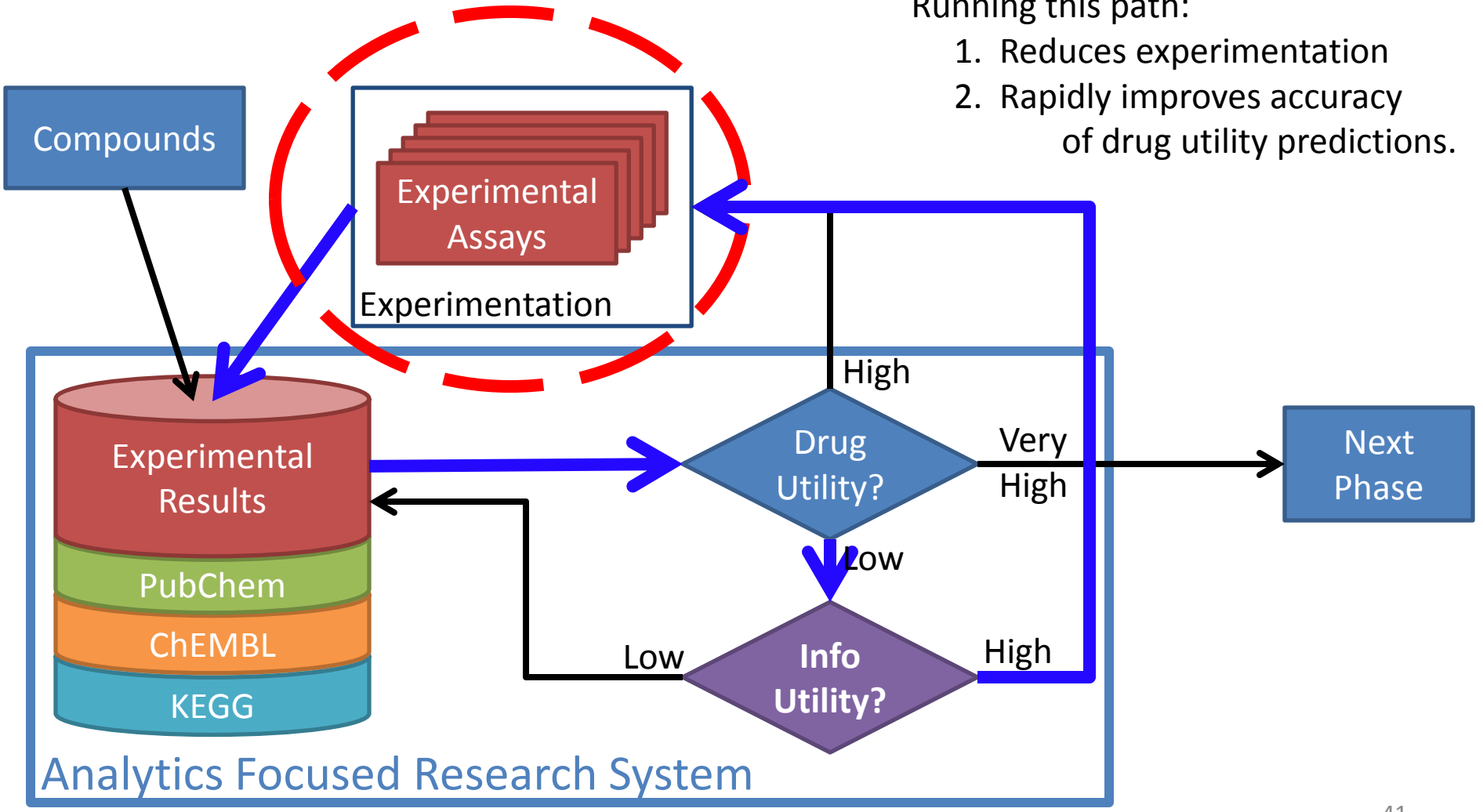
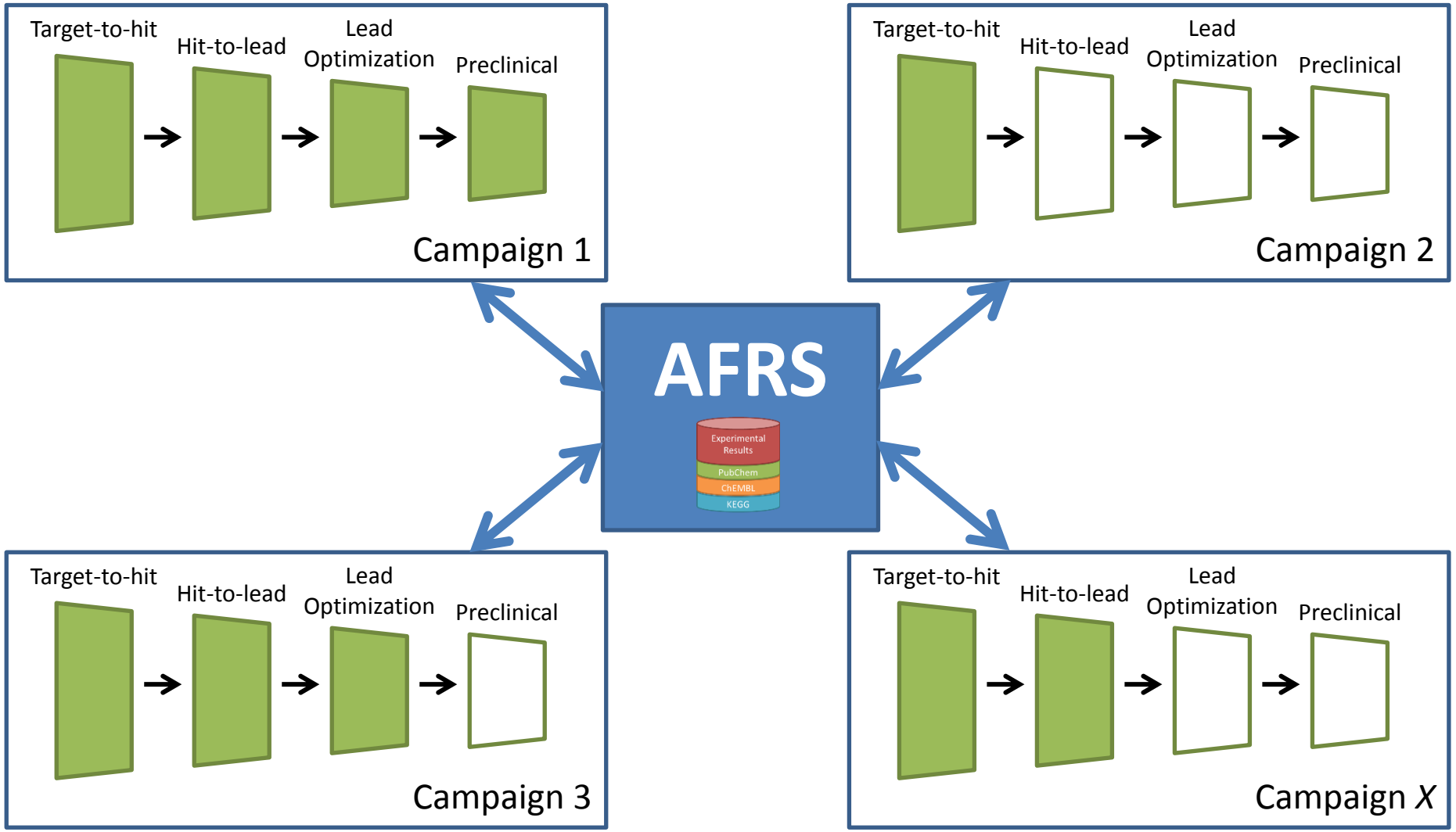
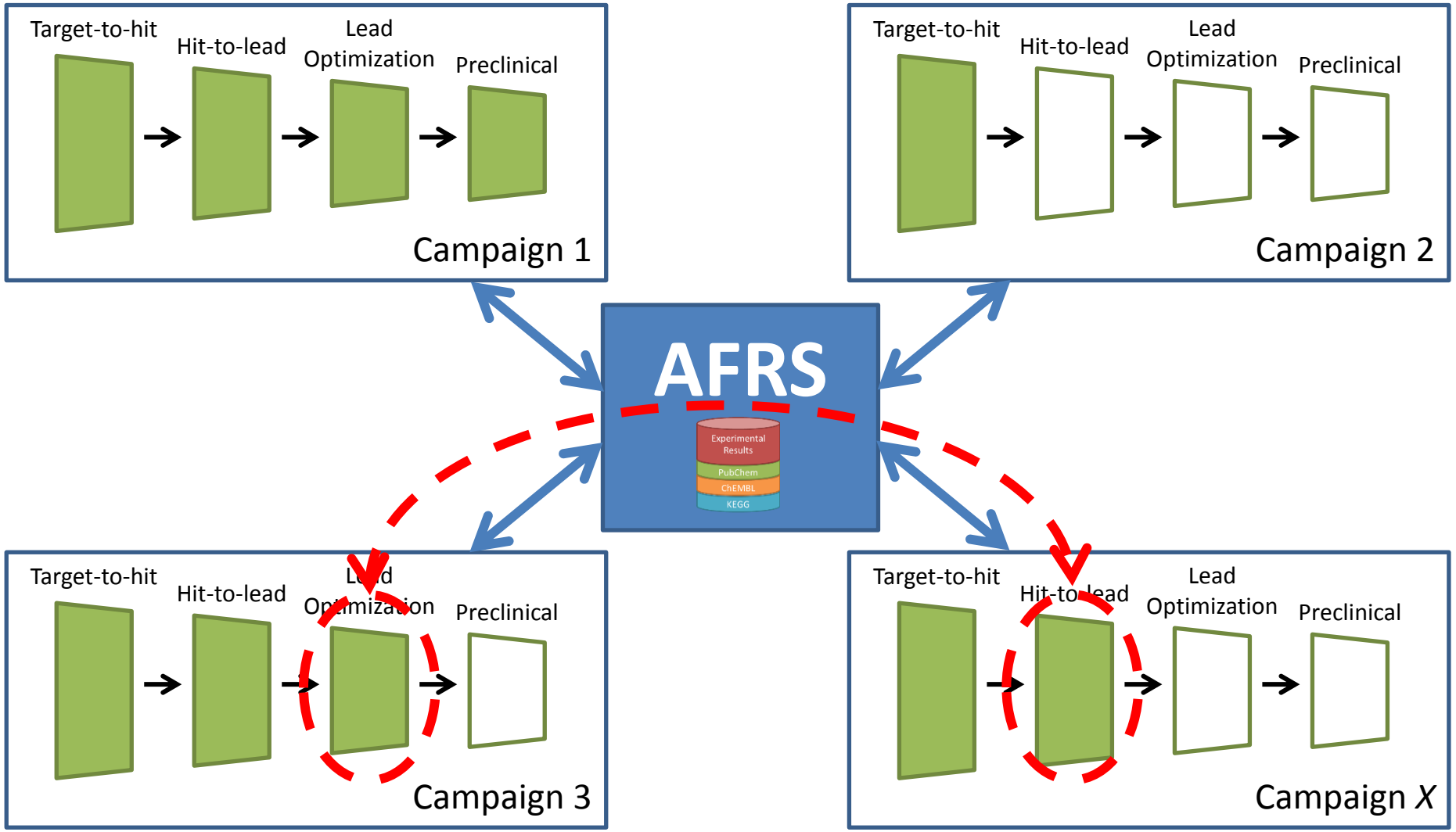


AFRS Approach Across Campaigns



AFRS Approach Across Campaigns



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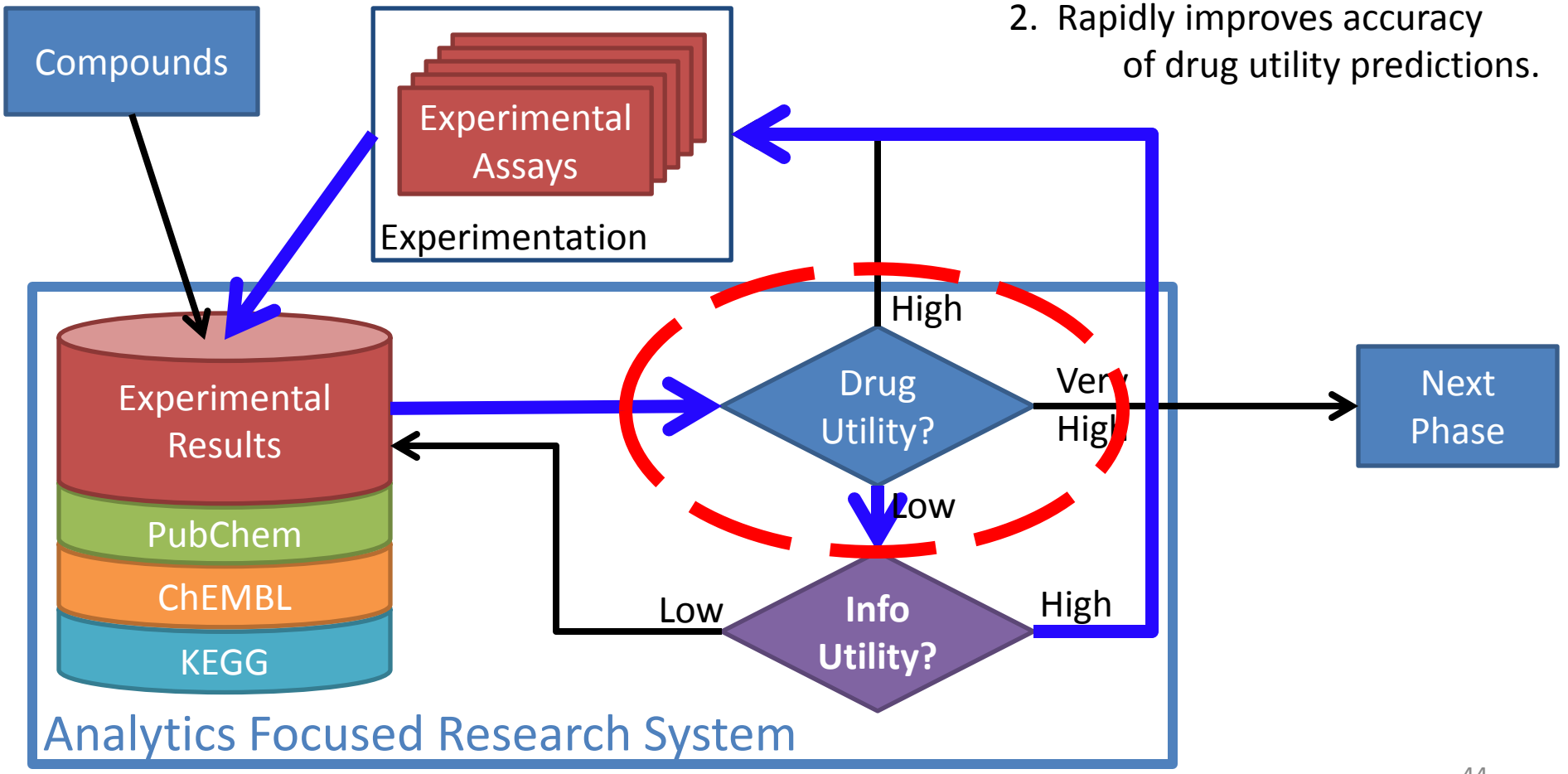

Synopsis

- Integrated system designed to enable these parts to interoperate:
  - Compound libraries
  - Diverse Experimentation methods
  - Extensive knowledge bases
  - Active machine learning-based predictions
- Synergistic relationship between all system components

Benefits

- Immediate Benefits:
  - Less experimentation to yield the same or better results - reduced time, lower cost
  - “Drug Utility” predictive accuracy improves every iteration within the campaign
- Long Term Benefits:
  - Combines and directs experimentation from many diverse modalities
  - Builds more informative corporate dataset for future studies
  - Continually building more accurate predictive models
  - Reduced attrition compared with using less predictive models learned from inadequate data