Genomic Selection:
A Step Change in Plant Breeding

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Celebrating 100 Years of Crop Improvement

People who contributed to research in this presentation

- Jean-Luc Jannink – USDA/ARS, Cornell University
- Elliot Heffner – Pioneer Hi-Bred International
- Nicolas Heslot – Ph.D. Student, Cornell University
- Jessica Rutkoski - Ph.D. Student, Cornell University
- Julie Dawson – Post doc, Cornell University
- Jeff Endelman – Post doc, Cornell University

Presentation Overview

Genomic (Genome-Wide) Selection

- Characterizing GxE using marker effects
- Integration in a breeding program
- Biparental and Multi-Family predictions
- Recurrent Genomic Selection

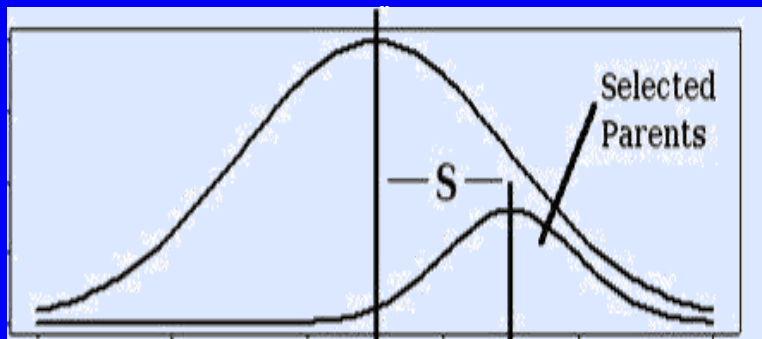
Molecular Breeding Goals

- Allele discovery
- Allele characterization & validation
- Parental & progeny selection for superior alleles at multiple loci to generate transgressive segregation

Increase response (R) from selection

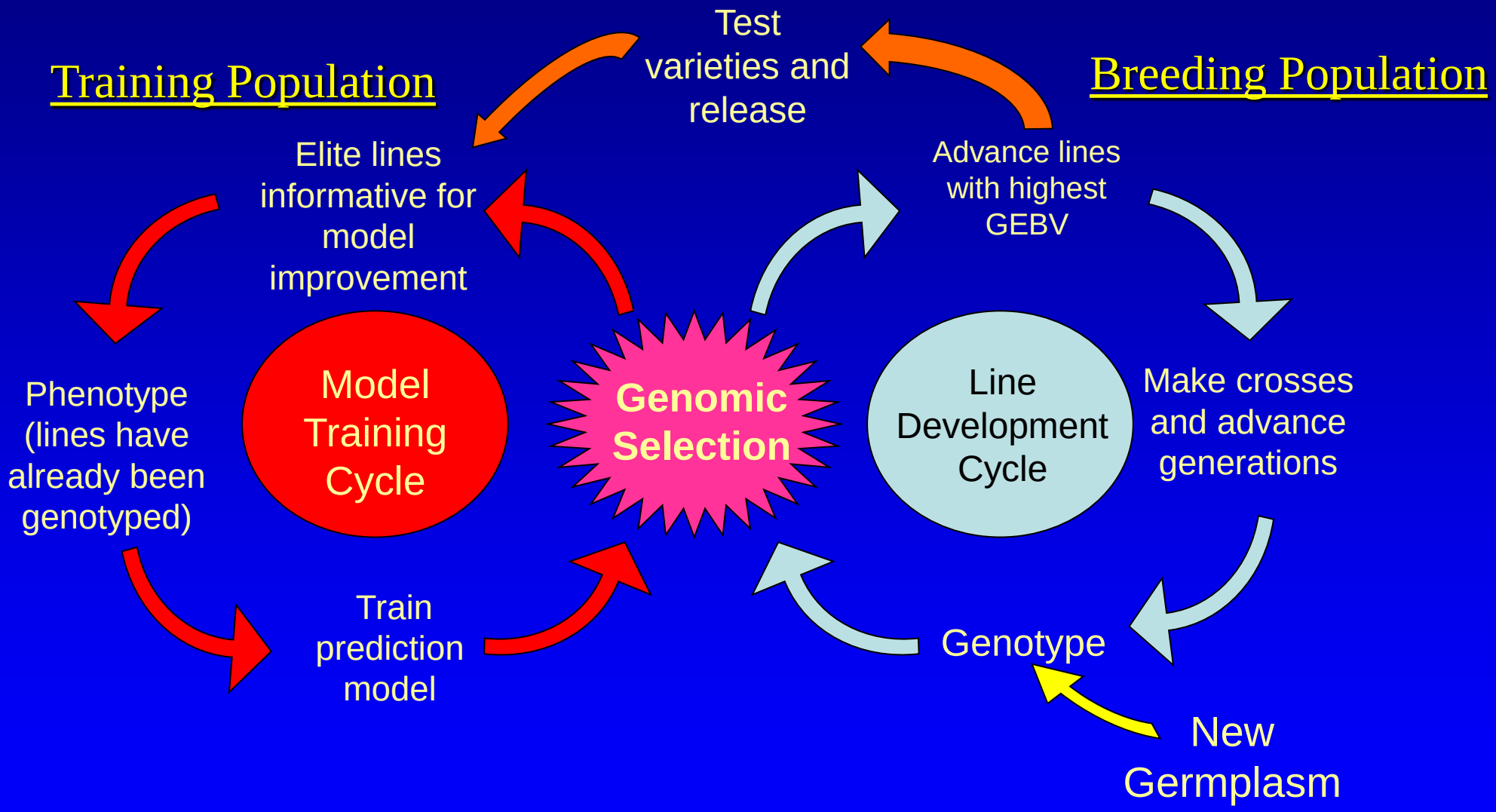
1) More accurate selection (r_A)
2) Larger selection differential (S)
   - Increase selection intensity by reducing costs
3) Shorter selection cycle time (t)

$$R = r_A^2 S / t$$



GS in a Plant Breeding Program

Heffner, Sorrells & Jannink. Crop Science 49:1-12



Genomic selection reduces cycle time & cost by reducing frequency of phenotyping

Factors Affecting the Accuracy of GEBVs

- Level and distribution of LD between markers and QTL
  - Meuwissen 2009: Minimum number of markers for across family= N*e**L where N*e* is the effective population size and L is the genome size in Morgans E.g. Wheat: 50x30=1500
  - Marker number must scale with effective population size.
- Size of training population
  - Larger is better and over time re-training models will be required
  - Meuwissen 2009: Minimum number of records for across family prediction = 2*N*e**L E.g. Wheat: 2X50x30=3000
- Heritability of the trait
  - More records are required for low heritability traits
- Distribution of QTL effects
  - Many small effect QTL or low LD favor BLUP for capturing small effect QTL that may not be in LD with a marker
  - Prediction based on relationship decays faster than prediction based on LD.

Choosing a Statistical Model for GS

Problem: Must estimate many QTL effects from a limited number of phenotypes or records (large 'p' small 'n' problem)

Previous Approach: Least Squares regression for variable selection

- Markers are fixed effects and an arbitrary threshold for significance is used to fit the markers
- Results in overestimation of significant effects and loss of small effects
- Options: Variable selection or shrinkage estimation can be used to deal with oversaturated regression models

Current methods: Linear mixed models, Bayesian estimation, Machine Learning

- No Testing for significance
- Many QTL effects, set as random effects, can be estimated simultaneously

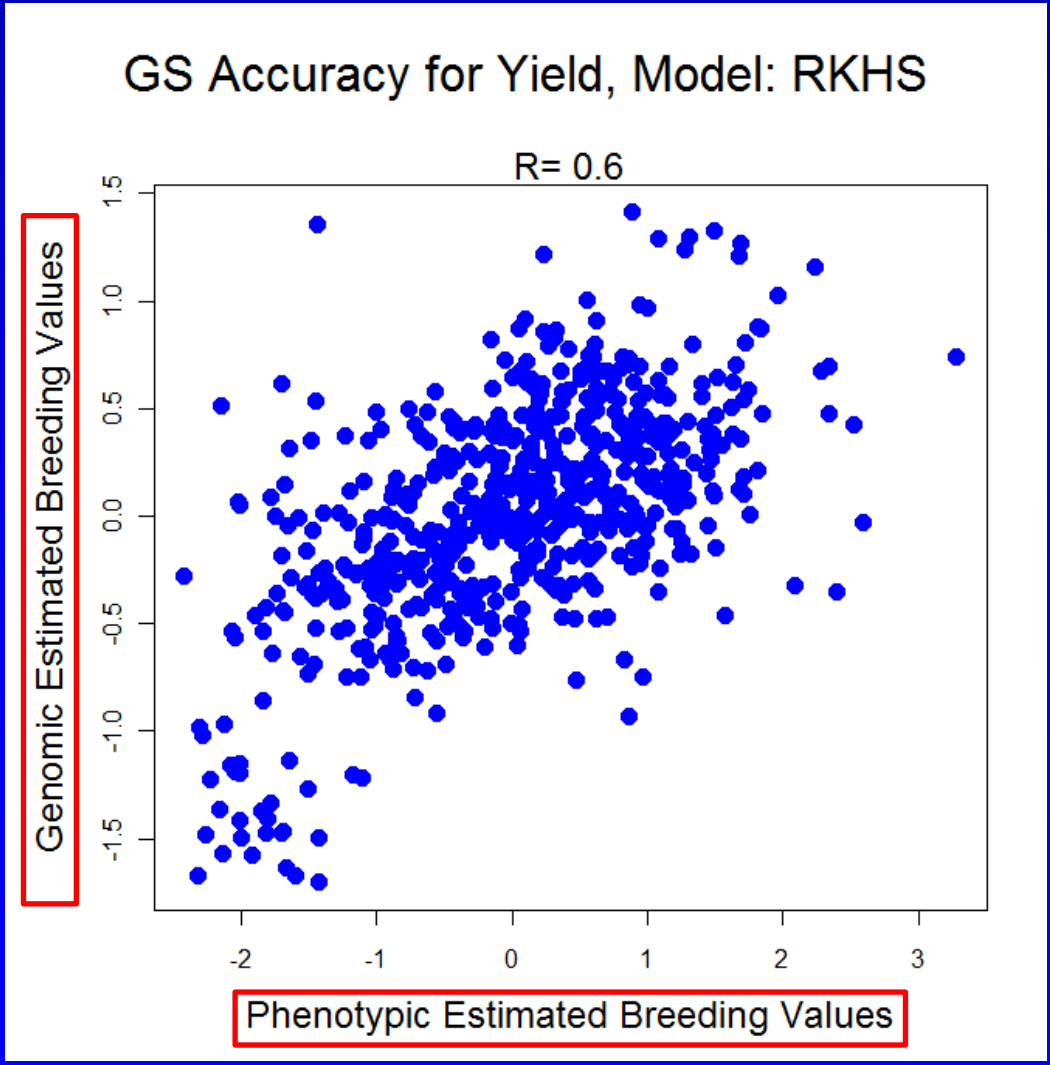
Choosing a Statistical Model for GS

Model performance is based on correlation between GEBV and True Breeding Value (TBV)

Accuracy (r) = Pearson's correlation coefficient using:

- Breeding values based on phenotype
- Breeding values estimated based on GS prediction models

r is analogous to the square root of the narrow sense heritability



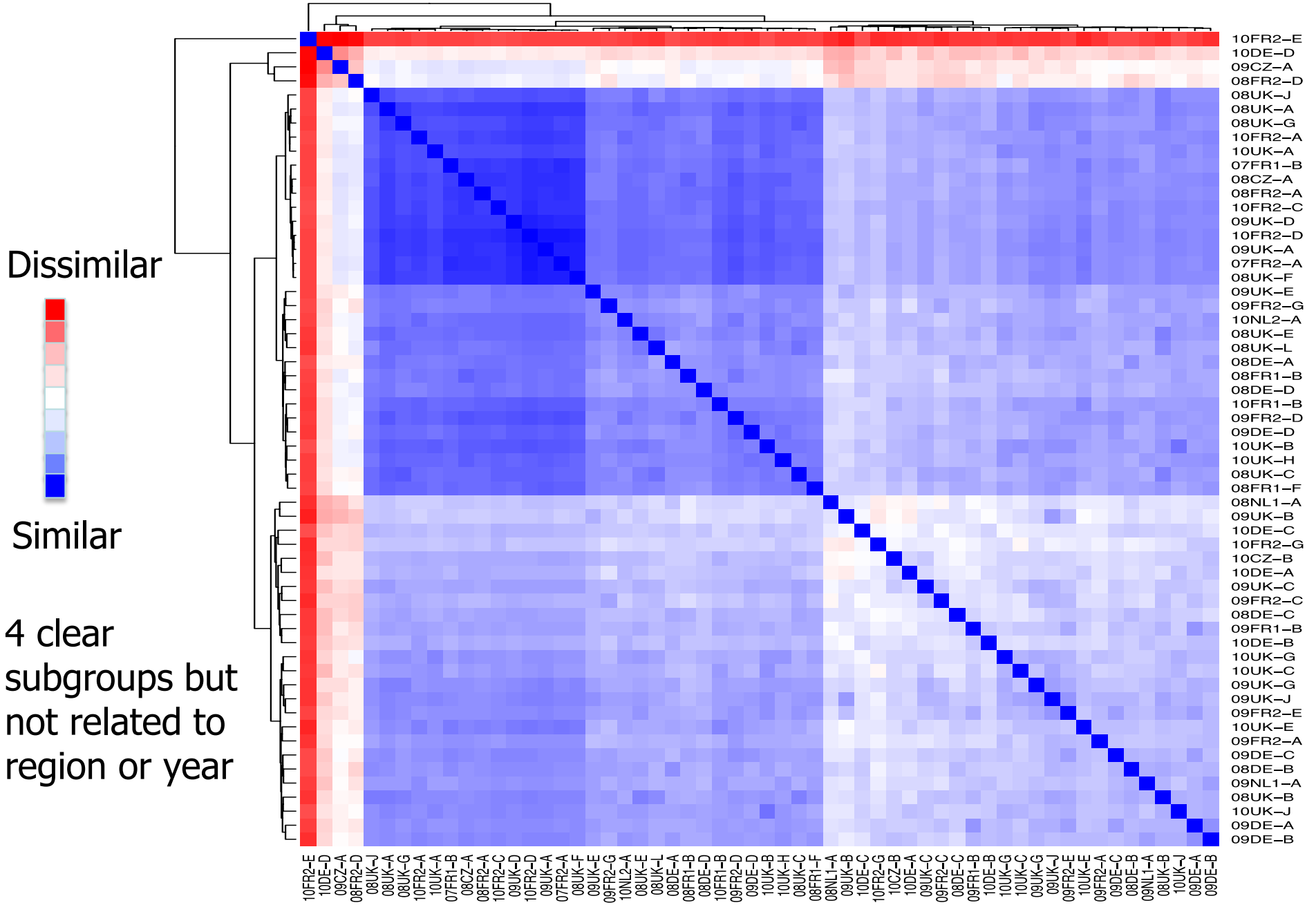
Optimizing Prediction using Marker Effects

Nicolas Heslot

- Limagrain Europe Barley
  - 996 F6 &F7 lines
  - 58 environments
  - 13,682 plots
  - Unbalanced – only 18 genotypes present in >50% of the environments
- Bayesian LASSO GS model
- Characterize allele-effect estimates for each test location
  - Identify outlier environments
  - Group relevant mega-environments

Use of Marker Effects to Cluster Environments

Marker effects for all lines in each environment formed a balanced dataset for computing Euclidean distances



4 clear subgroups but not related to region or year

Outlier environments were identified but there was no appreciable gain in accuracy.

Optimizing the Composition of the Training Population
(Heslot et al TAG in review)

Train GS model in each environment

↓

Compute mean accuracy of each training environment for predicting line performance in the other environments, rank them

↓

Remove environment one at a time starting from the least predictive

↓

Train and cross validate a GS model on the remaining training population: Predictive set

↓

Predict the removed data with the GS model: Unpredictive set

↓

Use both accuracy measurements to decide the cut-off point

Uses the predictive ability of an environment to optimize the composition of the training population derived from the complete dataset

Optimizing the Composition of the Training Population
(Heslot et al TAG in review)

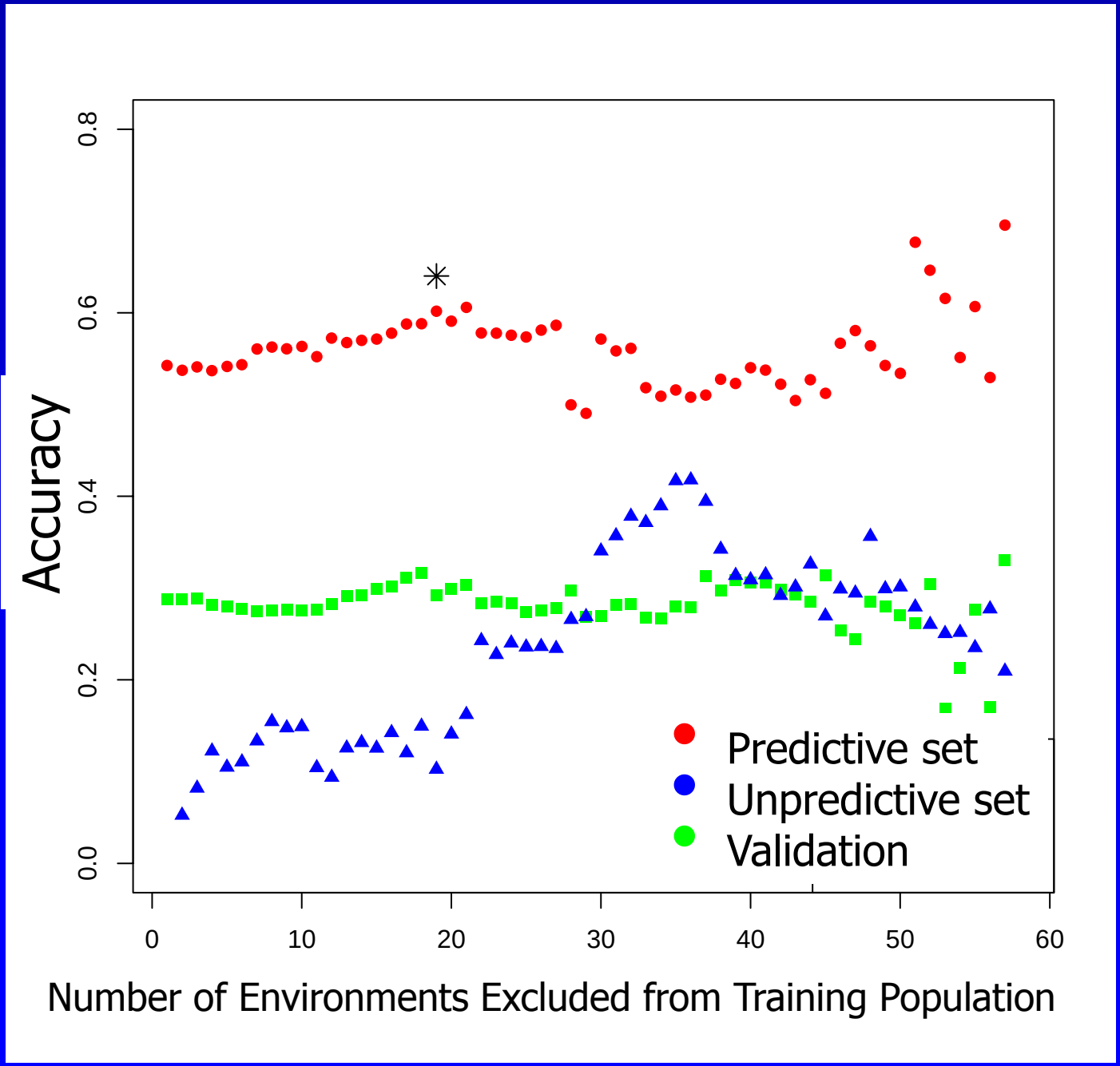
Remove least predictive environments one at a time, then cross validate

Prediction accuracy rose from 0.54 to 0.61 and no change in heritability

Some outlier environments were included in the optimal model

Accuracy in the validation set increased from 0.279 to 0.292

Only 1 of the 996 barley lines were excluded in the optimal model training set



Genomic Selection Experiments in the Cornell Wheat Breeding Program

Elliot Heffner

- Genomic Selection in Biparental Populations: Heffner et al. 2011. Crop Science 51: doi: 10.2135
- Genomic Selection Across Multiple Families in the Breeding Program: Heffner et al. 2011. The Plant Genome 4: 65

Jessica Rutkoski

- Genomic Selection for Adult Plant Stem Rust Resistance
- Genomic Selection for Fusarium Head Blight Resistance
- Recurrent Genomic Selection

Genomic Selection Experiments in the Cornell Wheat Breeding Program

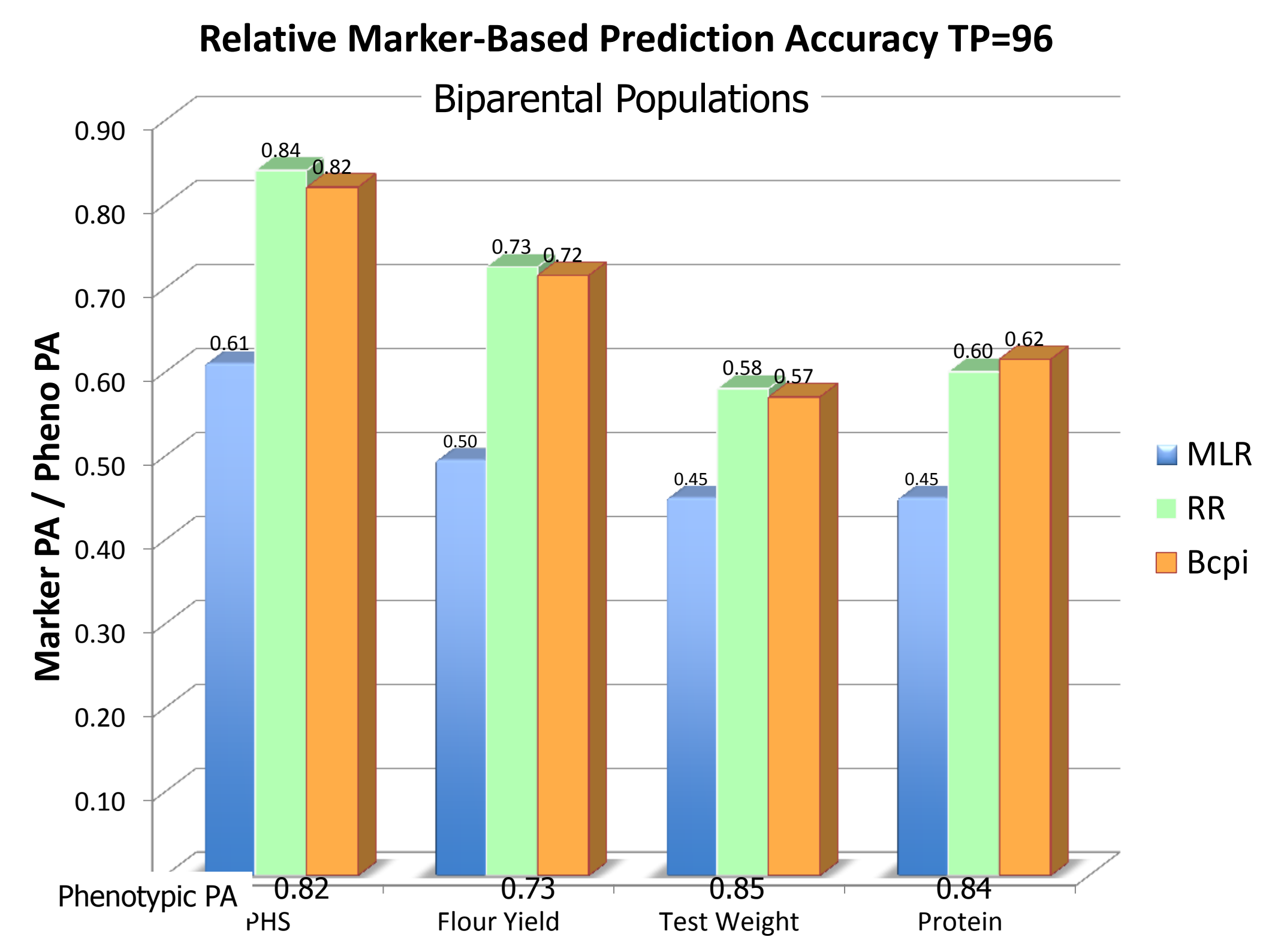
Elliot Heffner

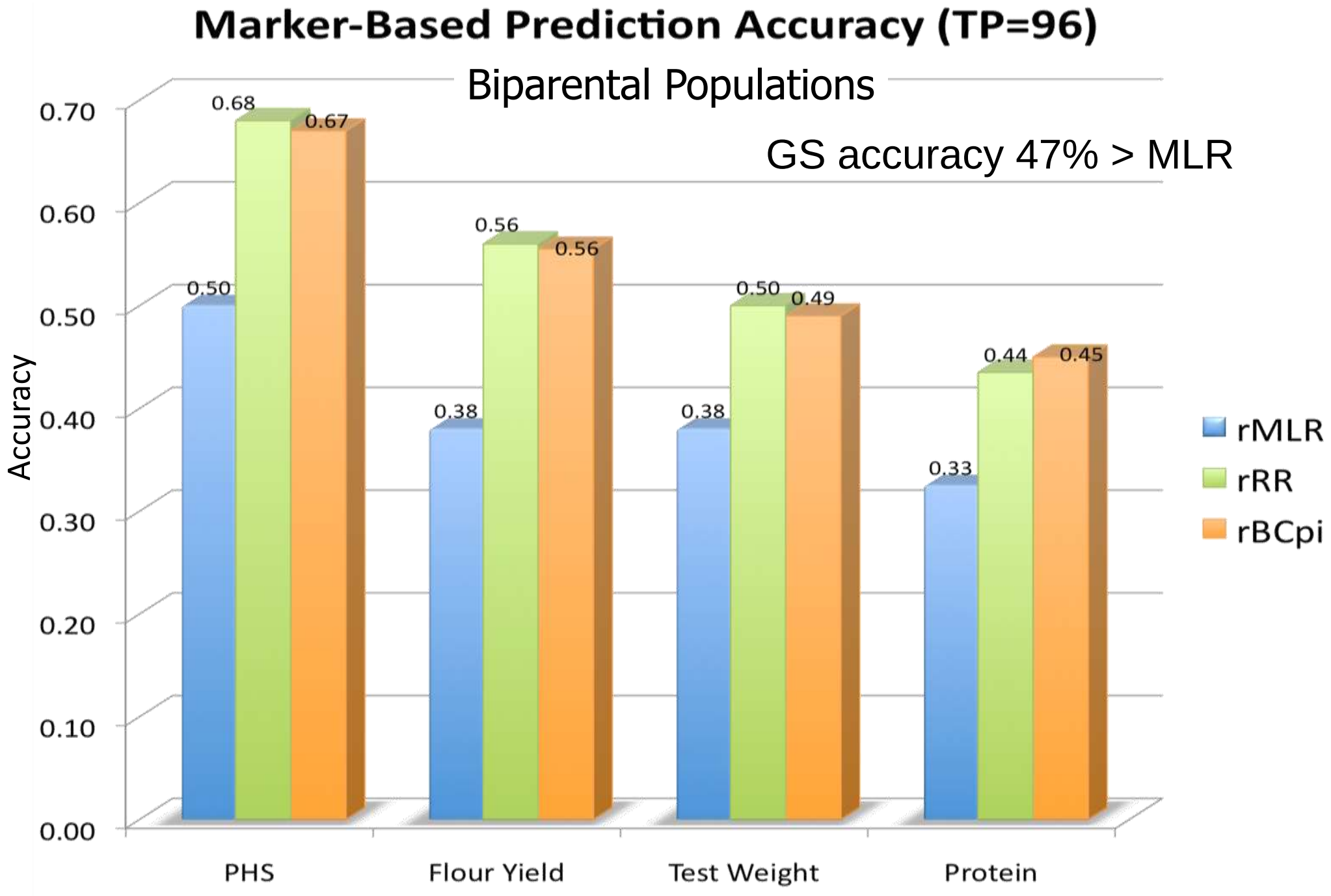
- Biparental Populations
- Cayuga x Caledonia (Soft White Winter)
  - 209 DH lines; 399 DArT Markers
  - Preharvest Sprouting 16 environments (6 years)
  - 9 Milling and Baking Quality traits - 3 years, one location per year
- Foster x KanQueen (Soft Red Winter)
  - 175 DH lines; 574 DArT Markers
  - 9 Milling and Baking Quality traits - 3 years, one location per year
- Across Multiple Families - Master Nursery
  - 400 advanced breeding lines (F7+)
  - Augmented field design
  - Three locations over 3 years, 2007-2009
  - DArT markers ~ 1500 polymorphisms
  - 13 agronomic traits

Evaluation Methods for GS in Biparental Populations

- Cross Validation
  - Model Training based on one year, validation on remaining (different) years
  - Lines in Validation Population (VP) are not included in the Training Population (TP)
- Training Population Sizes = 24, 48, 96
- Marker Number = 64, 128, 256, 384, 399, 574

- Prediction Models
  - MLR: Multiple Linear Regression - Forward/Backward $p<0.2$
  - RR: Ridge Regression BLUP - equal variance, all markers
  - BayesCpi: Equal variance, optimized pi for non-zero markers
- Phenotypic Prediction Accuracy
  - Based on the Correlation of Phenotypes from TP year with the VP Phenotypes in the Validation Years


Relative Marker-Based Prediction Accuracy TP=96
Biparental Populations
Marker PA / Pheno PA
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.61
0.84
0.82
0.50
0.73
0.72
0.45
0.58
0.57
0.45
0.60
0.62
MLR
RR
Bcpi
Phenotypic PA
0.82
PHS
0.73
Flour Yield
0.85
Test Weight
0.84
Protein


Marker-Based Prediction Accuracy (TP=96)
Biparental Populations
GS accuracy 47% > MLR
Accuracy
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.68
0.67
0.50
0.56
0.56
0.38
0.50
0.49
0.38
0.44
0.45
0.33
PHS
Flour Yield
Test Weight
Protein
rMLR
rRR
rBCpi

Biparental vs. Multi-Family GS

Biparental

1) Population specific
2) Reduced epistasis
3) Reduced number of markers required
4) Smaller training populations required
5) Balanced allele frequencies
6) Best for introgression of exotic germplasm

Multi-Family

1) Allows prediction across a broader range of adapted germplasm
2) Allows sampling of more environments
3) Cycle duration is reduced because retraining model is on-going
4) Allows larger training populations
5) Greater genetic diversity

Multi-Family GS Models

- Two conventional MAS models
  - With or without the Kinship Matrix as a covariate
  - Two- stage analysis
    - Association analysis - test for significant loci
    - Multiple linear regression – estimate effects of significant markers
- Four GS models

Model	Marker effects	All markers have a non-zero effect	Markers have equal variances
Association w/o K	Fixed		NA
Association w/ K	Fixed		NA
Ridge Regression	Random	✔	✔
BayesA	Random	✔	
BayesB	Random		
BayesCπ	Random		✔

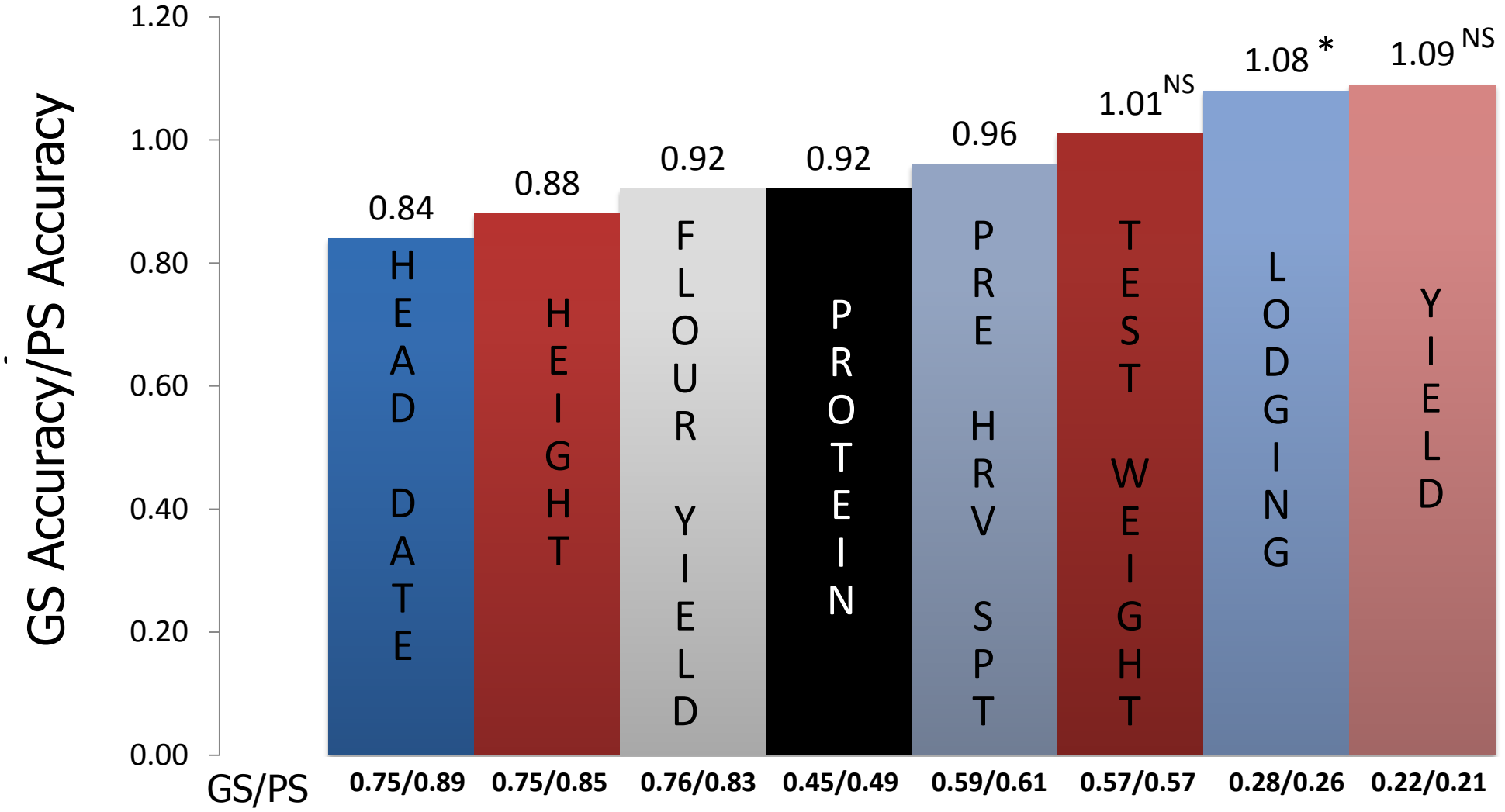
Results

- MAS model accuracy
  - Model w/o Kinship (0.48) was similar to model with Kinship (0.44)
- Small range in GS model accuracy
  - 0.60 (BA); 0.59 (RR and BB); 0.58 (BC)
- r_{GS} was 25% greater than r_{MAS}
- r_{PS} 33% greater than r_{MAS}
- r_{PS} 7% greater than r_{GS}

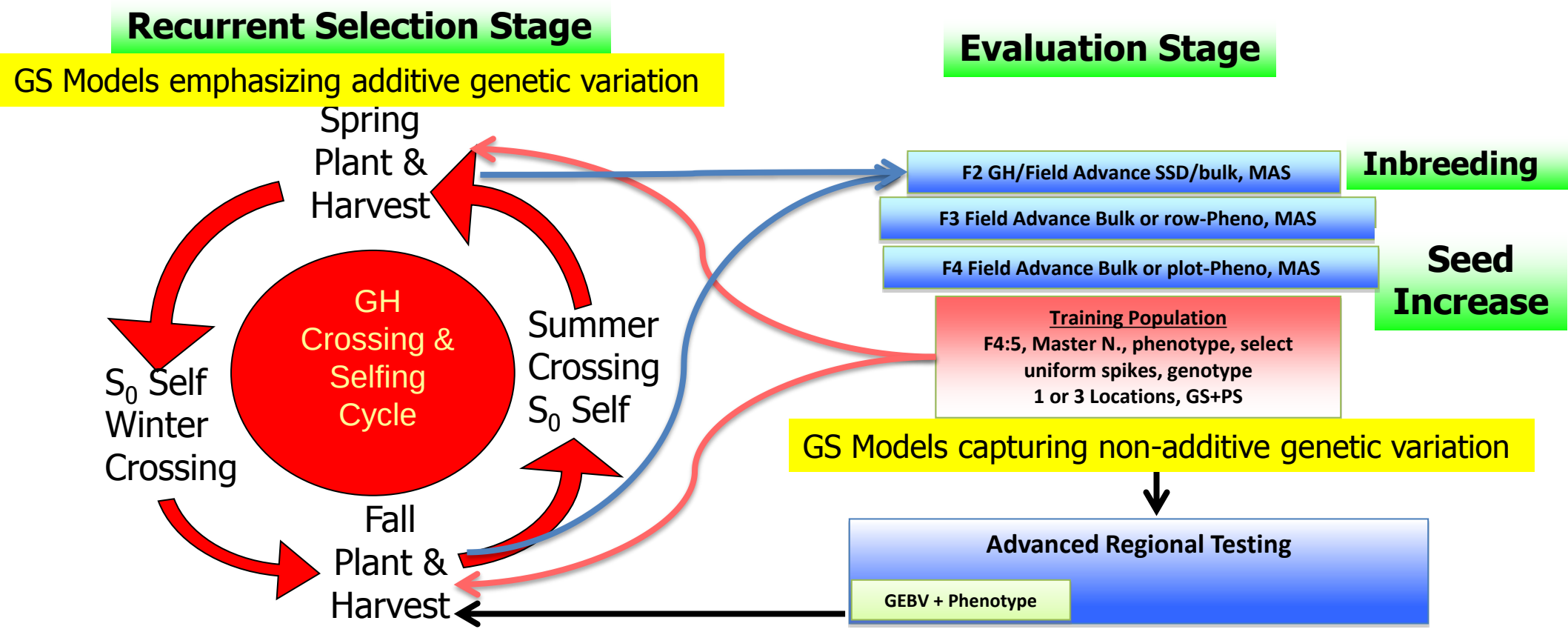
Method	Low	High	Mean	MarkerSel/ PhenoSel
MAS (AA)	0.19	0.65	0.48	0.75
GS (BA)	0.22	0.76	0.60	0.95
Pheno	0.21	0.89	0.64	-------

Relative GS and PS Prediction Accuracy: Multi-Family

TP Size = 288 Marker Number =1158



Cornell Wheat Breeding Program



Planting GS-selected individuals (S_0), intermating, self-pollination and S1 harvesting seed occur twice a year
F_2s can be field or GH planted depending on space available. MAS &/or GS can be applied
F_3s will begin seed increases of selected individuals in single rows
F_4s will be phenotyped and 50 F_5 spikes selected for uniformity and for GBS genotyping
Selected lines enter the Master Training Nursery
Each year selected lines are entered in the regional trials

Genomic selection for quantitative disease resistance in wheat

Jessica Rutkoski

Stem rust of wheat, *Puccinia graminis* f.sp. *tritici*

Fusarium head blight of wheat *Fusarium*

Evaluation of GS Models for Fusarium Head Blight Resistance

(Rutkoski et al The Plant Genome In press)

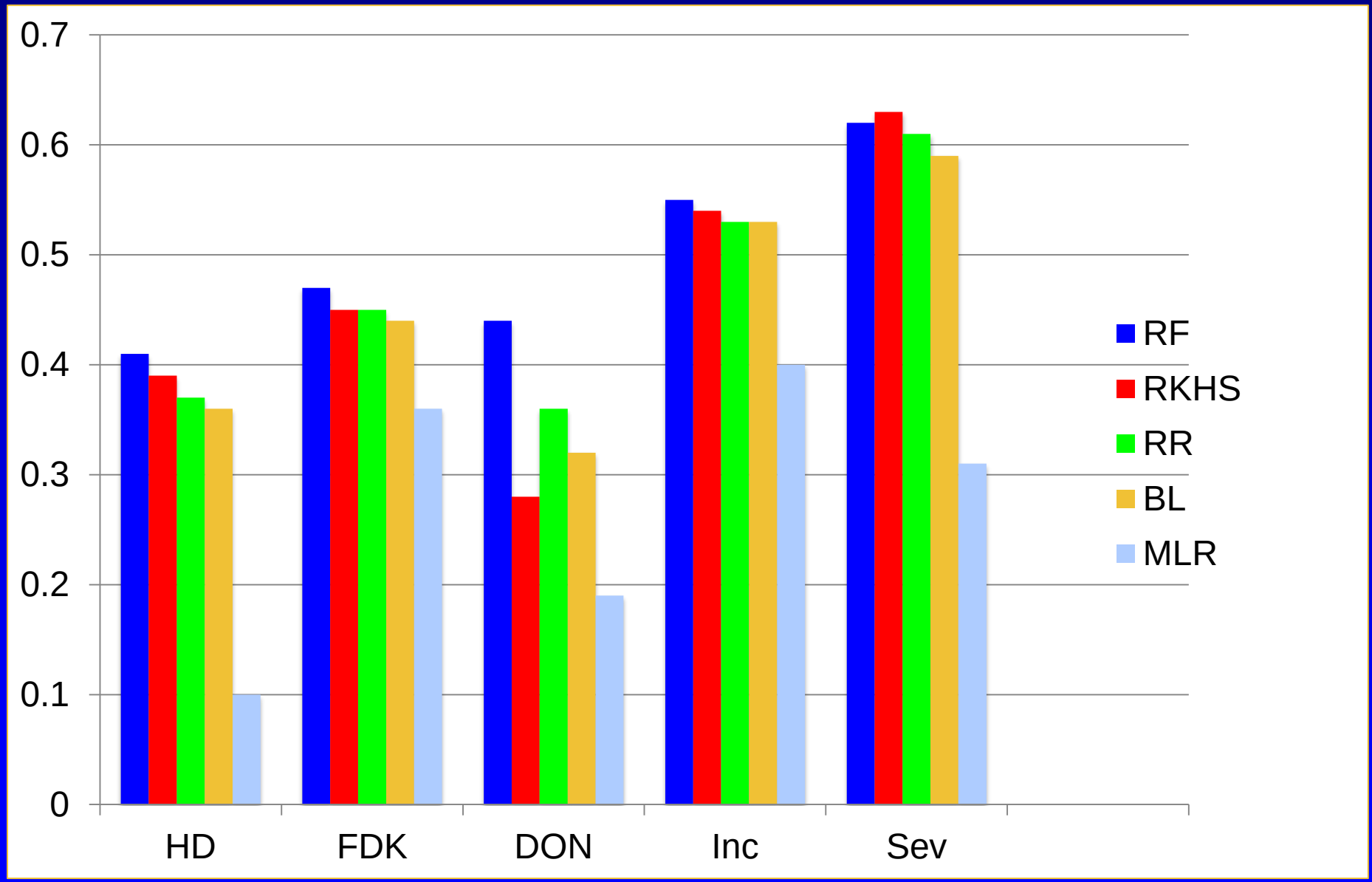
- Cooperative Nursery Data – 3 years, 3 nurseries, 60 environments
- Traits: Incidence (Inc), Severity (Sev), Fusarium damaged kernels (FDK), Incidence/Severity/Kernel quality index (ISK), Deoxynevalenol (DON), Heading Date (HD)
- GS Models: Ridge Regression, Bayesian LASSO, Reproducing Kernel Hilbert Spaces, Random Forest, Association mapping with a Q+K matrix+multiple linear regression with markers as fixed effects
- Population Size: Training – 132, Predicted – 33
- Cross validation: 5 fold, repeated 10 times


M. McMullen


M. McMullen

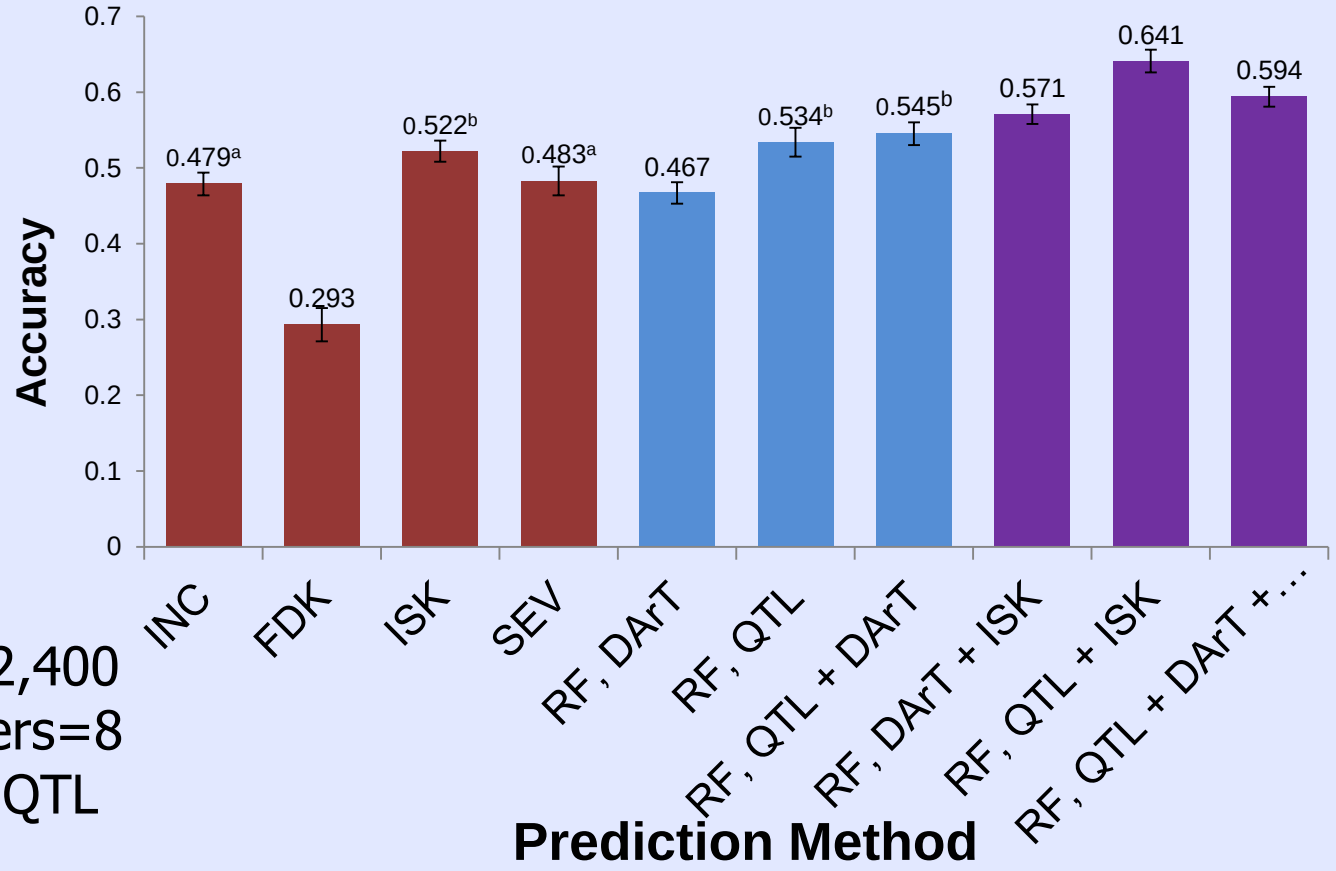

J. Miller

Model Accuracies for Fusarium Head Blight Resistance



Comparison of Prediction Accuracies for DON

(Rutkoski et al The Plant Genome In press)



DArT markers=2,400
QTL=SSR markers=8
(30) linked to 5 QTL

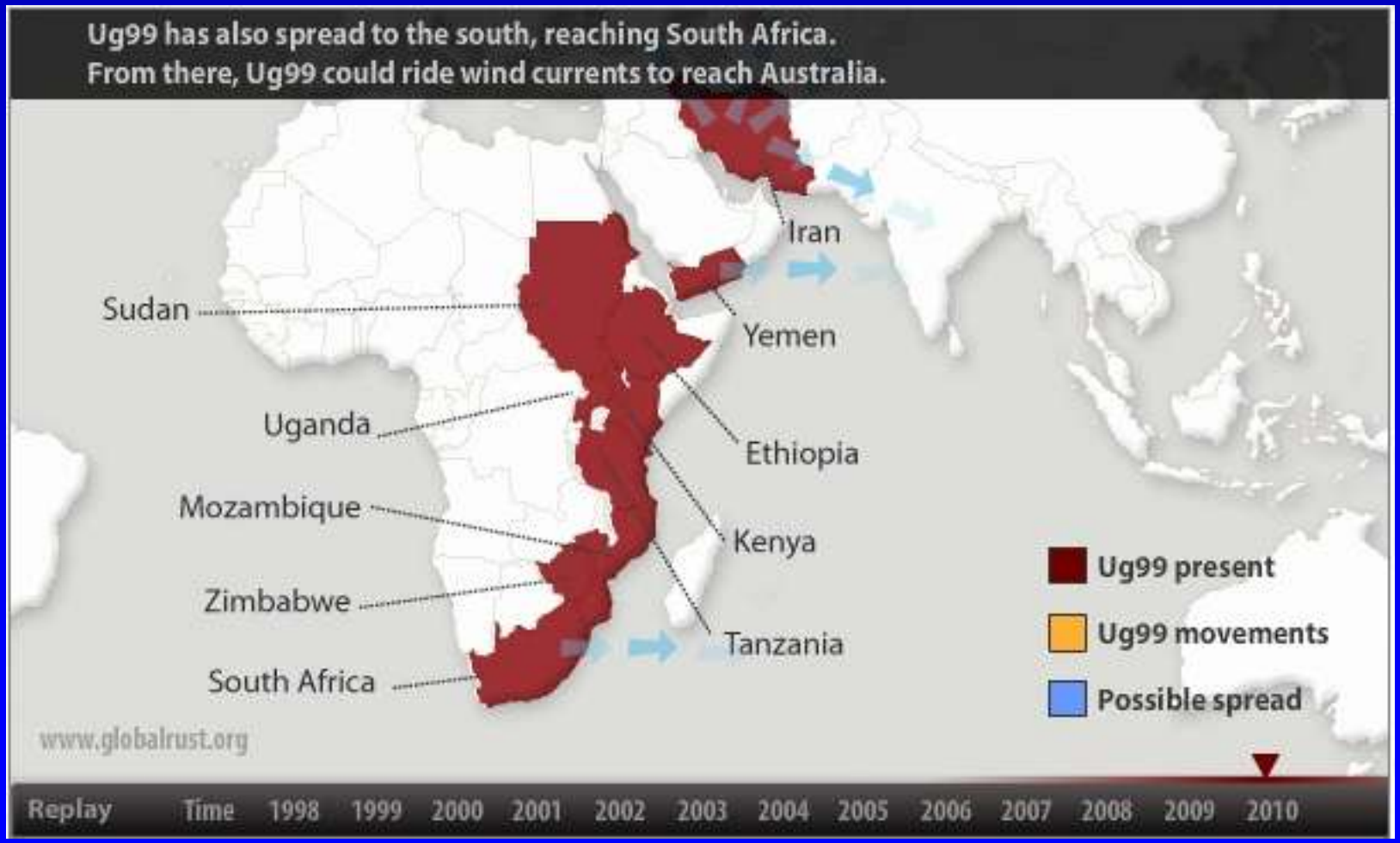
Correlated traits: Incidence (INC), fusarium damaged kernels (FDK), severity (SEV), and the index (ISK)

Most accurate GS model: Random forest (RF)

RF prediction model combining markers and correlated traits

Durable Rust Resistance in Wheat
Funded by the Bill & Melinda Gates Foundation

Since the 1999 discovery of virulence on *Sr31* in Uganda, Ug99 races have overcome *Sr36* and *Sr24* and spread north to Iran and south to South Africa



Stem Rust Resistance- Two Types:

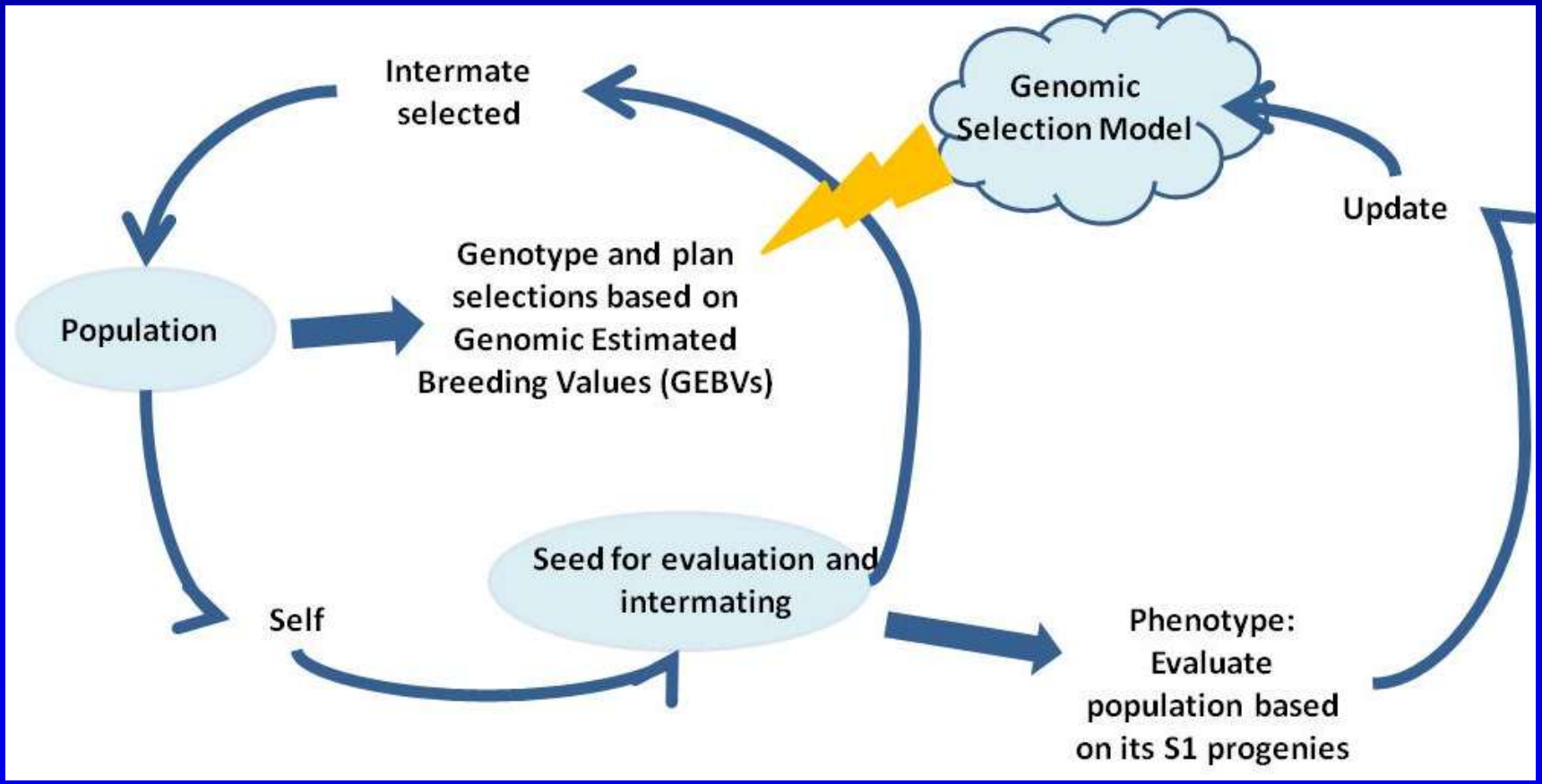
All-stage resistance- conferred by major R-genes that provide complete resistance

VS.

Adult plant resistance- conferred by additive loci that alone do not provide complete resistance

Recurrent Genomic Selection for Adult Plant Resistance to Stem Rust

Jessica Rutkoski



Summary: Genomic Selection

- GS differs from MAS and Association Breeding in that the underlying genetic control and biological function is not known.
- Breeders can implement GS without the upfront cost of obtaining that knowledge.
- GS preserves the creative nature of phenotypic selection to sometimes arrive at solutions outside the engineer's scope.
- Most important advantages are reductions in the length of the selection cycle and associated phenotyping cost resulting in greater genetic gain per year.

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- USDA National Institute of Food and Agriculture, NRI Triticeae Coordinated Agricultural Project 2011-68002-30029 Improving Barley and Wheat Germplasm for Changing Environments
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- USDA National Needs Fellowship Grant 2008-38420-04755: Provided Fellowship for Jessica Rutkoski
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- US Wheat & Barley Scab Initiative: Provided funding for the fusarium head blight research

USDA United States Department of Agriculture

KARI

Limagrain Europe

CIMMYT

Questions?