QUANTITATIVE MEDICINE

Transforming Drug Discovery™

Technical Discussion

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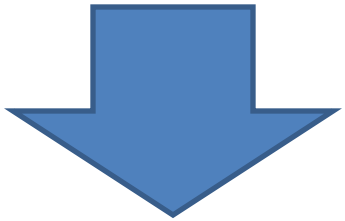
Active Learning System Name Change

Analytics **F**ocused **R**esearch **S**ystem (*AFRS*™)



Computational **R**esearch **E**ngine (*CoRE*™)

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Agenda

- Assay Prioritization Study Overview
- Assay Prioritization Results
- Next Steps

Assay Prioritization

- Can we prioritize assays for testing to be used to predict certain types of toxicity?

ToxCast Data

- Total Assays: 1197
  - ACEA – change in cell growth kinetics
  - AttaGene – reporter gene assay
  - BioSeek - ELISA
  - Cellumen - HCS
  - CellzDirect – change in expression levels
  - GenTronix – *in vitro* measure of growth arrest
  - NCGC - reporter gene assay
  - NovaScreen – enzyme inhibition assays
  - Solidus – Microarray?
  - **ToxRefDB – Many toxicity measures**

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Toxicities of Interest (39):
Liver (15 assays)
Central Nervous System (14)
Kidney (10)

Methodology

- Measure correlation between assay results and known toxicities
- Order assays by correlation with known toxicities
- For each toxicity, build models with increasing numbers of assays
- Check accuracy of models for each assay set using cross-validation
- Select the top *n* assays which yield minimum error.

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Relevant Assays Discovered

Nervous System Toxicity	Relevant Assays
DEV_rabbit_Developmental_Neurosensory_Brain	7
DEV_rat_Developmental_Neurosensory_Brain	9
CHR_Mouse_Brain_1_AnyLesion	0
CHR_Mouse_Brain_2_PreneoplasticLesion	0
CHR_Mouse_Brain_3_NeoplasticLesion	0
CHR_Mouse_Nerve_1_AnyLesion	0
CHR_Mouse_Nerve_2_PreneoplasticLesion	0
CHR_Mouse_Nerve_3_NeoplasticLesion	0
CHR_Rat_Brain_1_AnyLesion	0
CHR_Rat_Brain_2_PreneoplasticLesion	0
CHR_Rat_Brain_3_NeoplasticLesion	0
CHR_Rat_Nerve_1_AnyLesion	0
CHR_Rat_Nerve_2_PreneoplasticLesion	0
CHR_Rat_Nerve_3_NeoplasticLesion	0

Liver Toxicity	Relevant Assays
CHR_Mouse_Liver_1_AnyLesion	1
CHR_Mouse_LiverNecrosis	2
CHR_Rat_Liver_1_AnyLesion	2
CHR_Rat_LiverHypertrophy	2
CHR_Rat_LiverTumors	7
CHR_Rat_Liver_3_NeoplasticLesion	9
CHR_Rat_LiverProliferativeLesions	10
CHR_Rat_Liver_2_PreneoplasticLesion	18
CHR_Mouse_Liver_2_PreneoplasticLesion	0
CHR_Mouse_Liver_3_NeoplasticLesion	0
CHR_Mouse_LiverHypertrophy	0
CHR_Mouse_LiverProliferativeLesions	0
CHR_Mouse_LiverTumors	0
CHR_Rat_LiverNecrosis	0
MGR_Rat_Liver	0

Only 56 of 734 assays relevant for these three toxicities!

Kidney Toxicity	Relevant Assays
CHR_Rat_KidneyNephropathy	2
CHR_Rat_KidneyProliferativeLesions	2
CHR_Rat_Kidney_2_PreneoplasticLesion	3
CHR_Mouse_Kidney_3_NeoplasticLesion	5
CHR_Mouse_Kidney_1_AnyLesion	0
CHR_Mouse_Kidney_2_PreneoplasticLesion	0
CHR_Mouse_KidneyPathology	0
CHR_Rat_Kidney_1_AnyLesion	0
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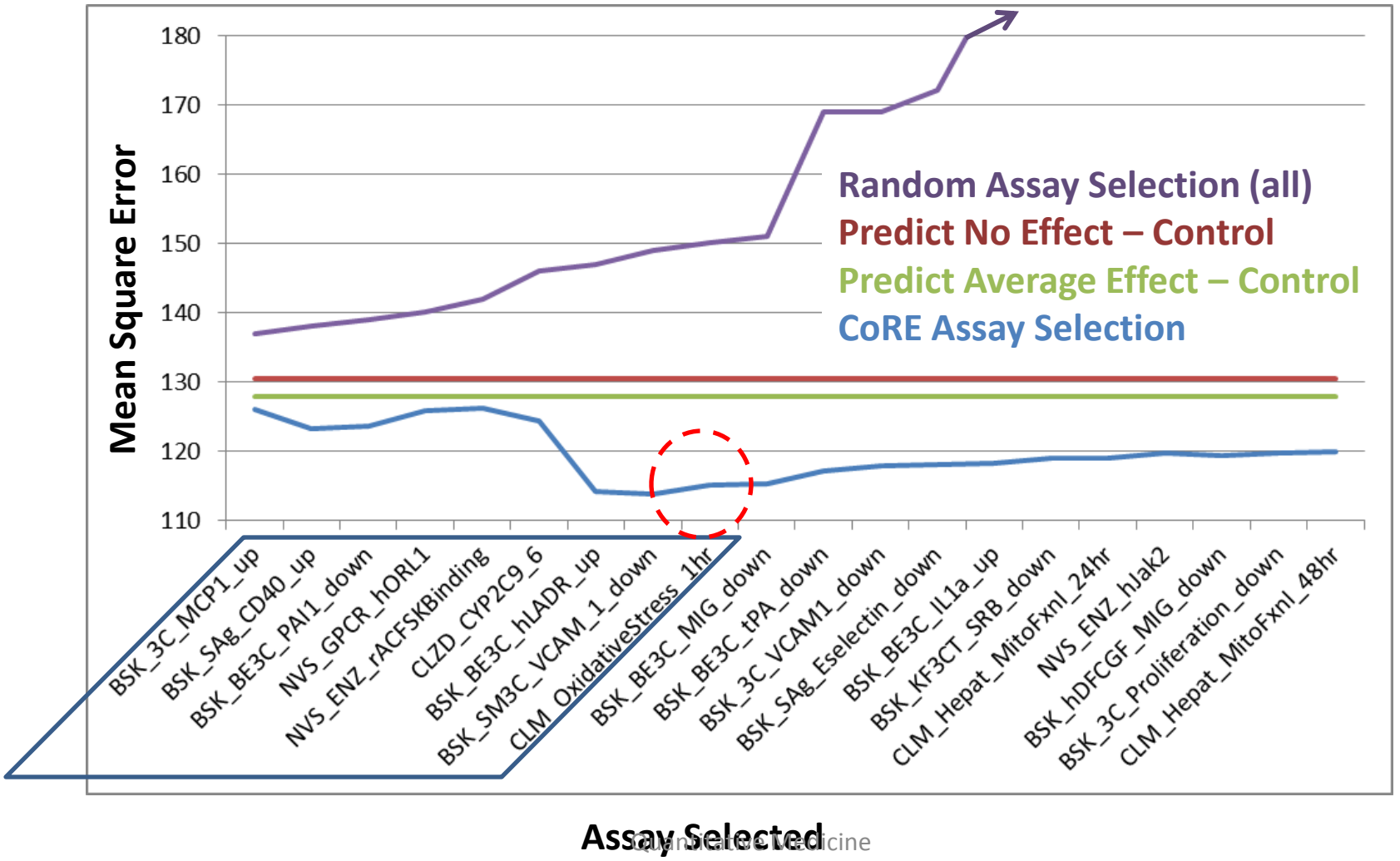
Error of Predictions with Selected Assays

DEV_rat_Developmental_Neurosensory_Brain



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Relevant ToxCast Data

- Total Assays: 1197 **(56/734 relevant to prediction)**
  - ~~ACEA – change in cell growth kinetics~~
  - AttaGene – reporter gene assay **(5/73 relevant)**
  - BioSeek – ELISA **(21/174)**
  - Cellumen – HCS **(7/57 relevant)**
  - CellzDirect – change in expression levels **(*7/42*)**
  - ~~GenTronix – *in vitro* measure of growth arrest~~
  - NCGC - reporter gene assay **(1/19)**
  - NovaScreen – enzyme inhibition assays **(15/292)**
  - ~~Solidus – Microarray?~~
  - **ToxRefDB – Many toxicity measures**

Results and Next Steps

- We have shown:
  - Effective prioritization of assays for predicting toxicity
    - Use – After synthesizing a new compound, save time and experimental effort in predicting toxicity.
  - Effective prioritization of experimentation for learning an accurate predictive model (80-90% reduction in experimentation to reach maximum accuracy)
    - Use – When running experiments to learn a predictive model for toxicity, use *CoRE™* to guide experimentation to only the most informative experiments saving cost and time.
- We want to demonstrate to you:
  - Combining these two approaches can yield significant savings in your experimental efforts

Study Data and Deliverables

- Dataset:
  - Multiple assays and compounds
  - Known relationships
  - Useful to you
- Deliverables:
  - Prioritization of assays
  - Expected savings had you utilized *CoRE*™ to direct experimentation
  - Confirmatory experimentation?

Quantitative Medicine

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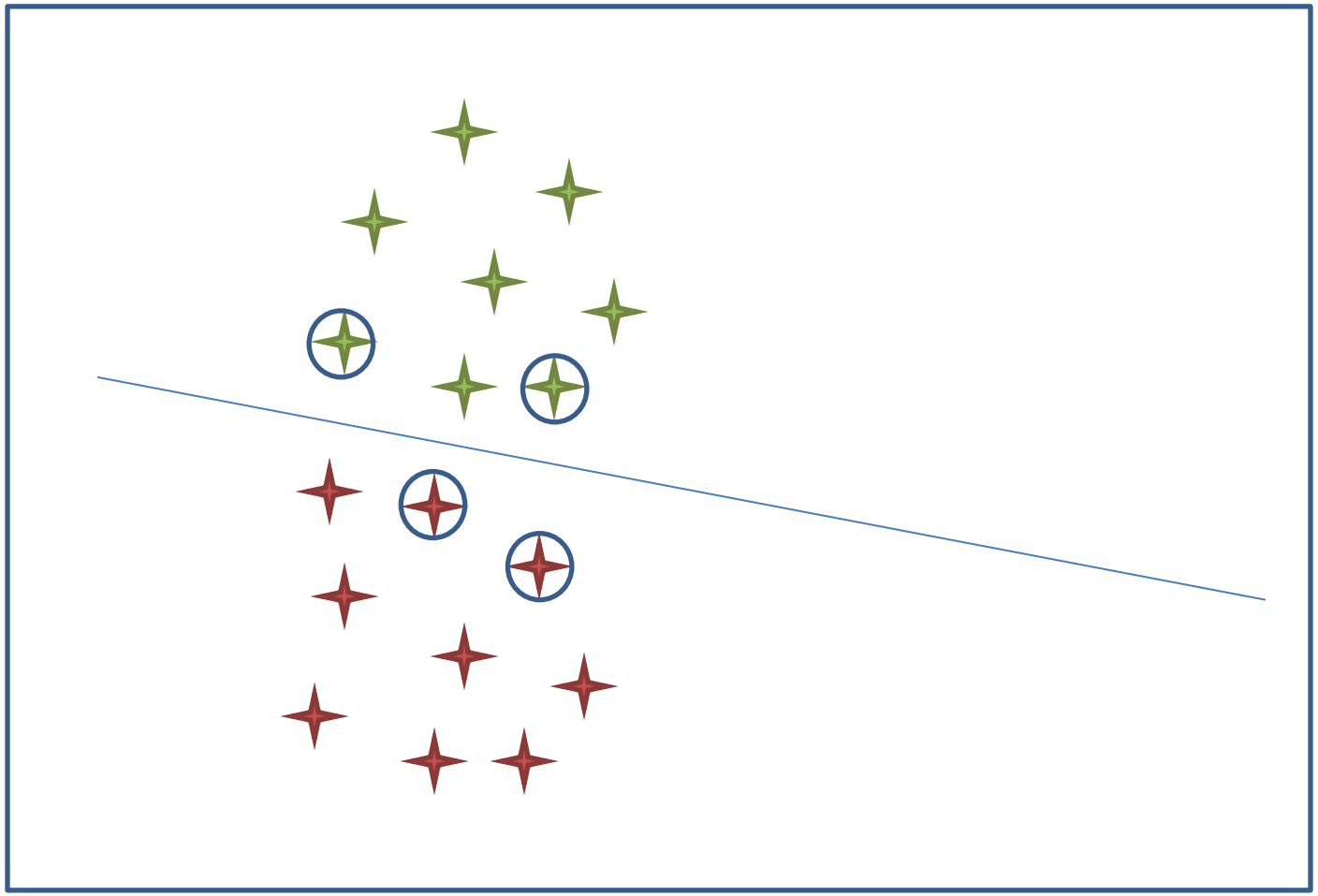
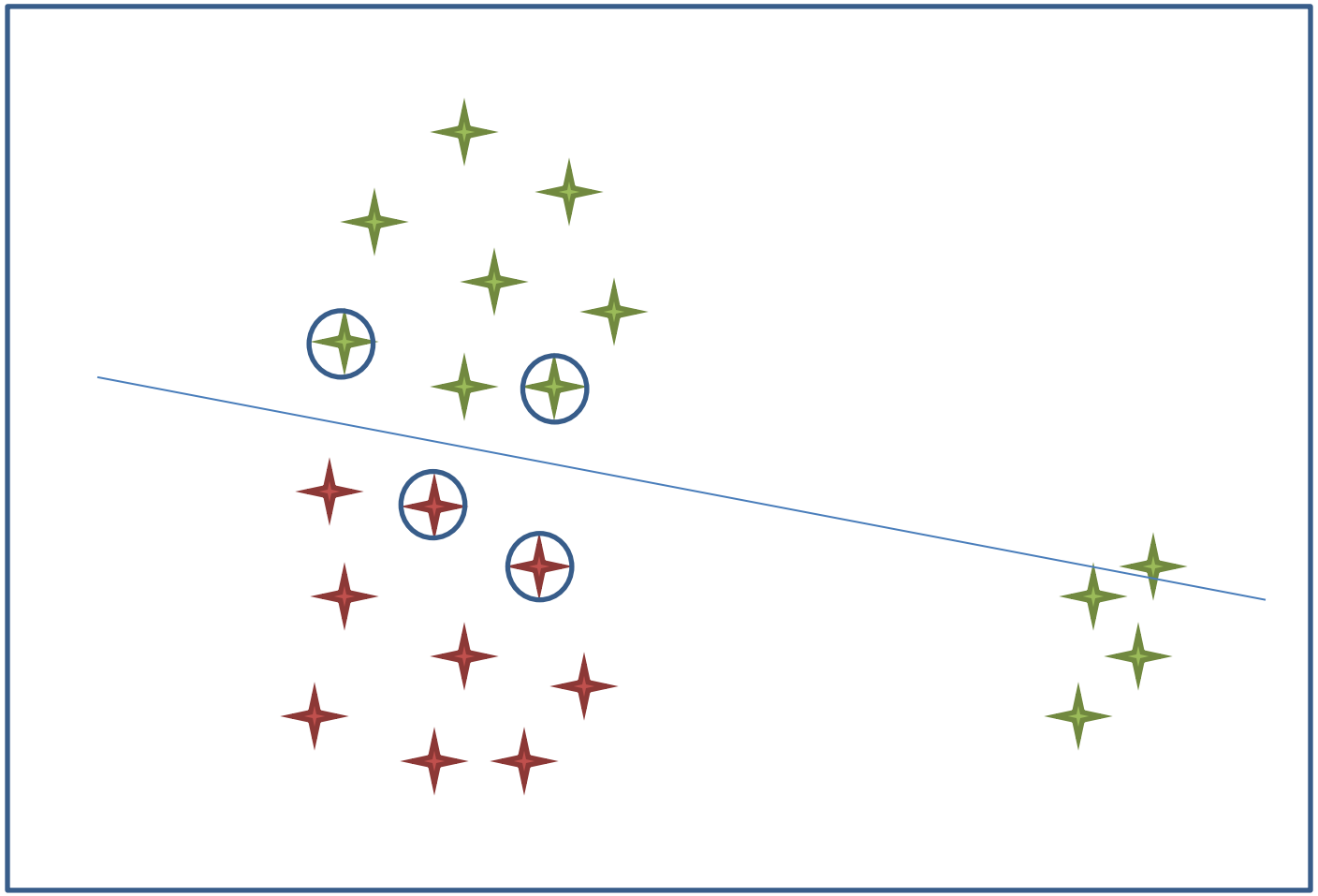
Build Predictive Model Using *CoRE*™



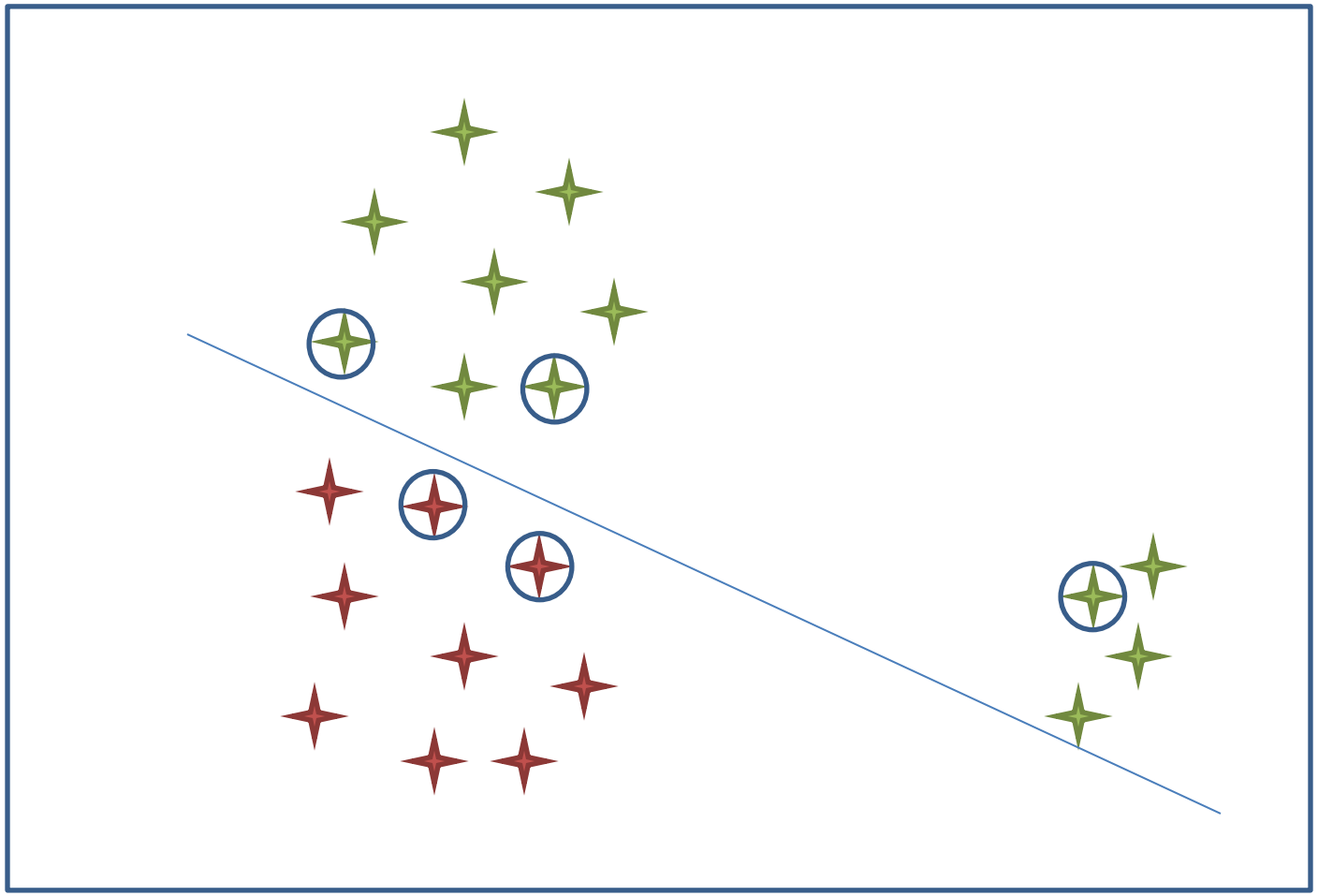
Chemical Space

Testing Predictive Model with New Compounds May Yield Poor Results



Chemical Space

A single iteration with *CoRE*™ can solve this problem immediately



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