



# QUANTITATIVE MEDICINE

Transforming Drug Discovery™

## Lundbeck Update Presentation

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# Agenda

- Hepatotoxicity Study Updates
- Next Study

# Hepatotoxicity Study Open Questions

1. What is the effect of historical data from previous studies on prediction accuracy?
2. What is the effect of using only compound features on prediction accuracy?
3. Can we effectively prioritize assays to predict toxicity? What is the effect on prediction accuracy when assays are removed?
4. What is the effect of utilizing neighboring compound and assay results on prediction accuracy?

# CoRE™ Simulation Protocol

- Datasets randomly divided into a training set (80%) and testing set (20%) for each simulation
- All results (Toxicity and HCS measures) were hidden from CoRE™
- For each round a compound was selected from the training set and the toxicity and HCS readouts were revealed to the learner
- A predictive model was learned from only the ***revealed*** training data
- Predictions were made for all compounds in the testing set

# Receiver Operating Characteristic

- What are we predicting?
  - Hepatotoxicity for all “unobserved” experiments in testing set
- How do we measure accuracy of those predictions?
  - Calculate a ROC curve by sweeping across prediction thresholds and comparing to hidden ground truth toxicity

# Comparison Method

**Purpose:** Develop a Model to Actively Learn and Accurately Predict Toxicity From HCS Data

**Standard Approach (single pass):**

**Selection method:** Choose a set of compounds randomly for “execution” from training set

**Prediction method:** Learn a RandomForest model based on HCS results to predict toxicity.

# Comparison Method

**Purpose:** Develop a Model to Actively Learn and Accurately Predict Toxicity From HCS Data

**CoRE Approach (Iterative):**

**Selection method:** Choose a single compound for “execution” from training set.

**Prediction method:** Learn a model using our prediction methods based on all revealed HCS results and our extensive library to predict toxicity.



# Data Sources

**Hepatotoxicity:** Your dataset

**HCS Measures:** Your dataset

**Structural Information:** Calculated structure based features from SMILES provided

**Historical Experimental Results:** Results from ~800 assays in which some of the compounds were previously tested

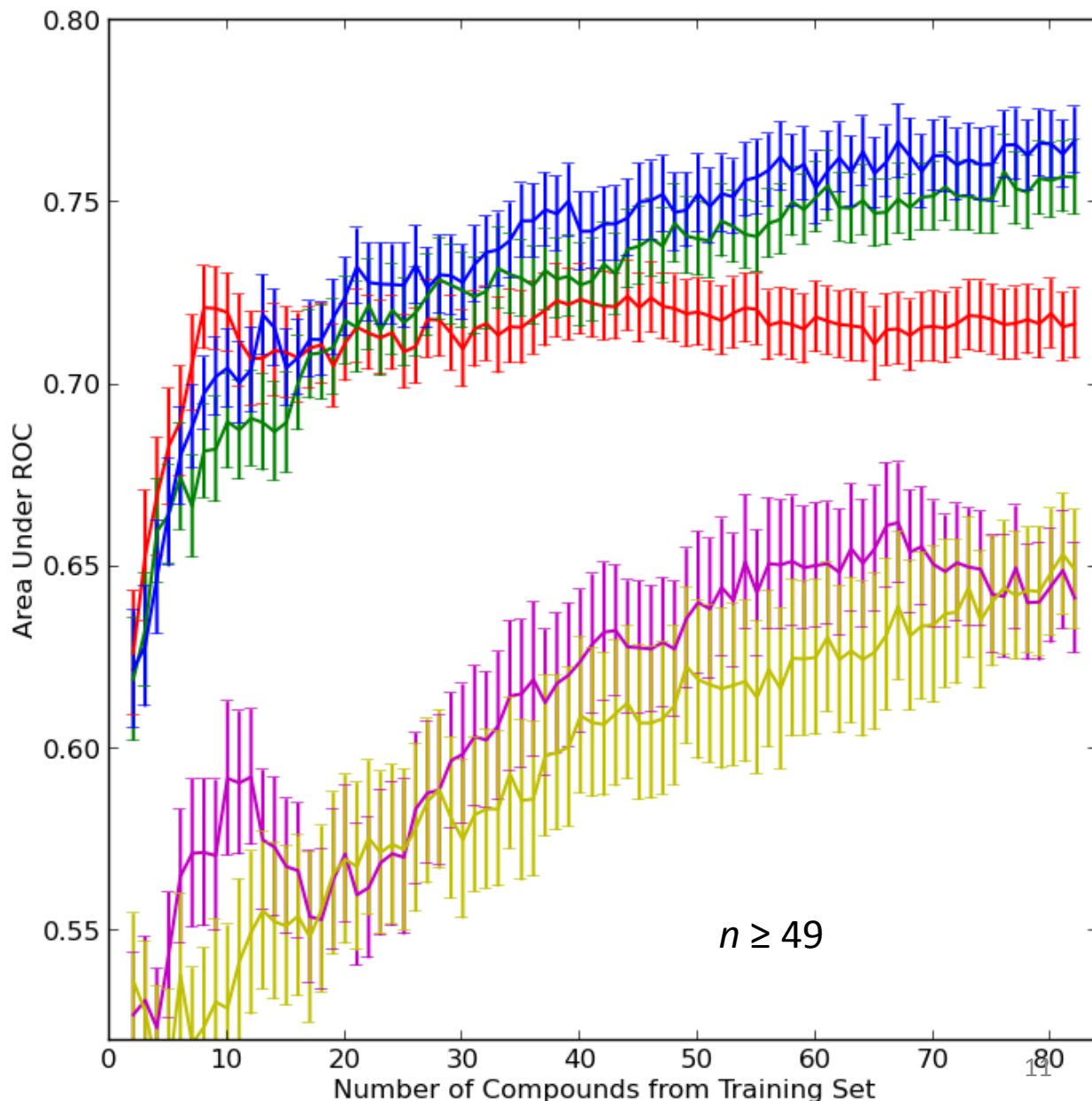
# Demonstration Goals

**Prediction methods** – Show that our methods and the data we use yield improvements in prediction accuracy

**Selection methods** – Show that our methods for selection of experiments yield significant savings in experimental efforts

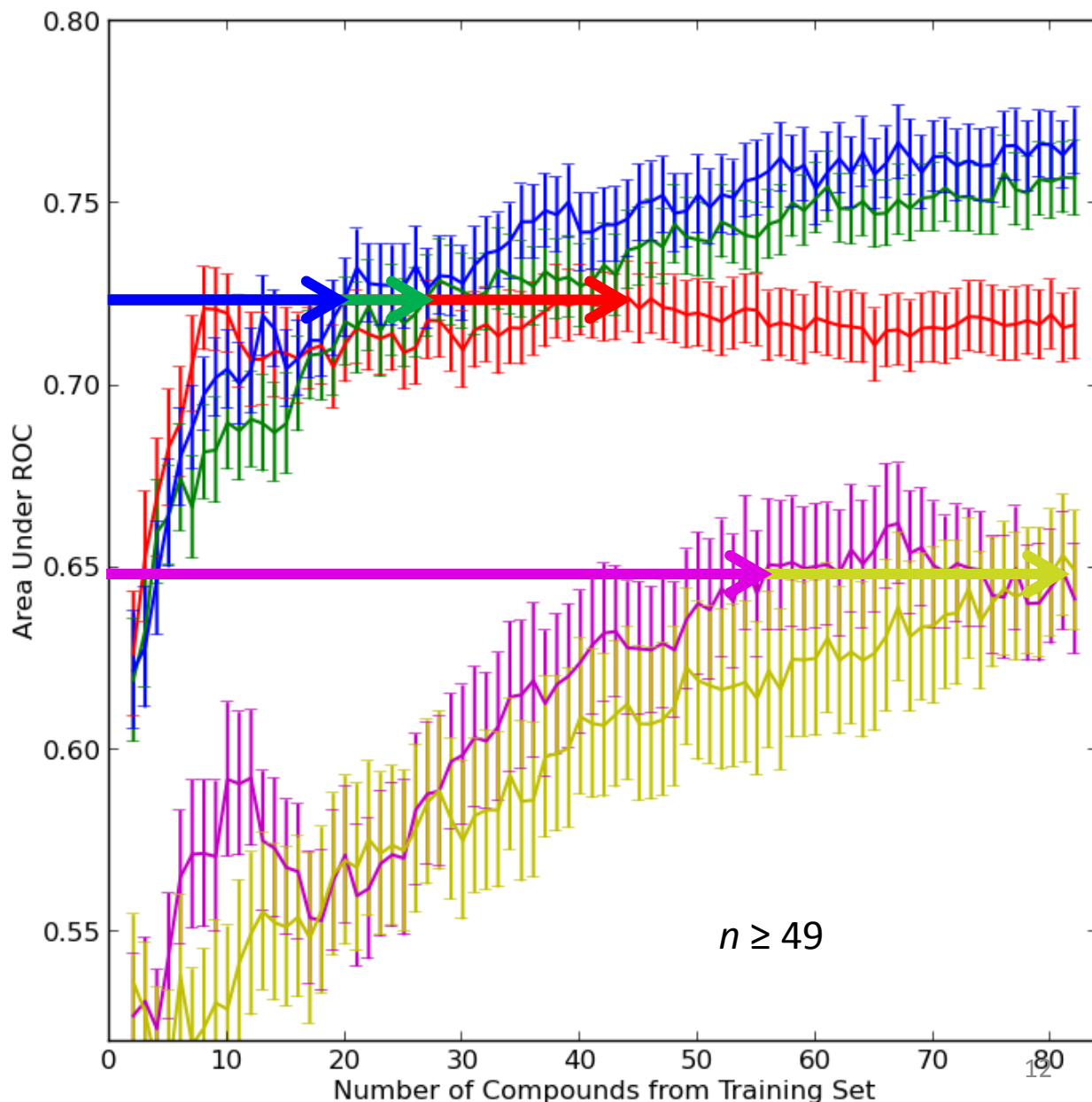
# Hepatotoxicity Simulation Results

- CoRE
- RandomForest – Uses *only* HCS Results
- CoRE – No Historical Data
- CoRE – Uses *only* Structural Data (CoRE Selection)
- CoRE – Uses *only* Structural Data (Random Selection)



# Hepatotoxicity Simulation Results

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- RandomForest – Uses *only* HCS Results
- CoRE – No Historical Data
- CoRE – Uses *only* Structural Data (CoRE Selection)
- CoRE – Uses *only* Structural Data (Random Selection)



# Hepatotoxicity Study Open Questions

1. What is the effect of extra data from previous studies on prediction accuracy?
2. What is the effect of using compound features only during predictions on prediction accuracy?
- 3. Can we effectively prioritize assays to predict toxicity? What is the effect on prediction accuracy when assays are removed?**
- 4. What is the effect of utilizing neighboring compound and assay results on prediction accuracy?**



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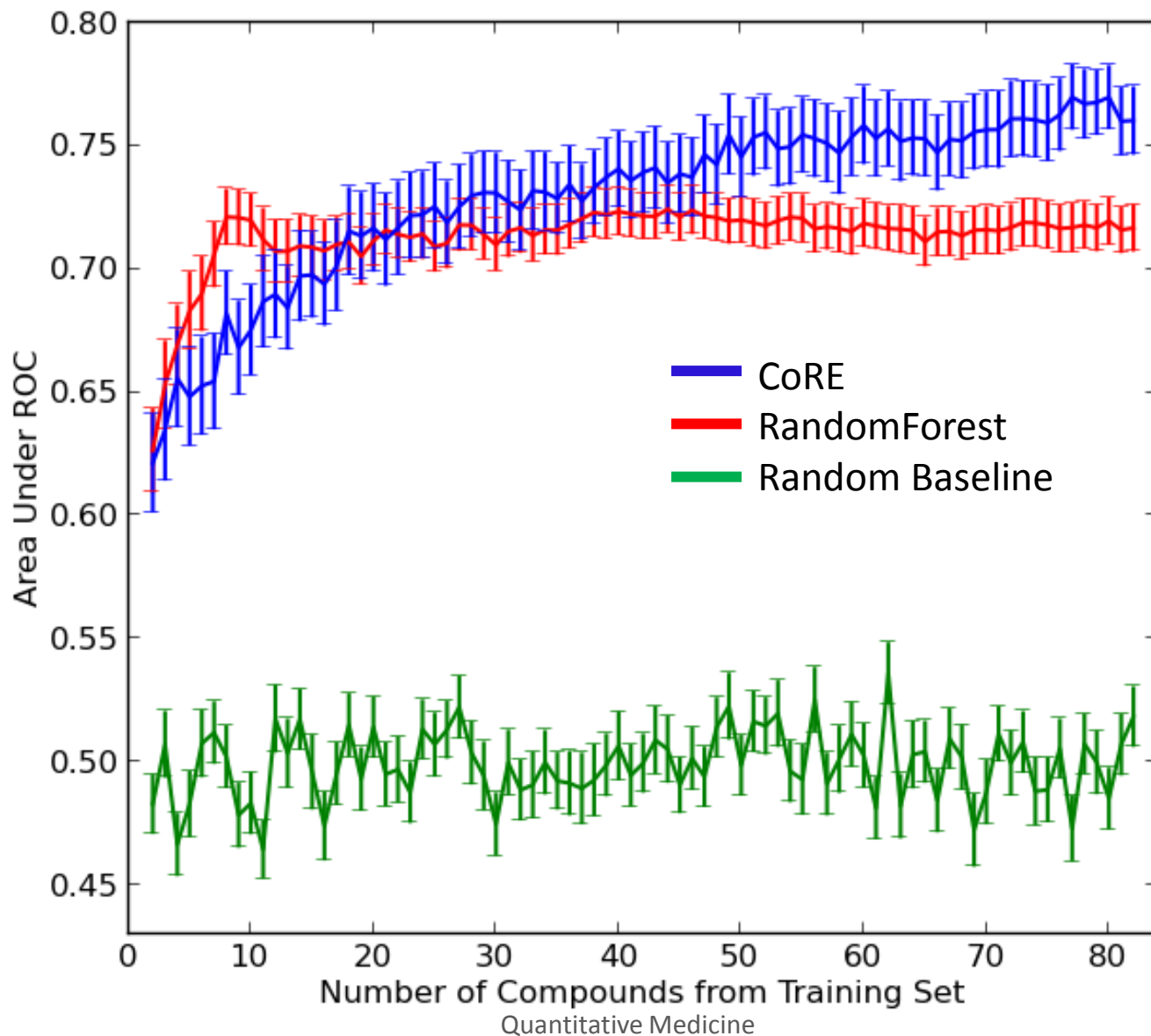
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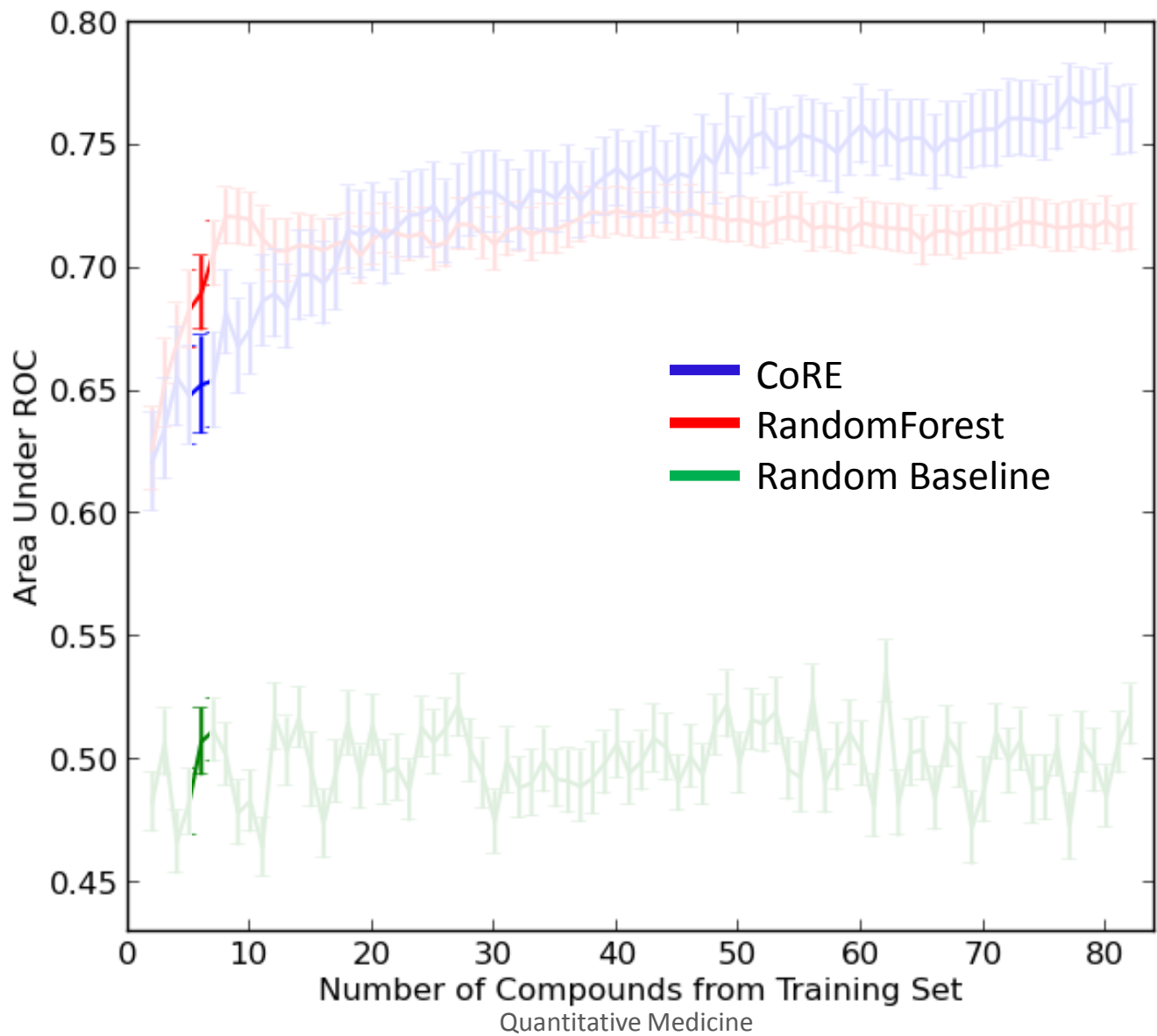
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# Hepatotoxicity Simulation Results

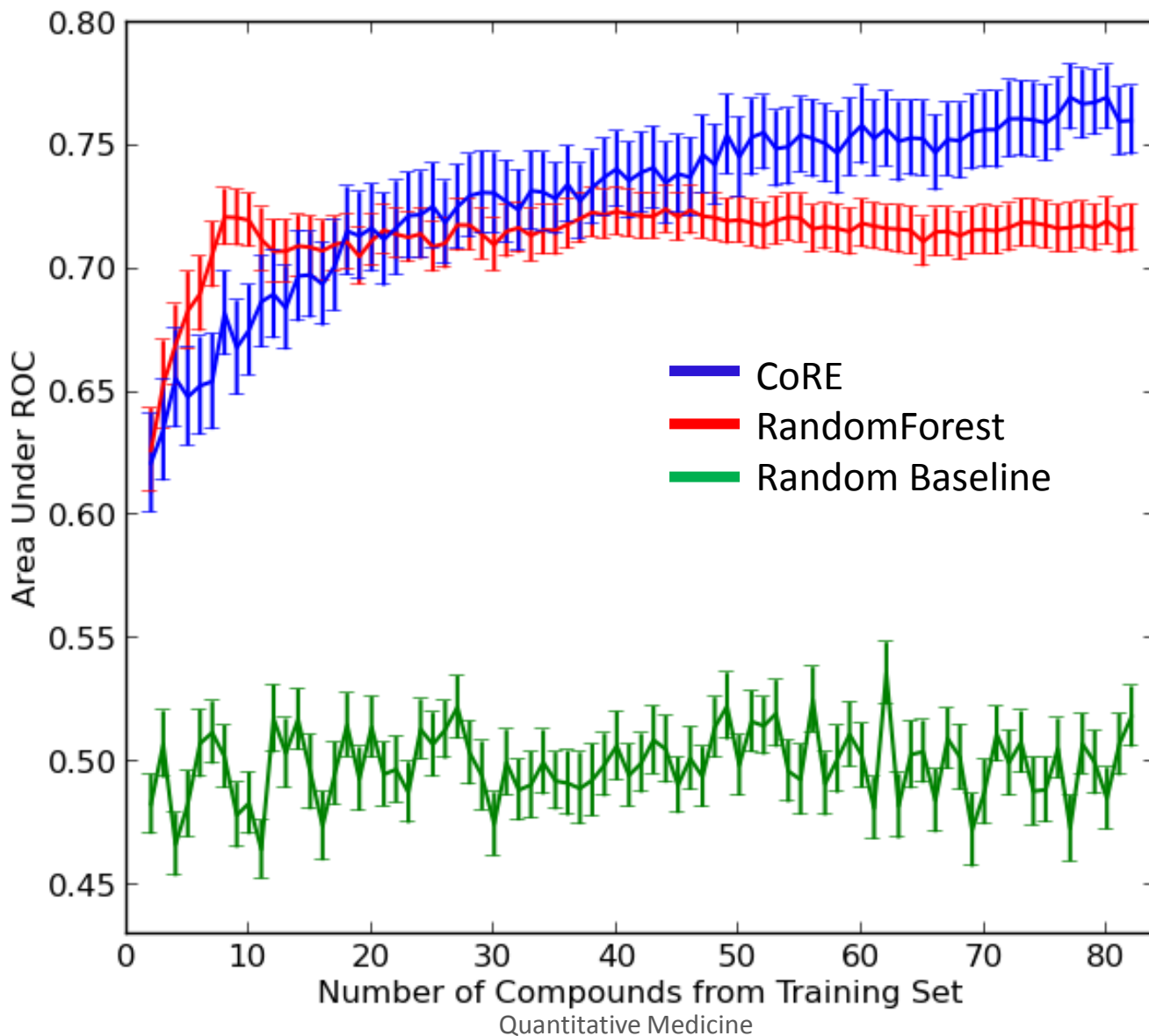


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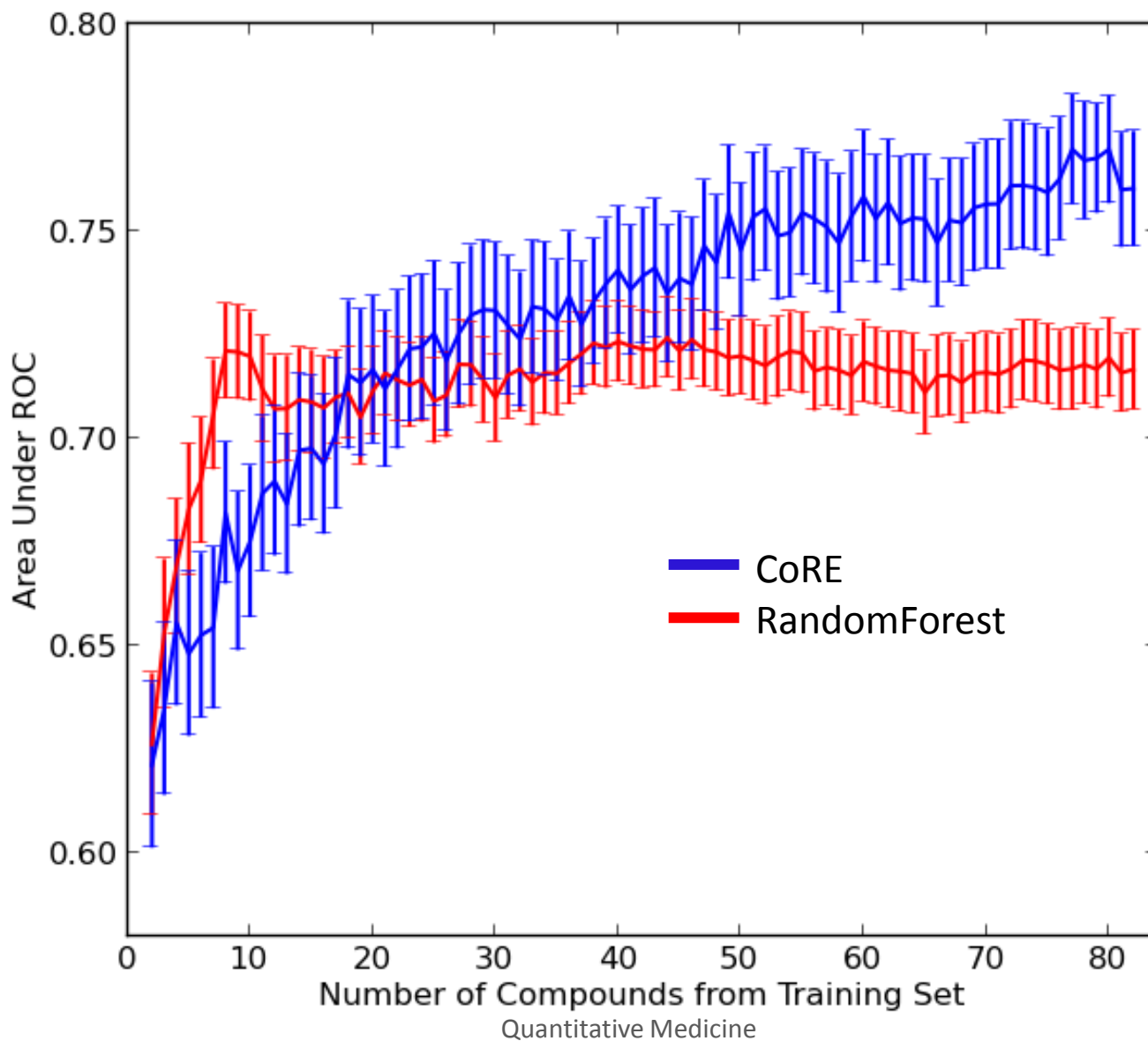




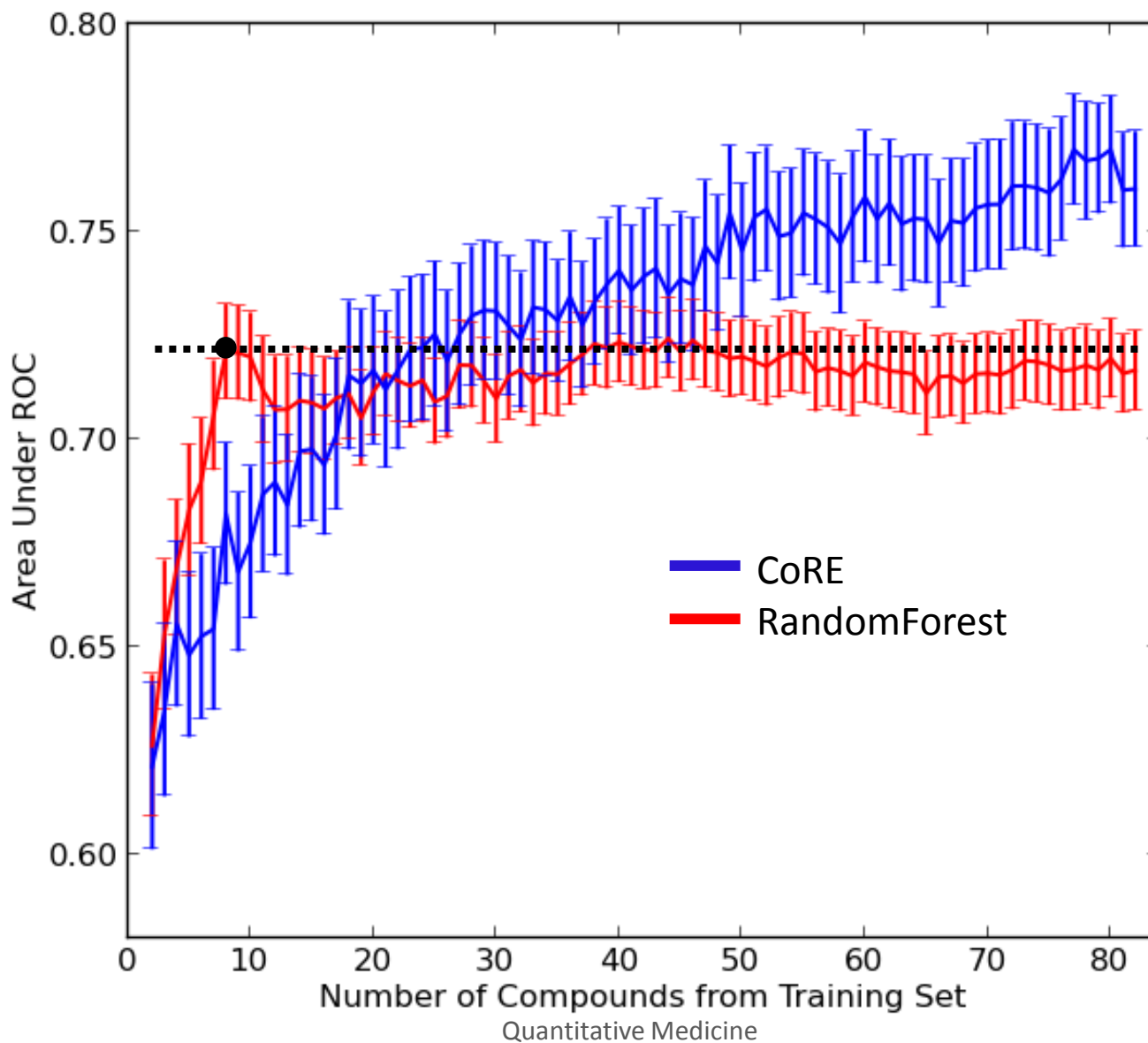
# Hepatotoxicity Simulation Results



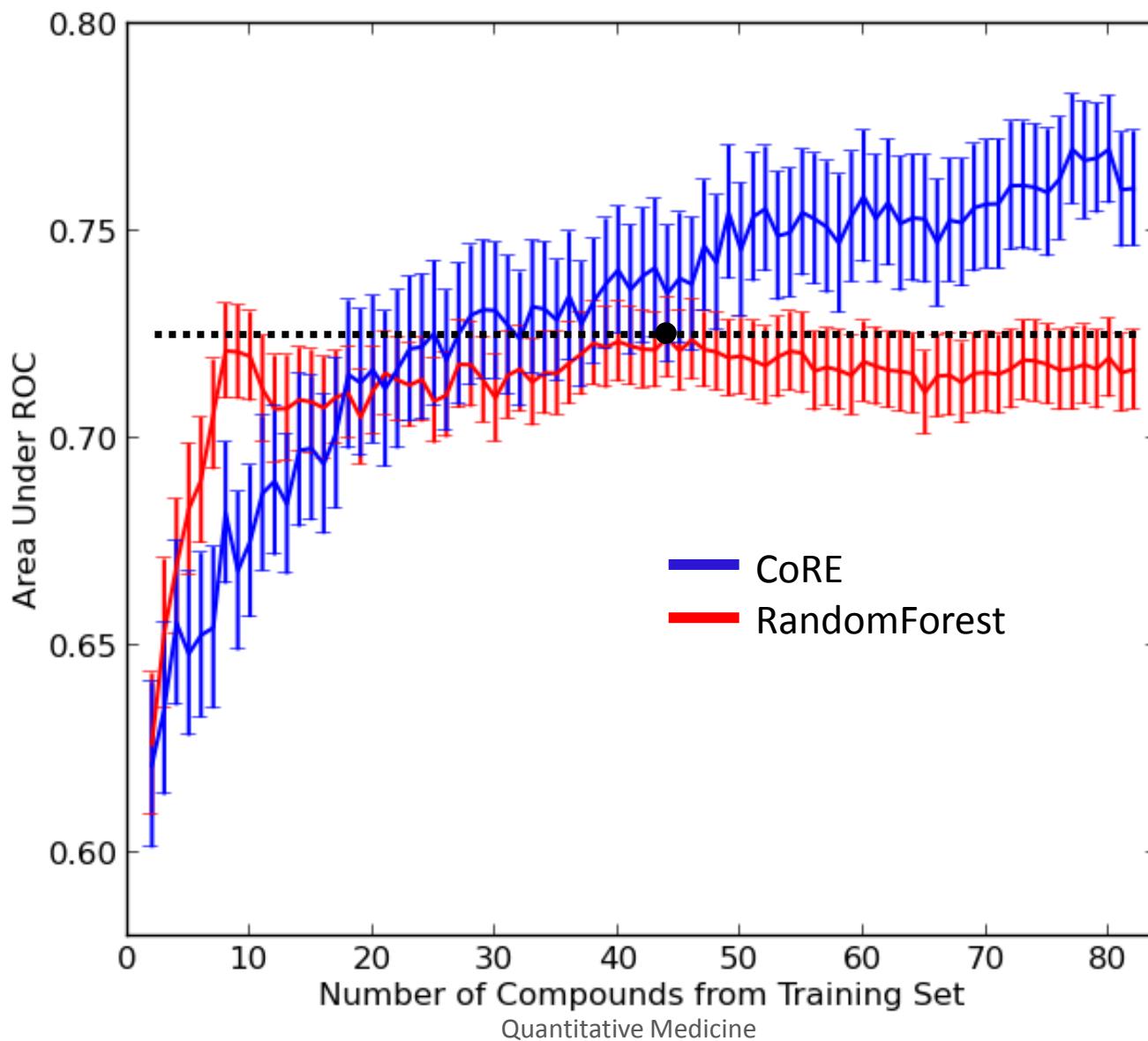
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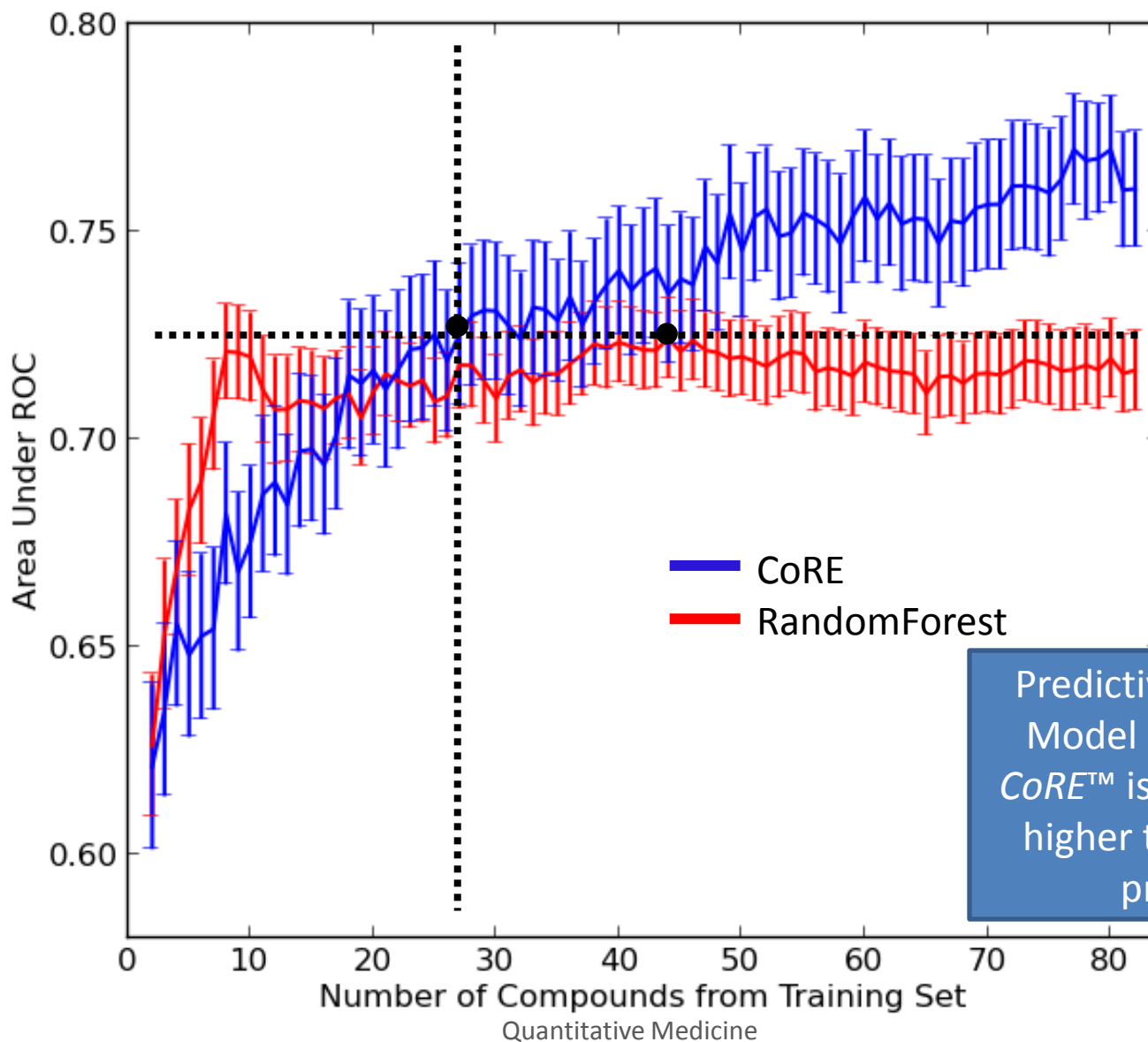
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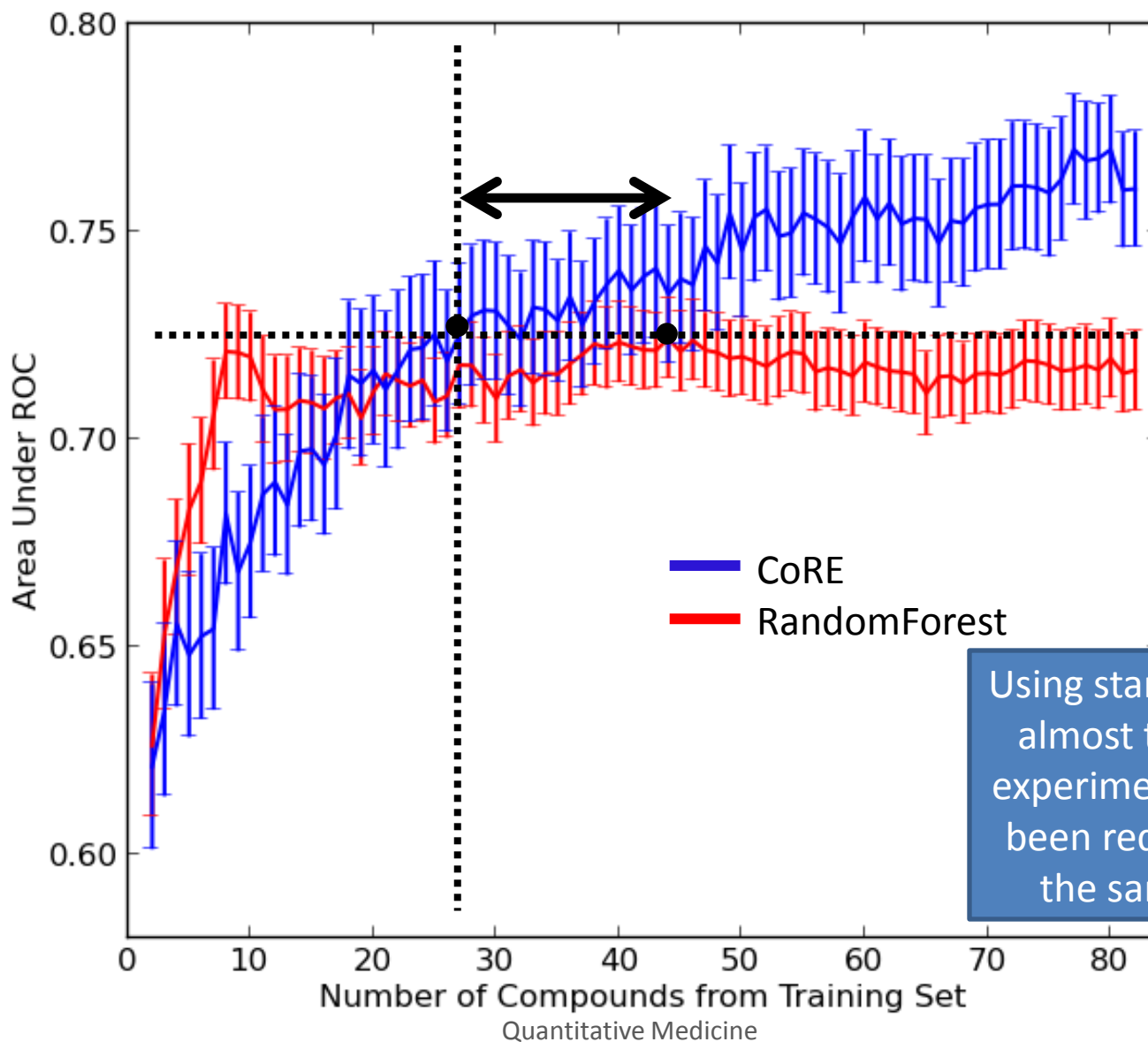


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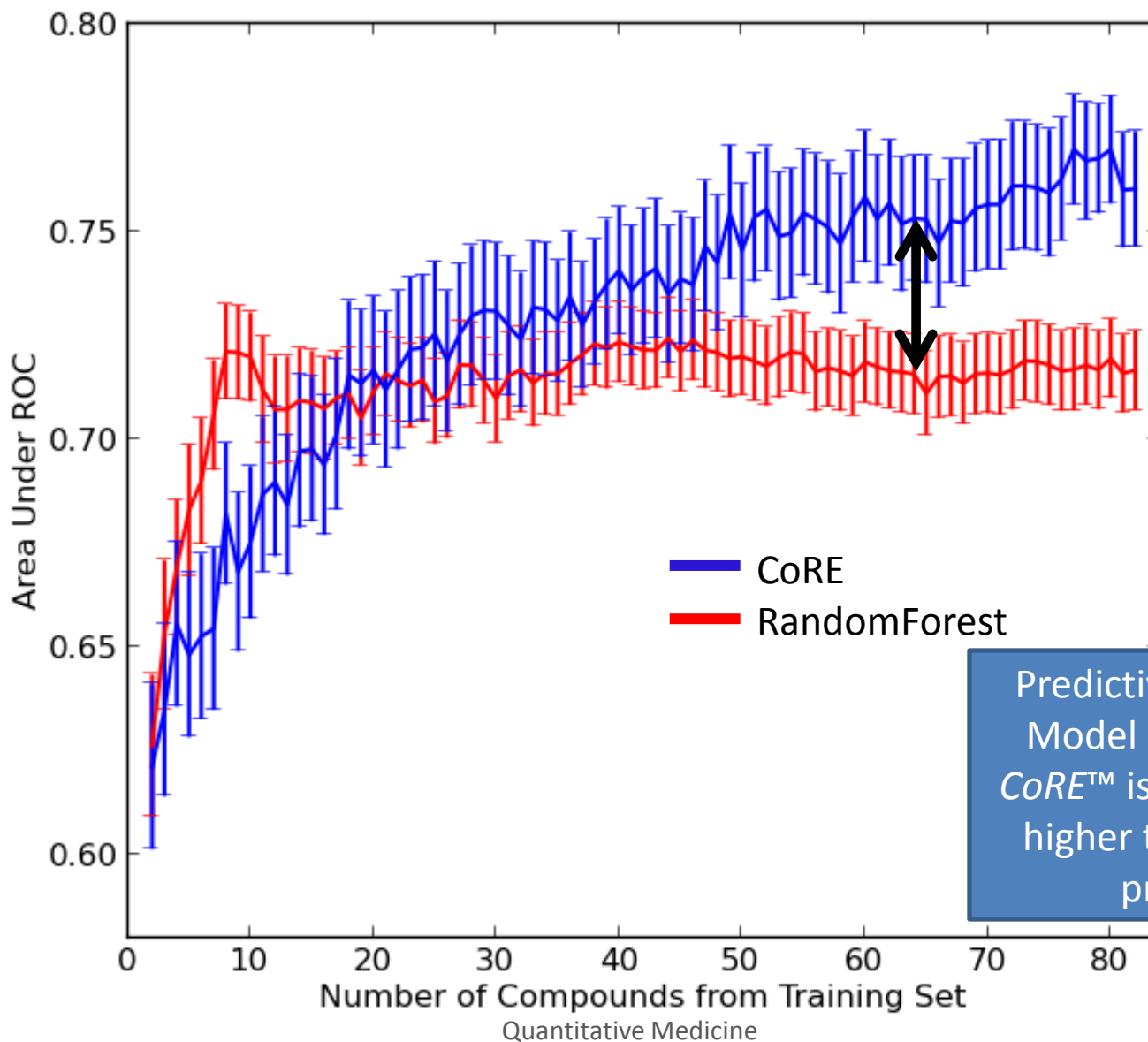
Predictive accuracy of Model learned using *CoRE*™ is in expectation higher than standard practices.

# Hepatotoxicity Simulation Results



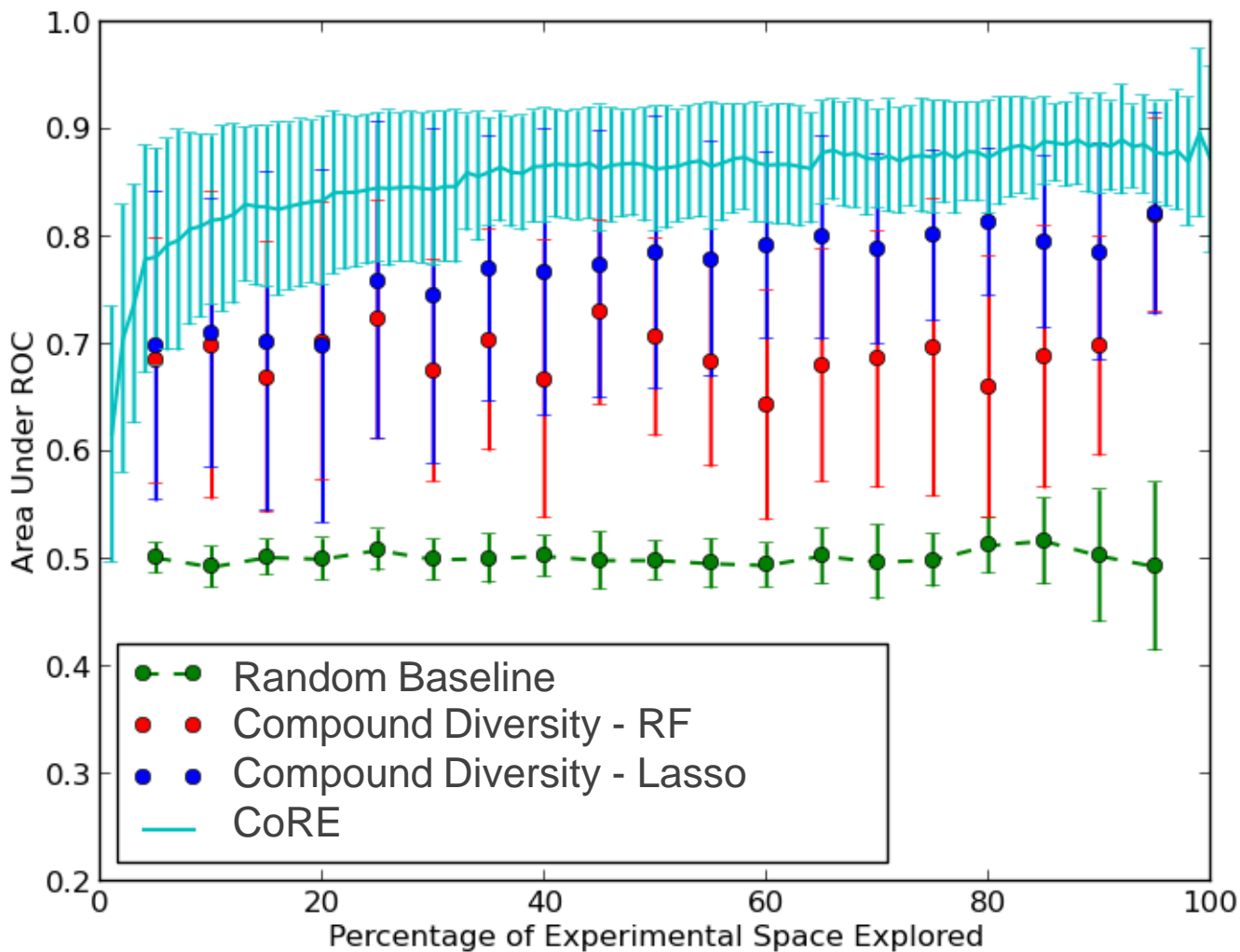
Using standard methods, almost twice as many experiments would have been required to reach the same accuracy.

# Hepatotoxicity Simulation Results



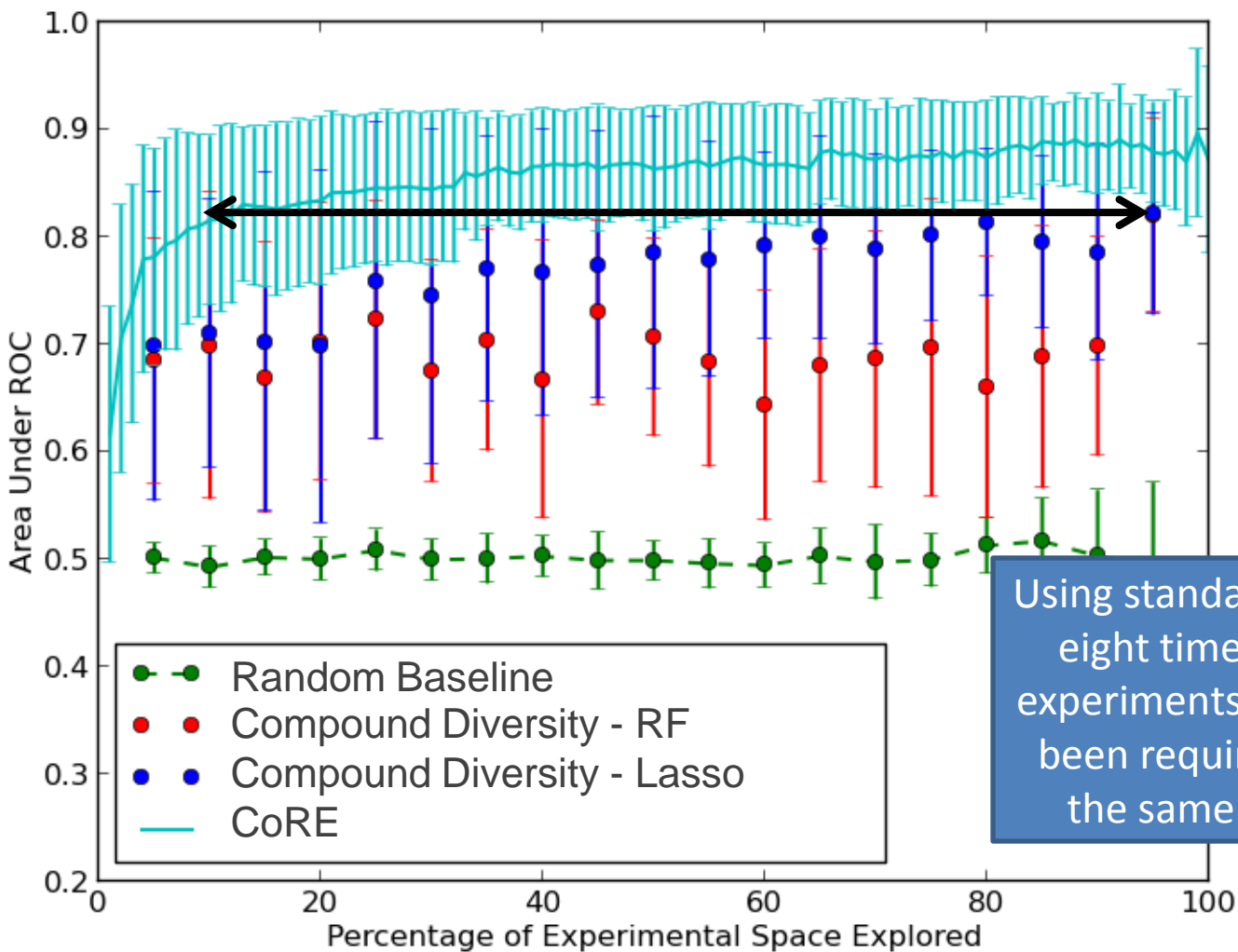
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# ToxCast Simulation Results





# ToxCast Simulation Results



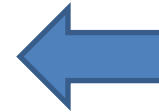
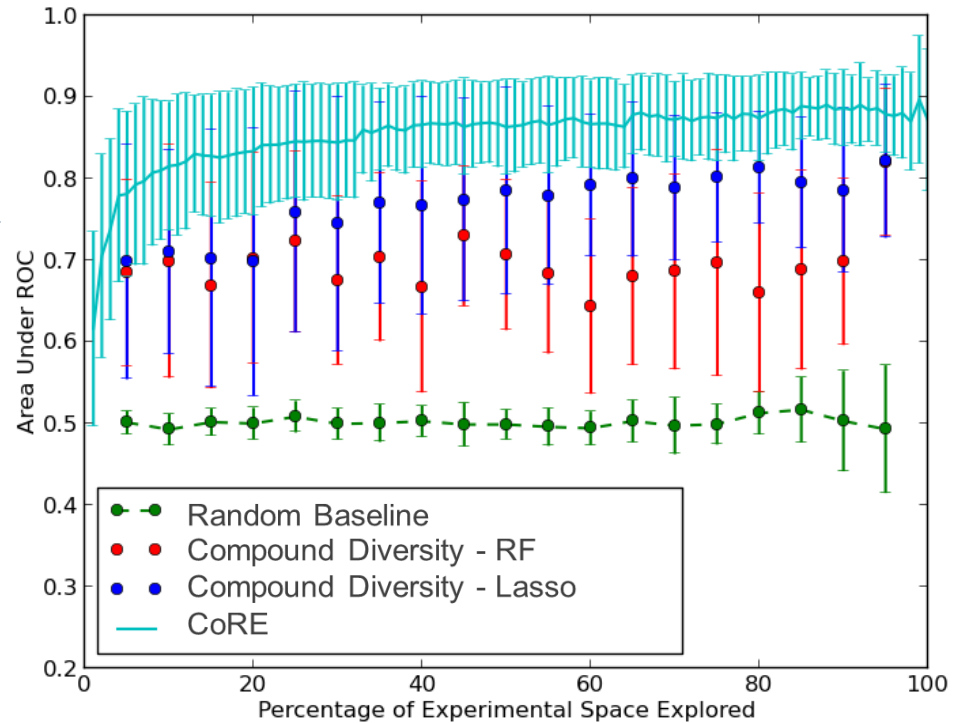
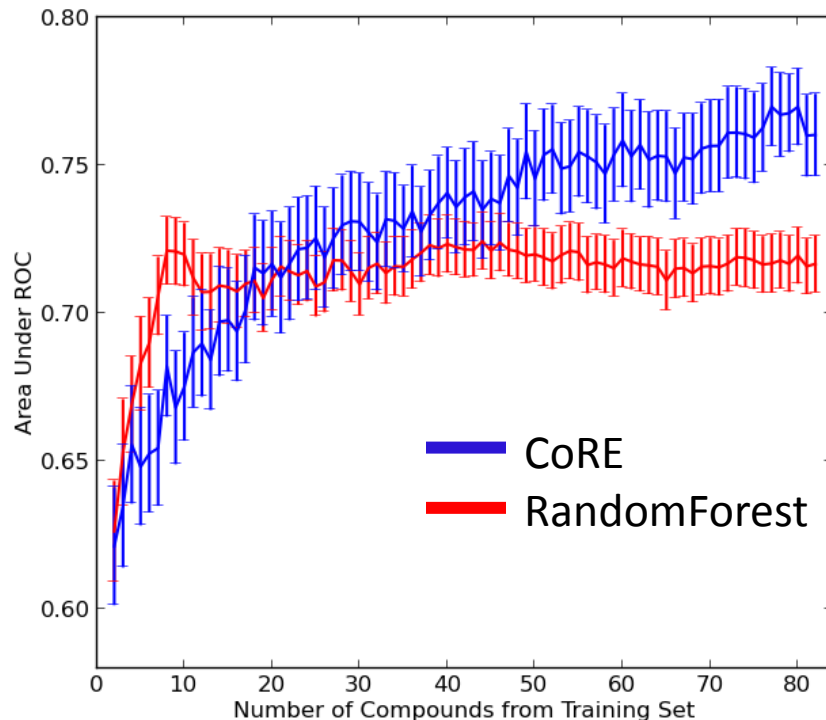
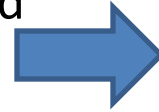
Using standard methods, eight times as many experiments would have been required to have the same accuracy.

# Comparison with Similar Simulations

## ToxCast

**Goal:** Predict all unobserved results in ToxCast

- 1200 assays
- 309 compounds



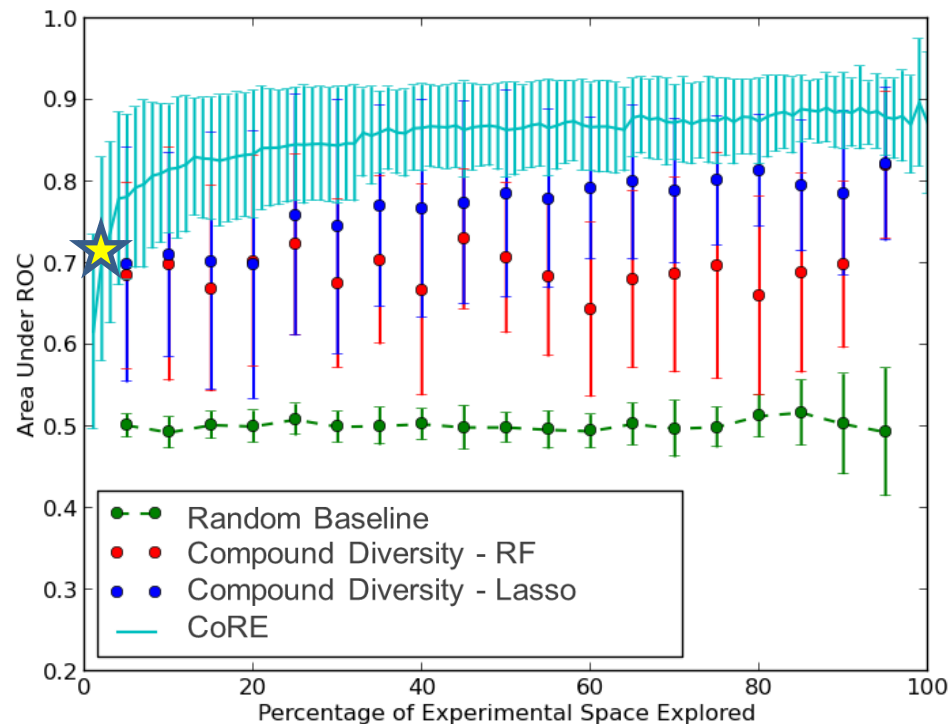
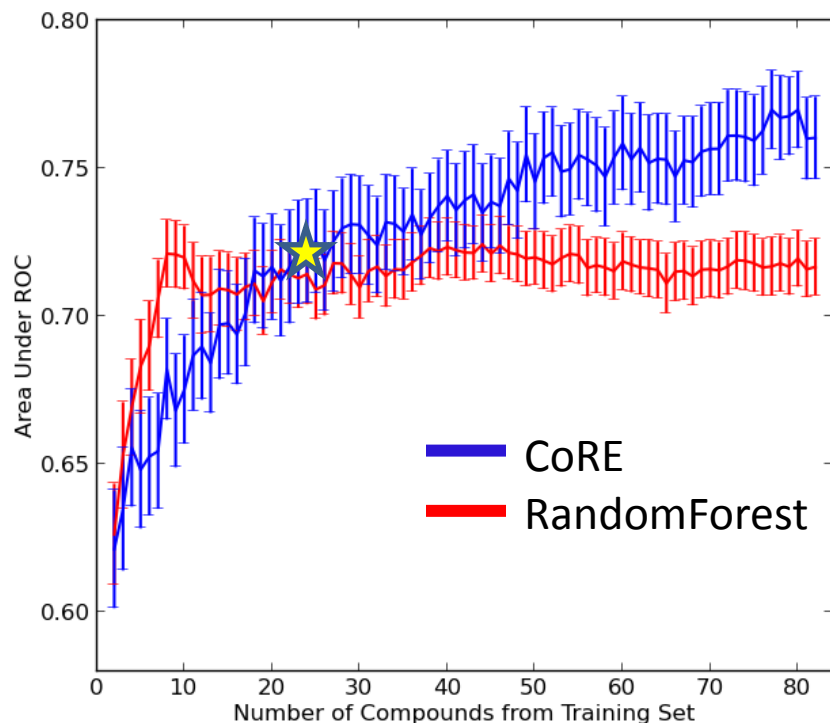
## Current Study

**Goal:** Predict toxicity

- 8 observations
- 105 compounds

# Comparison with Similar Simulations

What caused the difference in cross-over points?

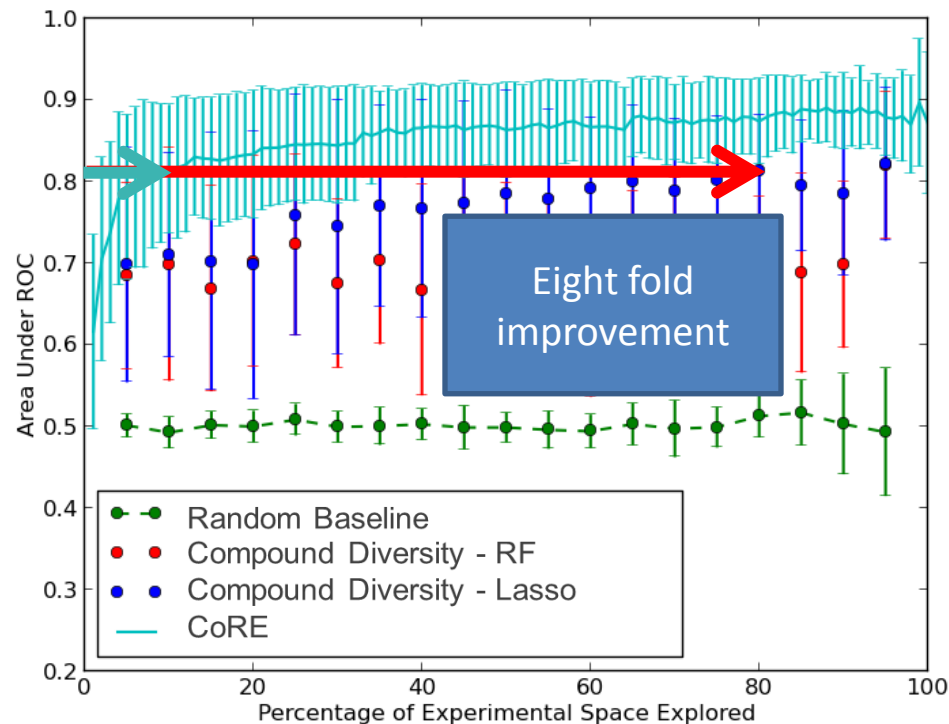
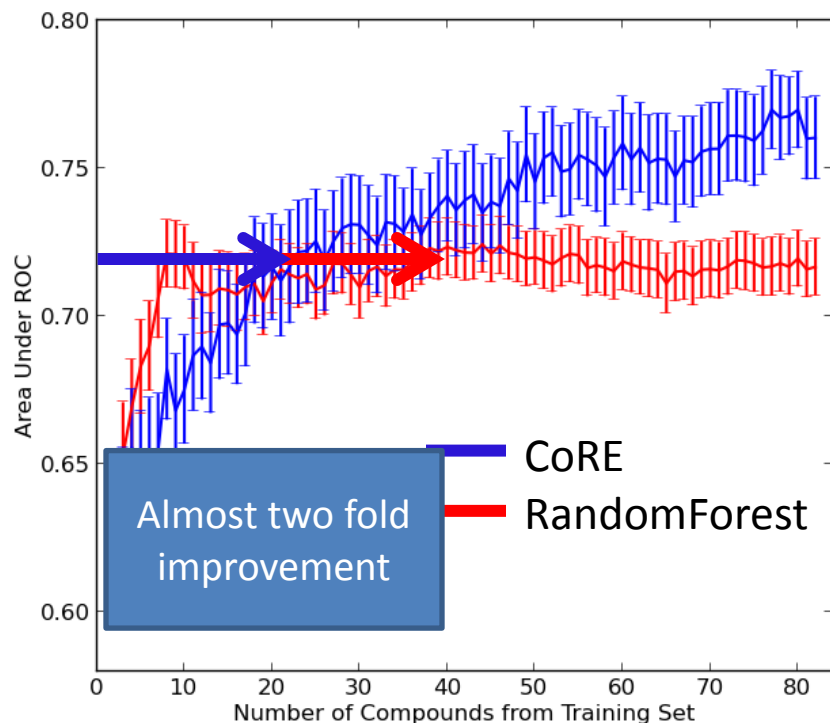


## Potential Explanations:

- Quality of data
- Selection of compounds
- Dimensionality of experimental space
  - PubChem: 1200 measurements, 309 compounds
  - Current 8 measurements, 105 compounds

# Comparison with Similar Simulations

What cause the difference in the fraction of experiments required to reach maximum accuracy?



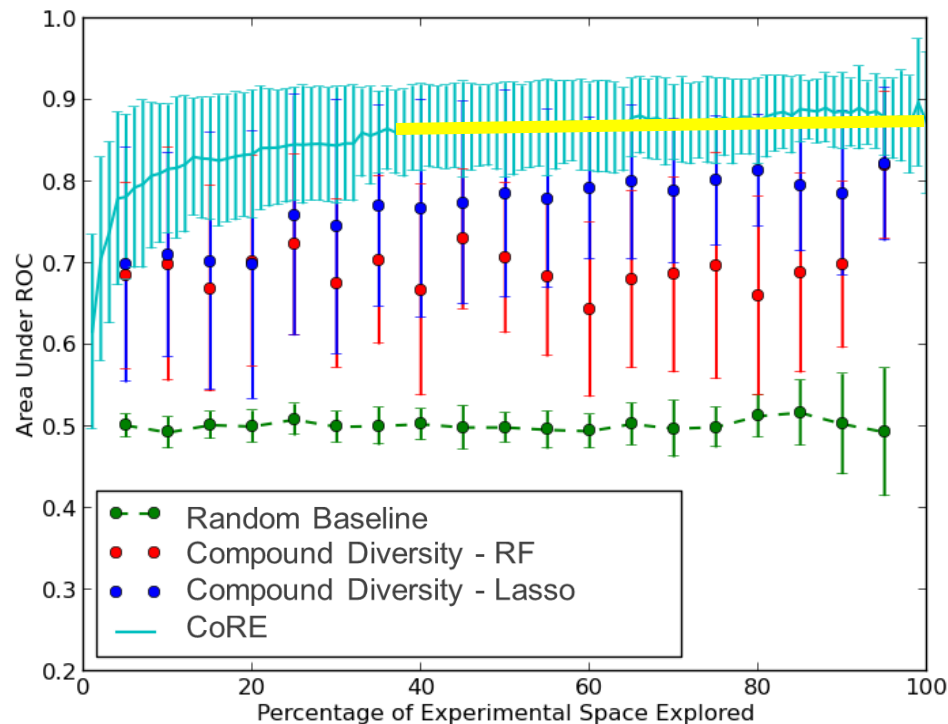
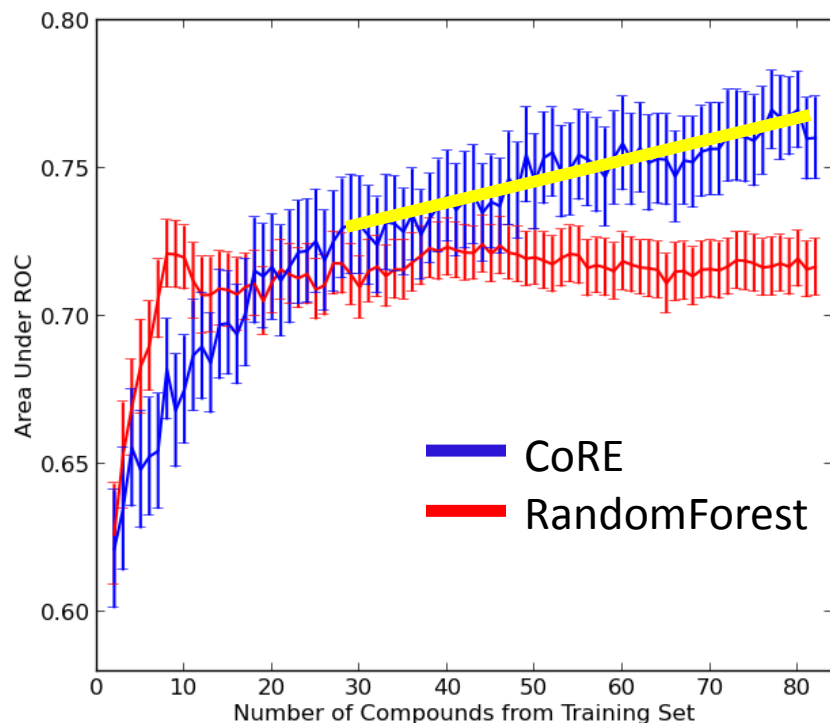
## Potential Explanations:

- Quality of data
- Selection of compounds
- Dimensionality of experimental space
  - PubChem: 1200 measurements, 309 compounds
  - Current 8 measurements, 105 compounds

# Comparison with Similar Simulations

Why does accuracy in this study improve continuously?

What is the upper achievable limit to toxicity prediction accuracy?



## Potential Explanation:

- Dimensionality of experimental space
  - PubChem: 1200 measurements, 309 compounds
  - Current 8 measurements, 105 compounds

# Prospective Uses of *CoRE*<sup>TM</sup> Model

- For a single compound:
  - **More accurately predict the toxicity**
  - Prioritize toxicology assays to most effectively eliminate compounds (faster-to-fail)
  - Find multiple targets for drug discovery
- For multiple compounds:
  - **Prioritize compounds for further testing**
  - **Select experiments to effectively expand the predictions to new areas of chemical space**
- For multiple assays:
  - Prioritize assays based on human toxicity predictivity

## Next Studies?

- Prospective study
- Retrospective polypharmacology study
- Extend Retrospective toxicity study:
  - More compounds
  - More assays
  - More toxicities



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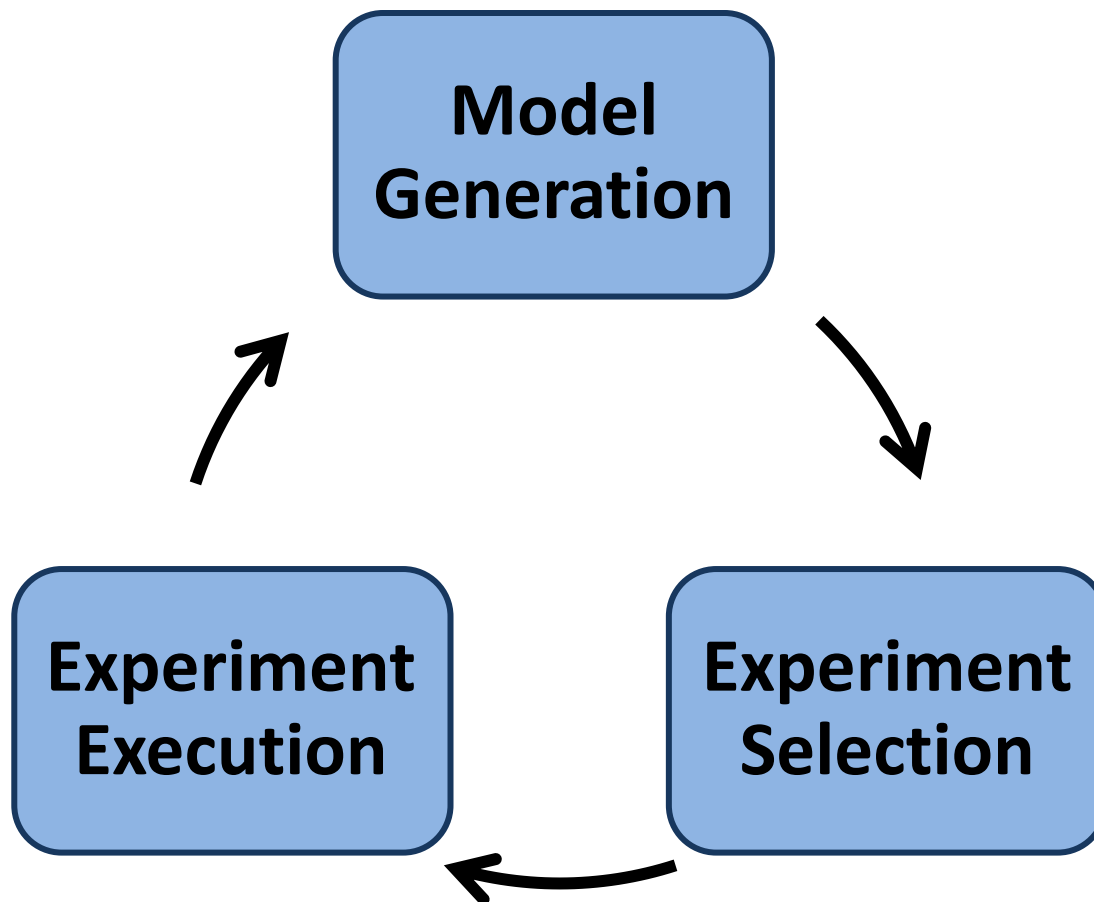
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# Active Learning Cycle



# CoRE™ Directed Study Types

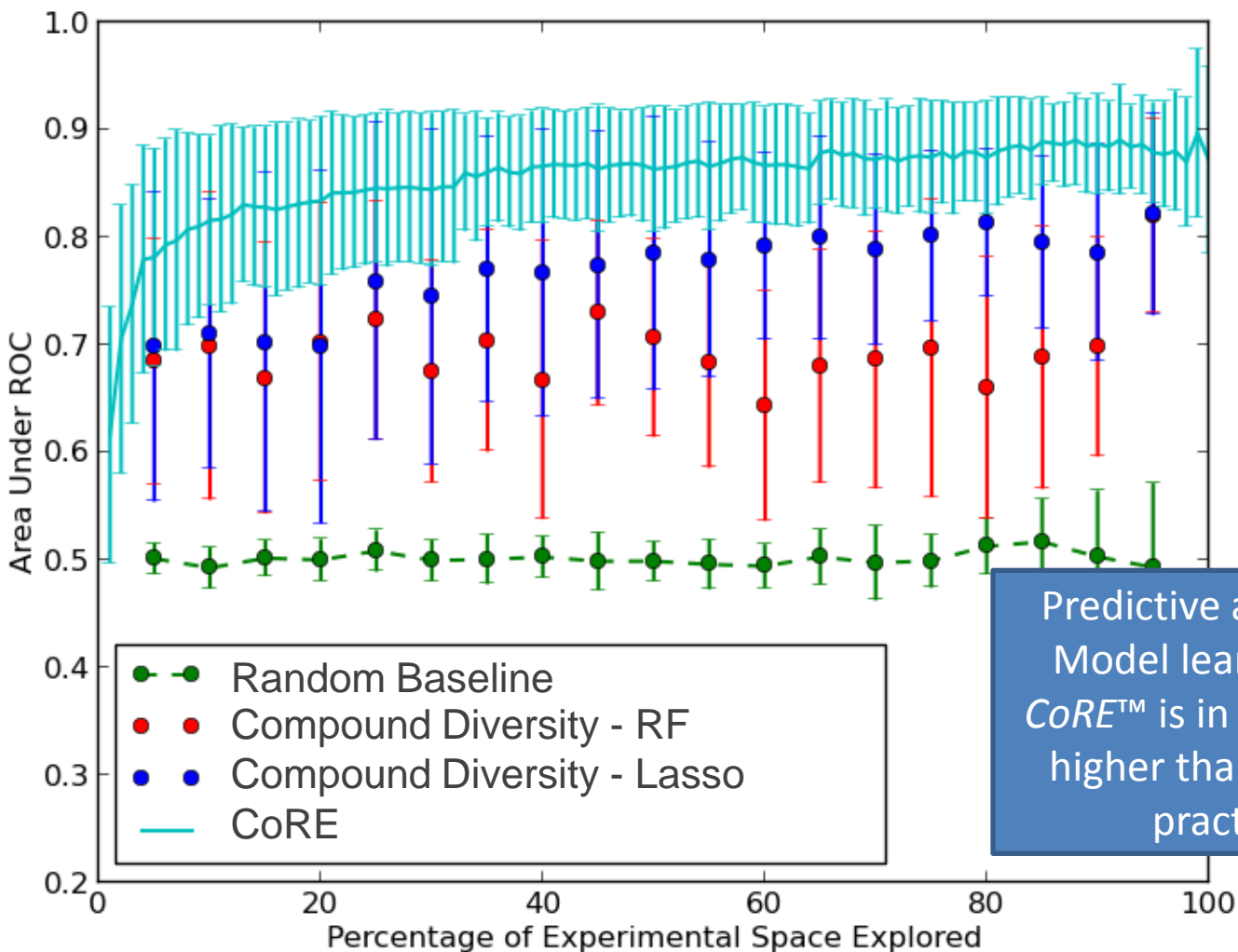
## Retrospective

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

## Prospective

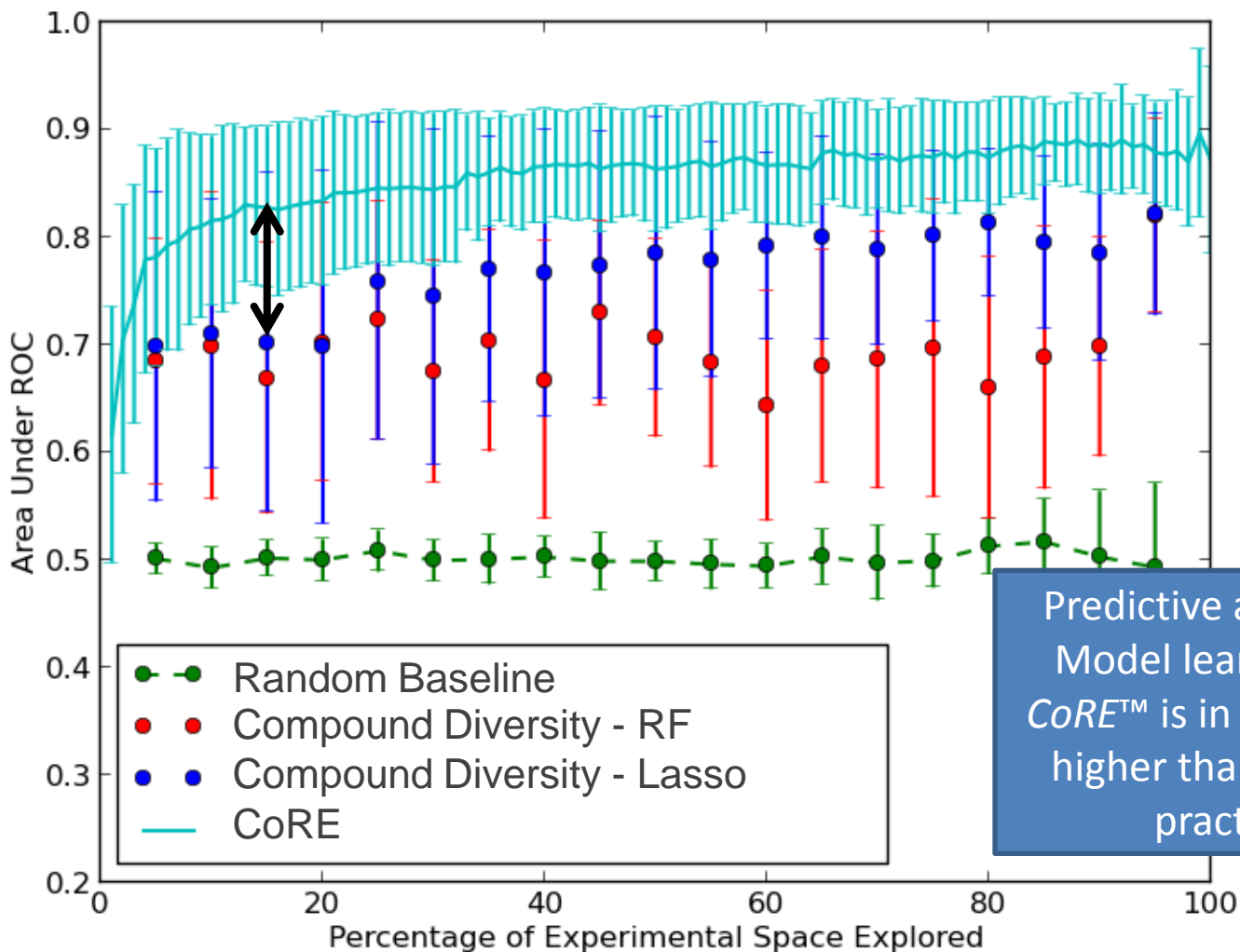
- Experiments Directed as Selected
- Yield *actual* improvements in accuracy and efficiency
- Likely to discover new useful knowledge through directed experimentation **and** CoRE™ analytics

# ToxCast Simulation Results



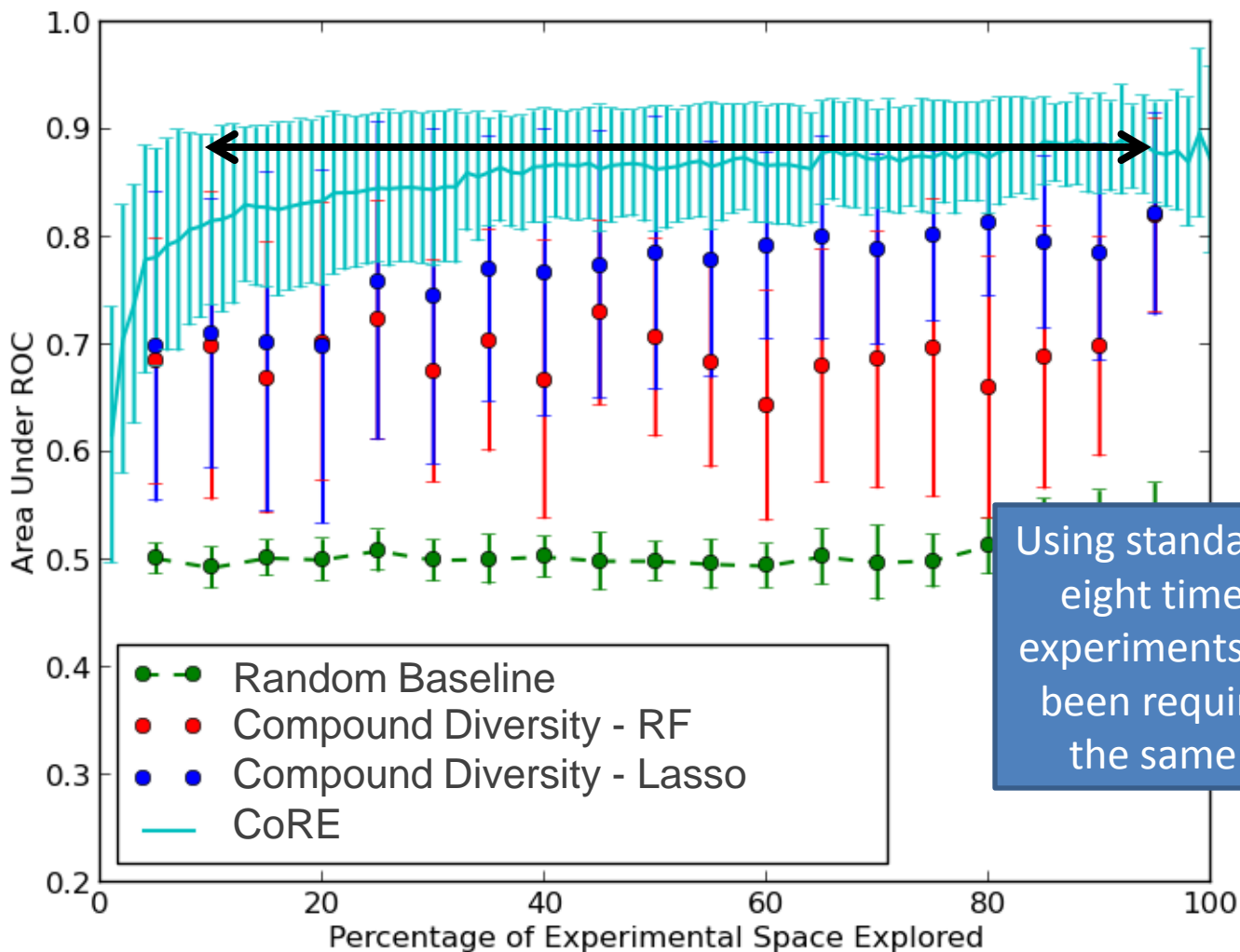
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