
# Genomic Selection
# From Livestock to Aquaculture
# Applications

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# Outline

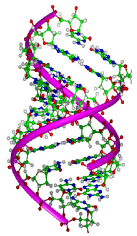
1. The State of Genomes
   - » livestock & aquaculture
2. Genomic Selection
   - » background & motivations
3. The State of the Art
   - » achievements & limitations
4. Genomic Selection 2.0
   - » sequencing populations and the final frontier?
5. Conclusions

1. The State of Genomes
   - Livestock
   - Aquaculture

# Genomic Selection & Sequence

- Genomic selection does not require a reference genome
  - » abbreviated GS
- BUT past & future tool development benefits from knowledge of sequence
  - » e.g. selection of SNP for spacing and coverage
- Stage of development of GS in species is associated with development of genome sequence
  - » amongst other things!

# Early Days: Towards a Sequence



**1953**
Watson and Crick

**1977**
DNA sequenced ΦX174 5,386 nt

**1990**
Human Genome Project launched

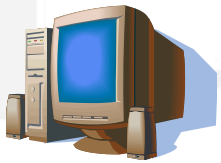
**1991**
PiGMaP project starts

'Halothane' gene test

**2001**
Draft human genome sequence

**1920s and 30s**
Fisher, Lush and others Population Genetics

**1970s +**
Advances in quantitative analysis



**1990s +**
Quantitative trait locus (QTL) mapping

**2001**
Genomic selection proposed

# Genomic Developments to 2011

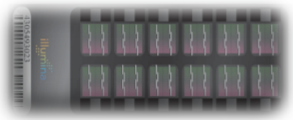
**2003**
Human genome sequence "finished"
$3 billion

**2004**
Chicken genome sequenced


**2005**
Dog genome sequenced

**2007**
Cat genome sequenced

**2008**
Bovine 50K SNP chip



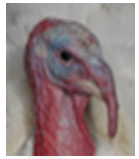
**2009**
Cattle genome sequenced

Horse genome Sequenced

**2009**
Pig 60K SNP chip

Sheep 60K SNP chip

**2010**
Turkey genome sequenced



**2010**
750K bovine SNP chips

# Genomic Developments to 2015

**2012**
Chicken 600K SNP chip

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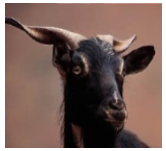
Pig genome sequenced


**2012**
Pig gene expression atlas



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Goat genome sequenced

**2013**
Duck genome sequenced

**2014**
Sheep genome sequenced

**2015**
Improved reference genomes – goat, pig, sheep, cattle, chicken,

**2015**
Pig 650K SNP chip

**2015**
Functional Annotation of Animal Genomes (FAANG) launched

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# Tools for Genomic Selection

| | Dairy Cattle | Beef Cattle | Sheep | Goats | Pigs | Layer Chick's | Broiler Chick's | Turkey | Duck |
|---|---|---|---|---|---|---|---|---|---|
| Reference genome | +++ | +++ | ++ | ++ | ++ | +++ | +++ | + | + |
| High-density SNP 'chips' available | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| Genomic Selection? | +++ | + | ++ | + | +++ | ++(+) | +++ | No | No |

# Genomic Developments to 2011

ROSLIN

**2003**
Human genome sequence "finished"
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Chicken genome sequenced


**2005**
Dog genome sequenced

**2006**
Salmon & trout cDNA micro-array

**2007**
Cat genome sequenced

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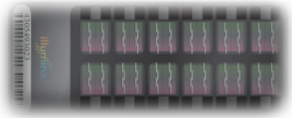
Bovine 50K SNP chip



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Sea bream cDNA micro-array

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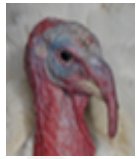

**2010**
750K bovine SNP chips

**2010**
Sea bass cDNA micro-array

**2011**
Cod genome sequenced

**2011**
Salmon & trout RAD-sequencing

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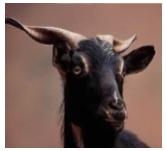

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**2012**
Pacific oyster genome sequenced

**2013**
Salmon 130K SNP chip

**2014**
Trout genome sequenced

Salmon genome sequenced

Sea bass genome sequenced

Carp genome sequenced

Catfish HD SNP array

Carp HD SNP array

Rainbow trout HD SNP array

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# Tools for Genomic Selection

| | Atlantic salmon | Rainbow trout | European sea bass | European sea bream | Turbot | Common carp |
|---|---|---|---|---|---|---|
| Reference genome | + | + | + | (+) | (+) | + |
| High-density SNP 'chips' available | Yes | Yes | No | No | No | Yes |
| Genomic Selection? | ++ | (+) | No | No | No | No |

FISHBOOST
The next level of aquaculture breeding

SANTIAGO DE COMPOSTELA 2015

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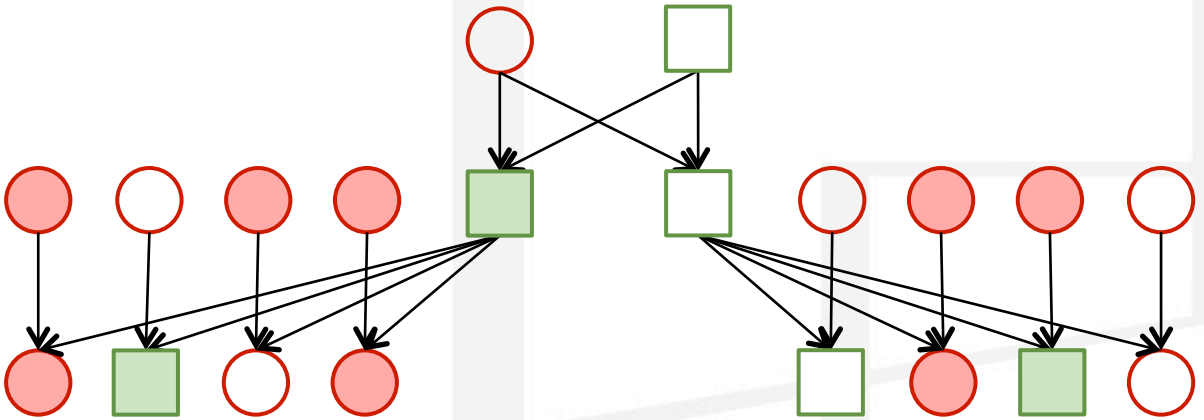
# Summary of Development

- Livestock species
  - Sequences published, refined
  - Expression atlases published and/ or major community efforts
  - Large number of SNP chips
    - multiple densities for most species to suit needs
    - imputation, GWAS etc
  - Genomic selection firmly established in major species
- Aquacultural species
  - Sequences at first draft
  - Early stage annotation and expression data
  - Some species with SNP chips
  - Genomic selection being introduced to some species

2. Genomic Selection
   - Background
   - Motivations

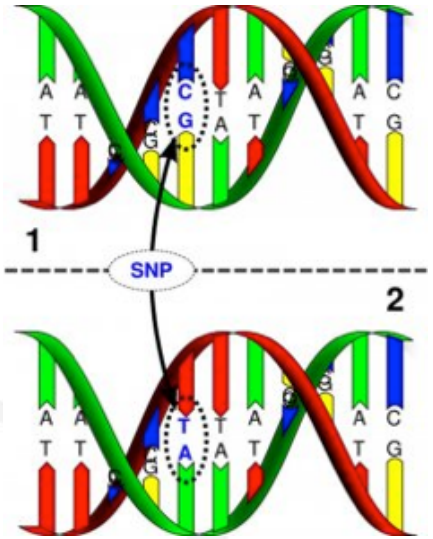
# Traditional Breeding

- Collect pedigree (○ □) phenotype (○ ●) information
  - » own performance (e.g. growth, …)
  - » sib-performance (e.g. carcass and meat quality, disease, …)
  - » progeny performance (e.g. milk yield, # eggs, …)
- Estimate genetic values by BLUP



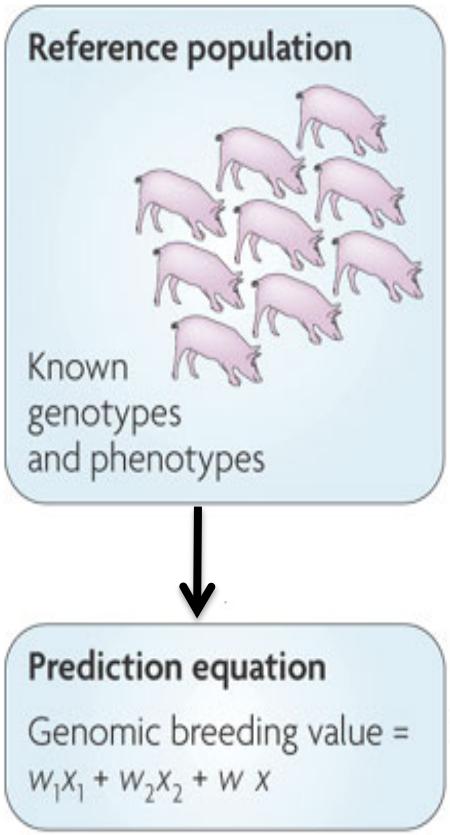
# Genomic Selection (1)

- Use abundant genome-wide markers
  - » e.g. SNP



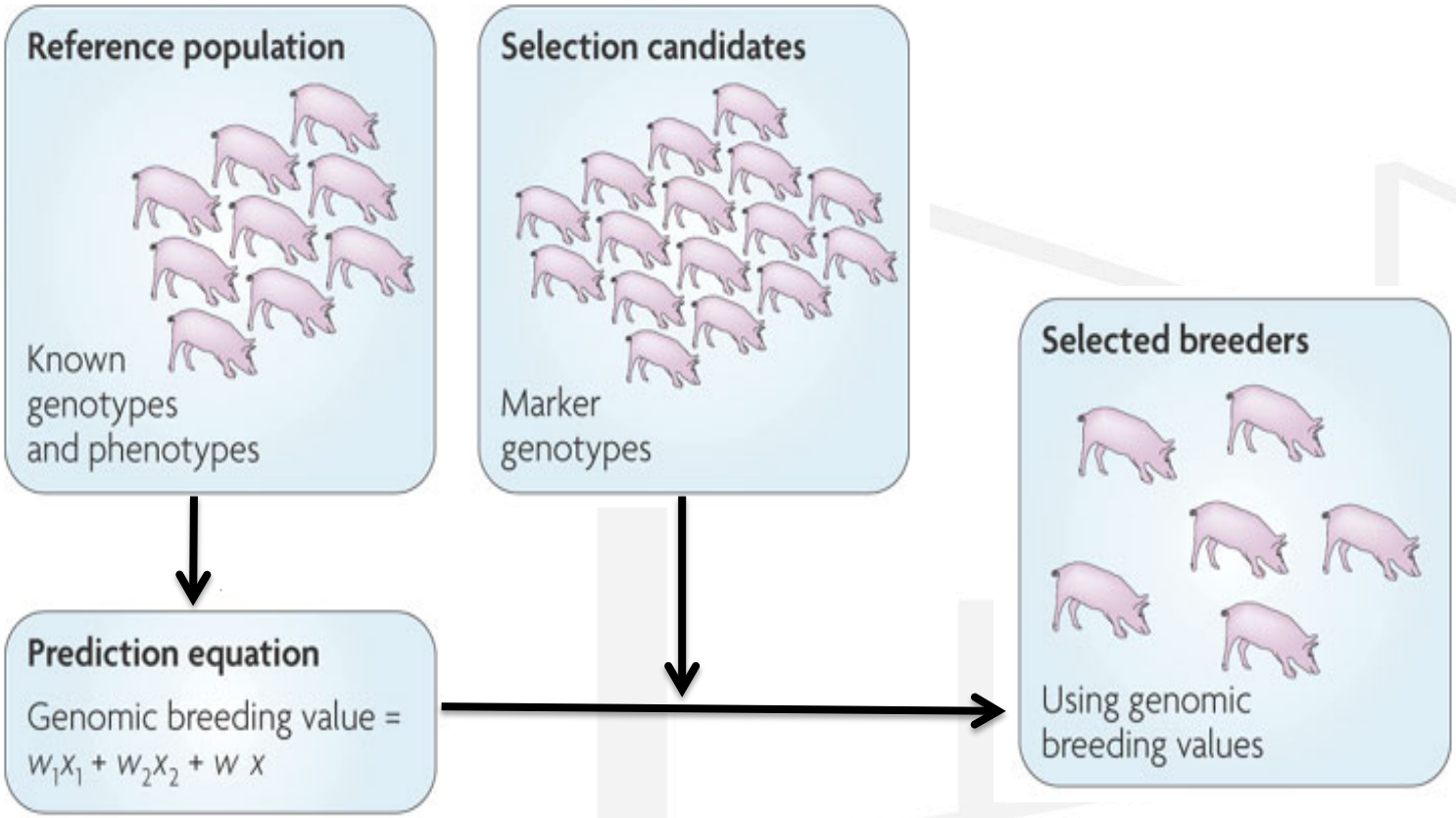
# Genomic Selection (2)

- Obtain predictions of Marker effects from Training Set



# Genomic Selection (3)

- Obtain predictions of candidates and select




Hayes & Goddard, 2009

# Some Important Properties

1. Accuracy of GS is dynamic
   - » bigger the training set, the more accurate the prediction
   - » BLUP accuracy is ~ static given structure of scheme
     - » f(data collected on close relatives, $h^2$)

# Some Important GS Properties

- Greater accuracy of Mendelian Sampling Term
  - » what makes us unique
  - » ancestors (e.g. sire) or collateral relatives (sibs) alone cannot estimate this
  - » source of continued gain beyond best parent
  - » selective advantage when controlling inbreeding
  - » explains ½ (or more) of genetic variance!
    - » i.e. within-family variance

# Some Useful GS Properties

- Prediction available early in life
  - » can consider selection in the absence of phenotypes
    - » e.g. disease phenotypes
  - » reduce generation interval

# GS & Gain

$$\text{Response} = \frac{\text{Selection Intensity x Accuracy x Diversity}}{\text{Generation Interval}}$$

- So GS adds gain through
  - » increases accuracy
  - » decreases generation interval
  - » can in some schemes add selection intensity
    - » e.g. avoiding random culling

3. The State of the Art
   - Livestock
   - Aquaculture

# GS Pioneers

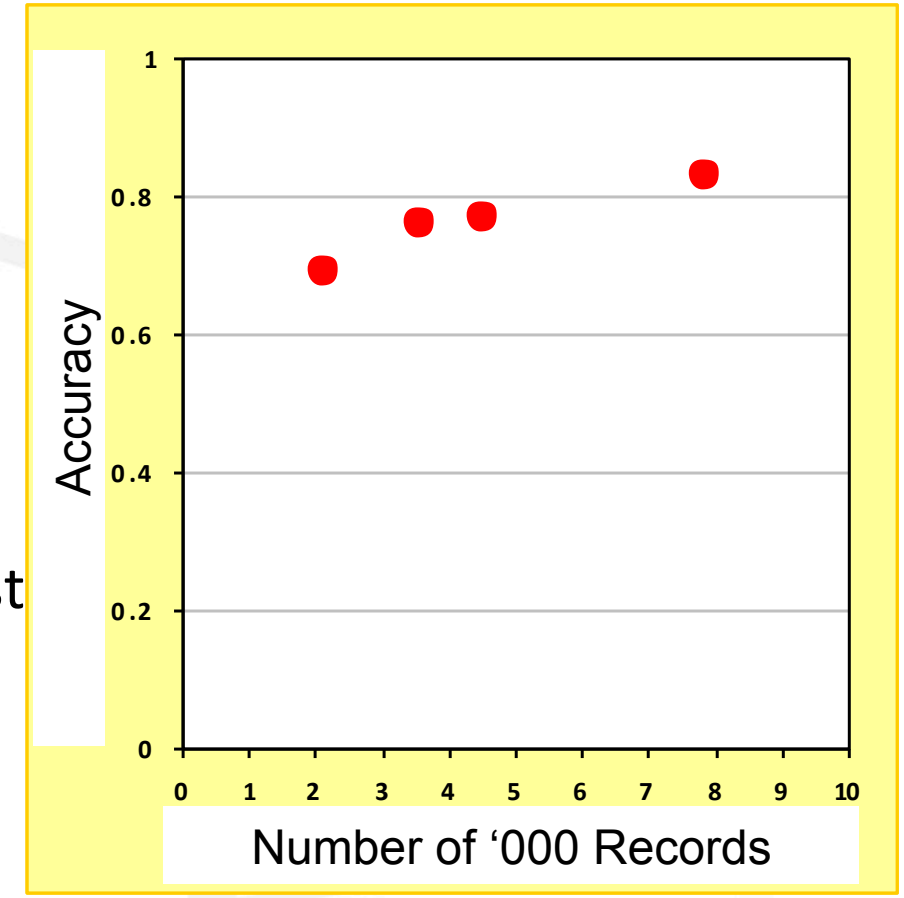
- Dairy breeding
  - » traditionally relied on progeny testing
  - » long generation interval
  - » high cost per bull tested

# GS Benefits in Dairy

- Benefits from prediction early in life
  - » screen more bulls more accurately before entering progeny test
    - » increase selection intensity
  - » only test the best bulls
  - » if GS predictions have high accuracy might avoid progeny test
    - » decrease generation interval

# GS Accuracy for Dairy

- Note
  - » high accuracy attained
    - » source USDA
  - » dynamic accuracy
- But
  - » require large number of bulls
  - » each bull has high accuracy test



# Dairy Advantages

- Costs of genotyping are covered by savings in progeny test
- Easy availability of large numbers of high-accuracy phenotypes on bulls
  - » i.e. the progeny test proofs
- Gains are potentially very large
- Safe implementation route as predictions on bulls can be compared emerging, accurate test results
- Animals are high value compared to cost of test

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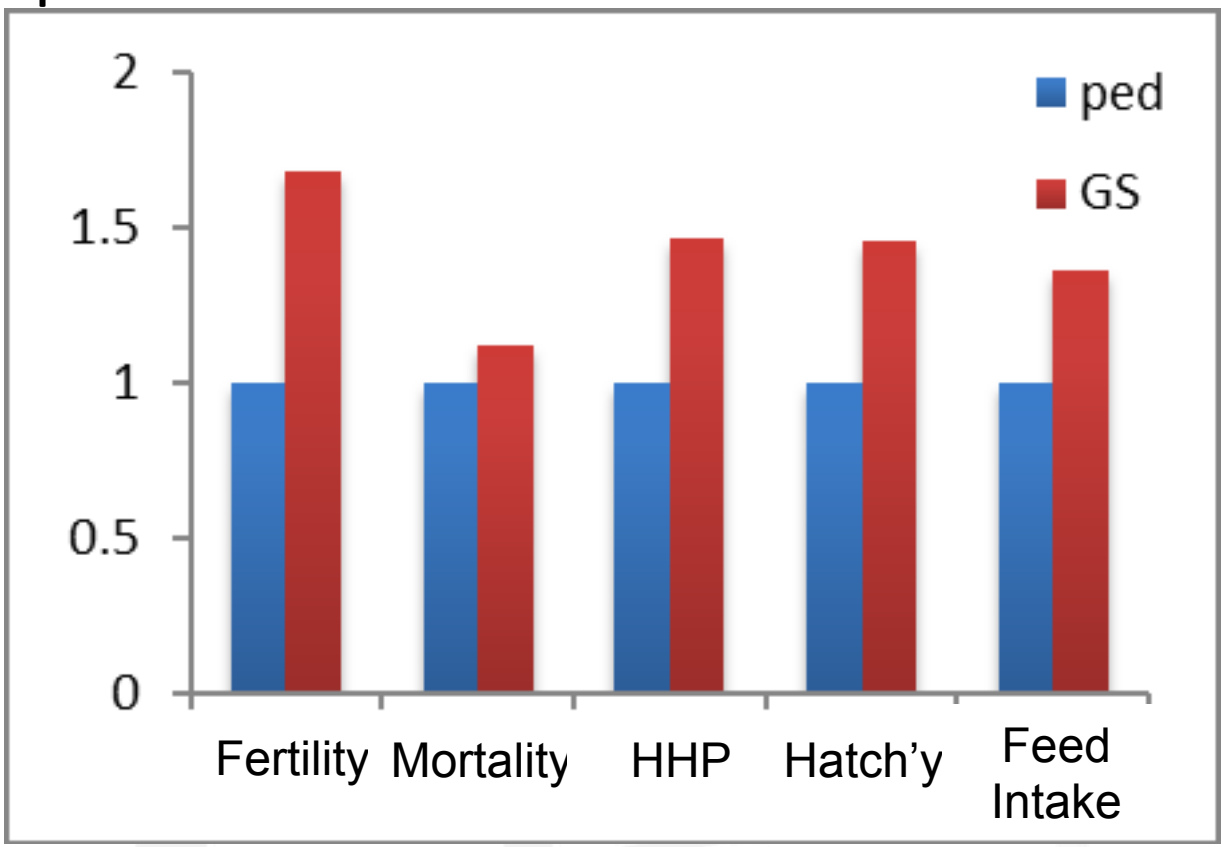
- G potentially very large
- Safe implementation route as predictions on bulls can be compared emerging, accurate test results
- Animals are high value compared to cost of test

What about sectors where animals have low individual value?

# GS Benefits in Broiler Chickens

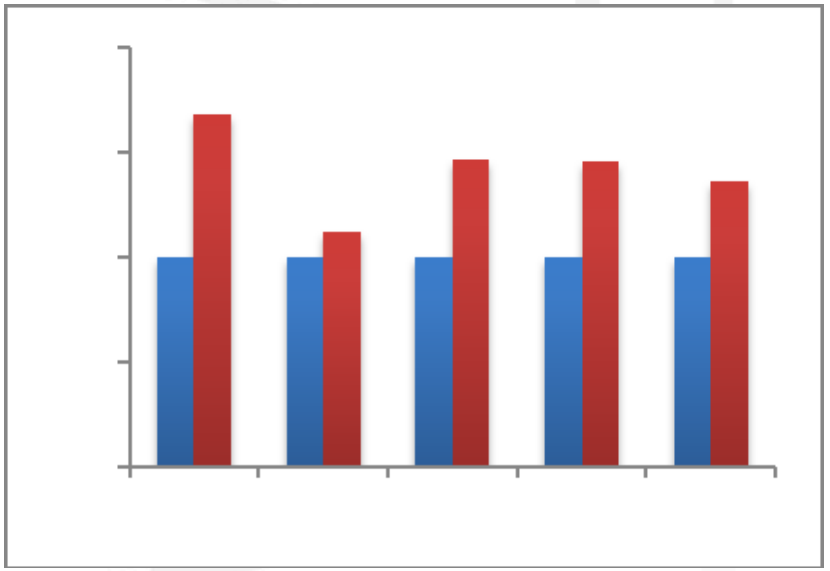
- Accuracy of GS compared to BLUP
  - » ~ 1.1 to 1.7
  - » will gain with time




From Wolc et al. 10th WCGALP, Vancouver, 2014

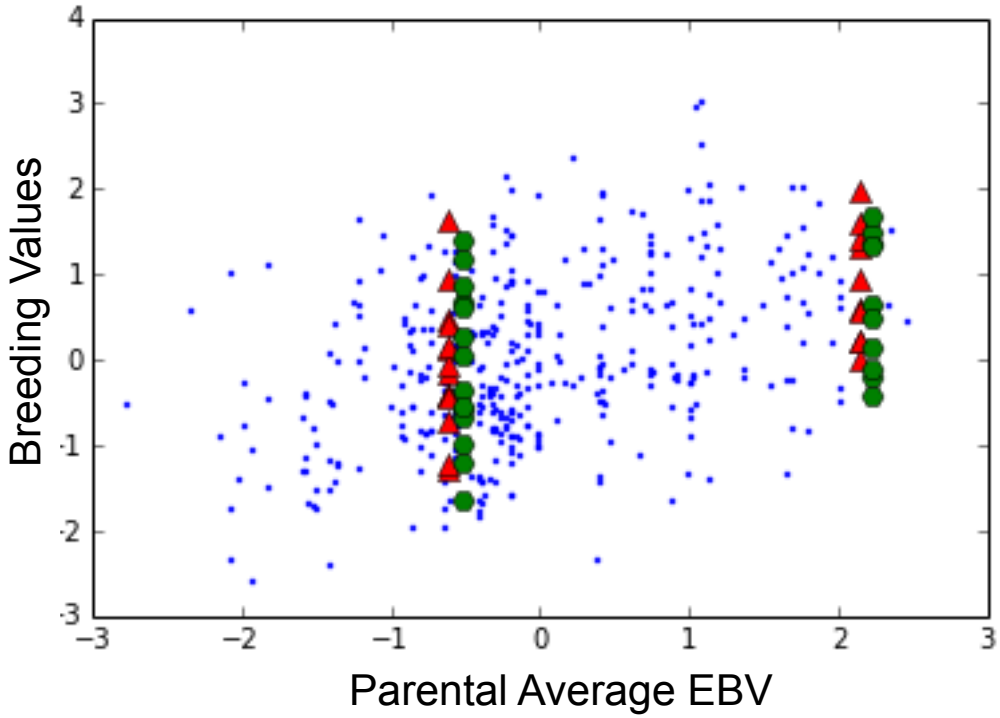
# GS Benefits in Broiler Chickens

- Valuable gains in sex-limited female traits with low $h^2$
  - » from estimate of Mendelian Sampling Term of males
  - » i.e. with no phenotype



# Value of Mendelian Sampling

- Red triangles: Mendelian genomic predictions
- Green circles: Validation from progeny means




From Wolc et al. 10th WCGALP, Vancouver, 2014

# Salmon Breeding

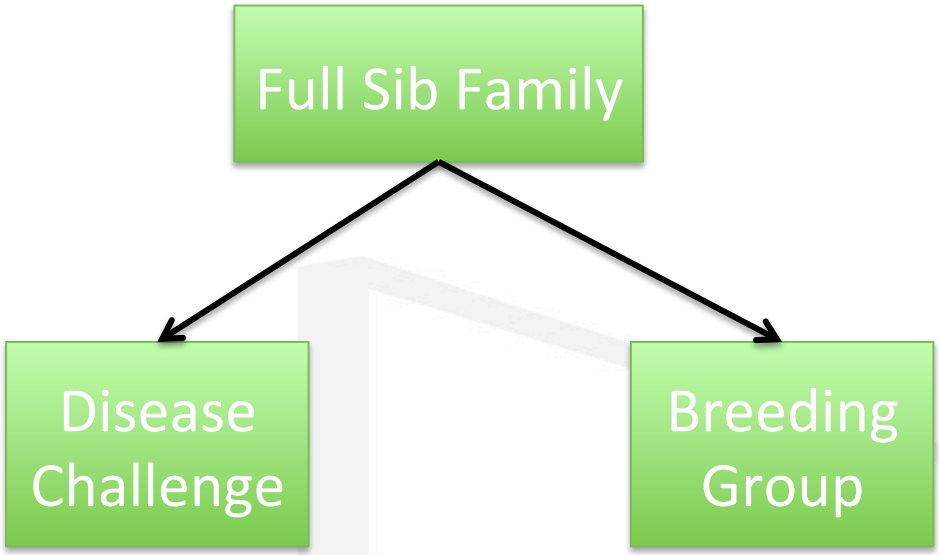
- Published results on GS are few
- Major study by Ødegård (2014)
  - » presenting this conference

# Salmon Breeding

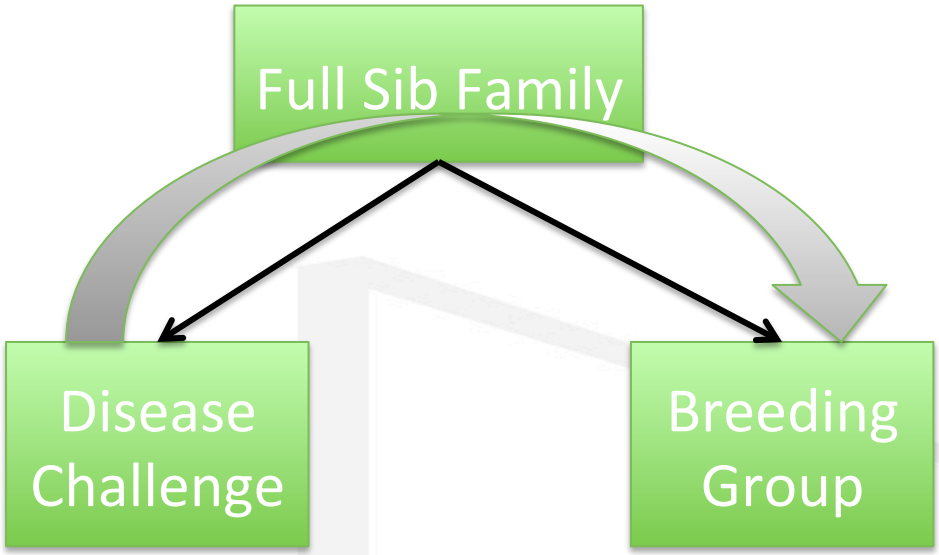
- Small to moderate training set size of 2000
- Accuracies from GS were better than BLUP
  - » 1.2-fold for Lice Resistance
  - » 1.1-fold for Fillet Colour
    - » BLUP for both traits was ~0.6

Ødegård et al. *Frontiers in Genetics* 5 (2014)

# Sib Testing

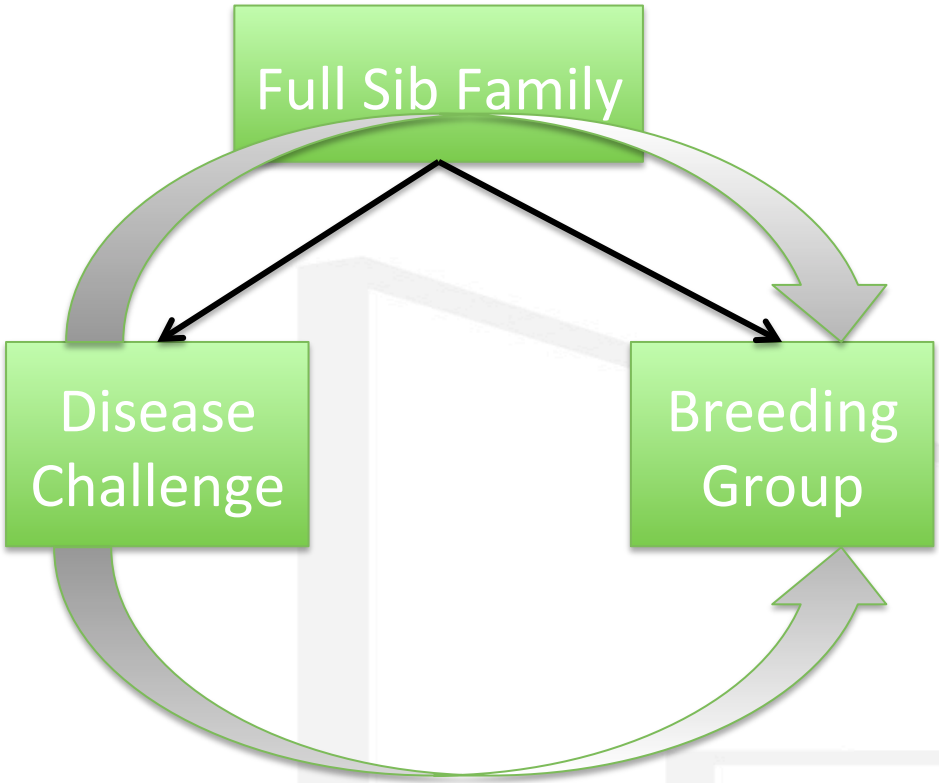


# Sib Testing with BLUP




- Information gained from test is only family mean

# Sib Testing with GS




- Information on family mean and desirable marker alleles within family both transferred to breeding group

# Sib Testing with GS

- Simulations show important benefits in accuracy
  - » estimate of Mendelian Sampling Term from markers
  - » require relatively few markers per chromosome (10-20)

Lillehammer et al (2013), Genet Sel Evol. 45

# Summary of Applications

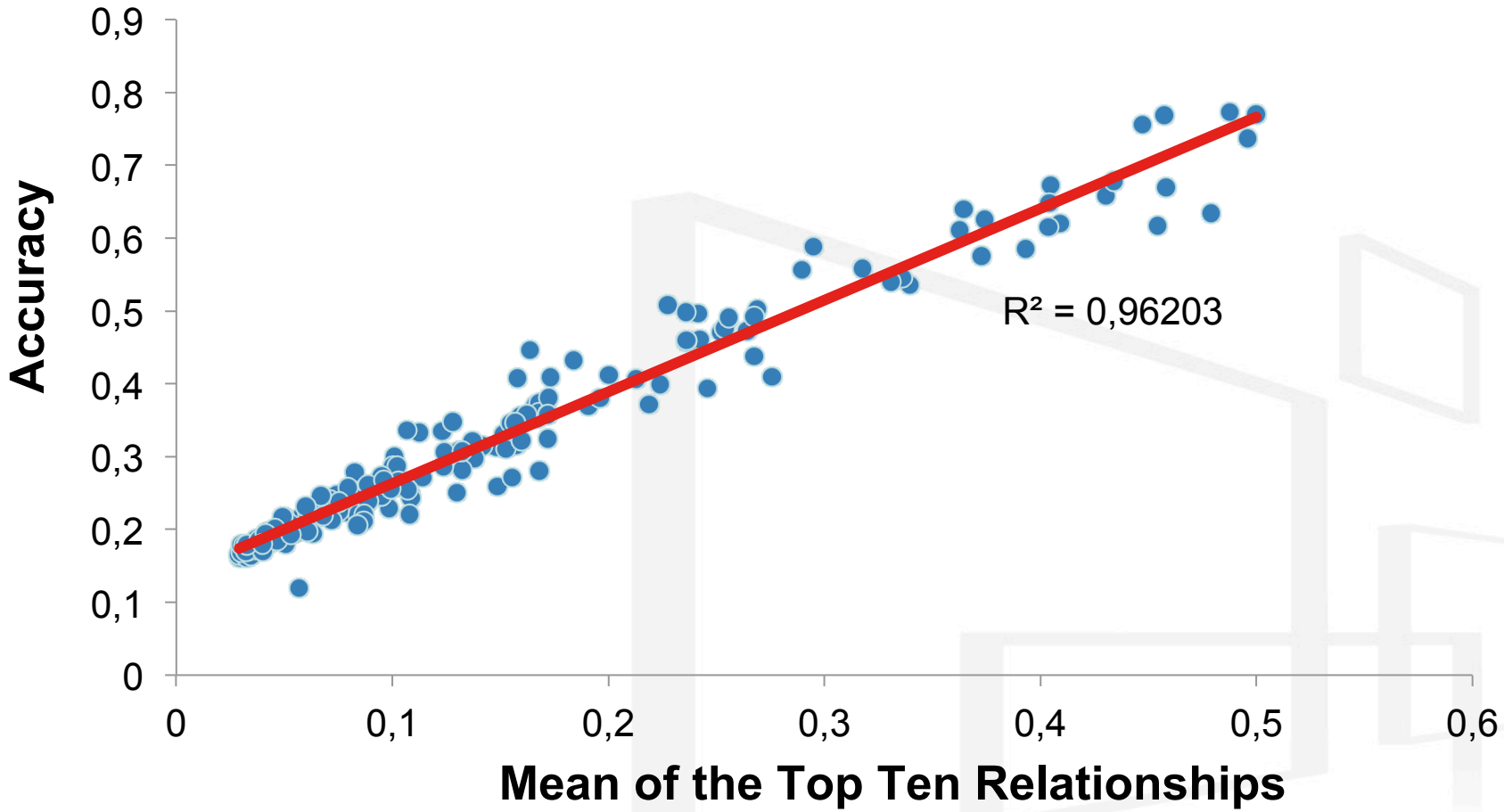
- GS has been implemented or is being implemented in all livestock species
  - » benefits over BLUP demonstrated
  - » benefits come from
    - » early prediction & reduced generation time
    - » better Mendelian sampling estimates, particularly for sex-limited traits
- Emerging evidence of benefits in salmon breeding
  - » exploits family structure in sib-testing
    - » c.f. livestock: more efficient training sets, lower SNP density needed
  - » GS models may benefit from separating within-family and between-family LD

4. Genomic Selection 2.0
   - Why isn't GS 1.0 Perfect?
   - Sequencing Populations
   - The Final Frontier?

# Why isn't GS 1.0 Perfect

- Markers effects are 'blind' predictions, not causal
  - » unable to predict unknown genetic correlations, e.g. GxE
  - » less than required for Precision Breeding
- Relies on linkage and LD, unlikely to capture full variance
  - » bovine 50k chip only captures 80% variance
- Can't predict well across breeds or lines
- Need large training sets for very good accuracies
  - » order 10,000s in livestock
  - » accuracy depends on how many close relatives
  - » but aquaculture populations often have many close relatives

# Accuracy and Relationships



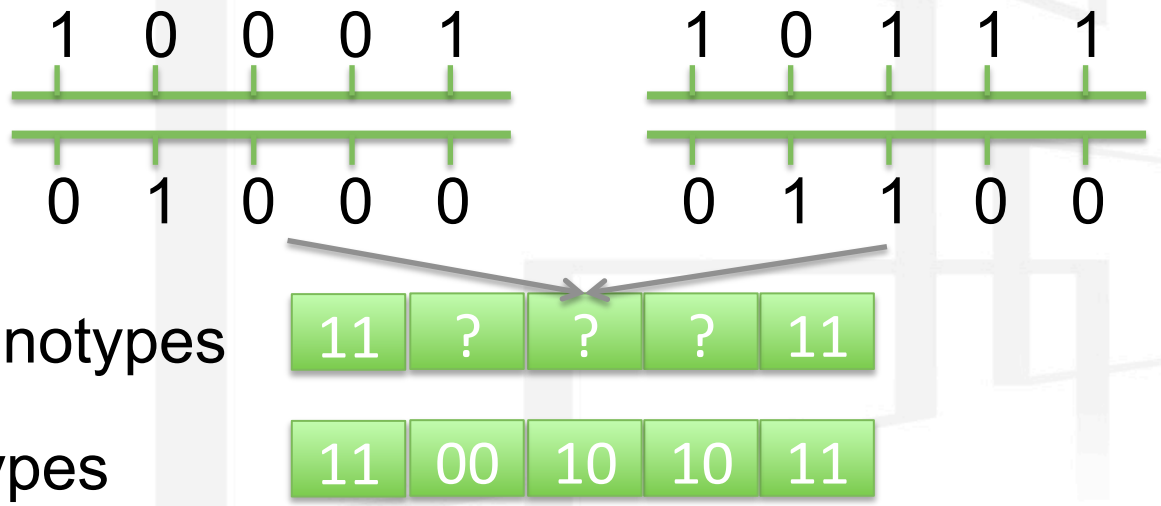

Clark et al. (2012)

# What can be done?

- Reduce cost of genotyping an individual
  - » obtain huge data

# Driving Down Unit Costs

- Imputing genotypes
  - » High density information for key individuals (e.g. sire)
  - » Low density information for candidates
  - » Exploit pedigree



# Power of Genotype Imputation

#Sires = 480
#Dams = 11,884
#Candidates = 100,000

60k chip = $120
6k chip = $48
3k chip = $35
384 chip = $20

| Scenario | MGD + PGD | Sire | Dam | Candidates | Individual cost | Accuracy of Imputation $R^2$ |
|---|---|---|---|---|---|---|
| SC1 | 0 | 60K | 0 | 384 | | 0.878 |
| SC2 | 384 | 60K | 384 | 384 | $20.58 | 0.929 |
| SC3 | 3K | 60K | 3K | 384 | $24.74 | 0.950 |
| … | | | | | | |
| SC16 | 60K | 60K | 60K | 60K | $120.00 | 1.000 |

Huang et al. (2012)

- AlphaImpute http://www.alphagenes.roslin.ed.ac.uk

# Driving Down Unit Costs

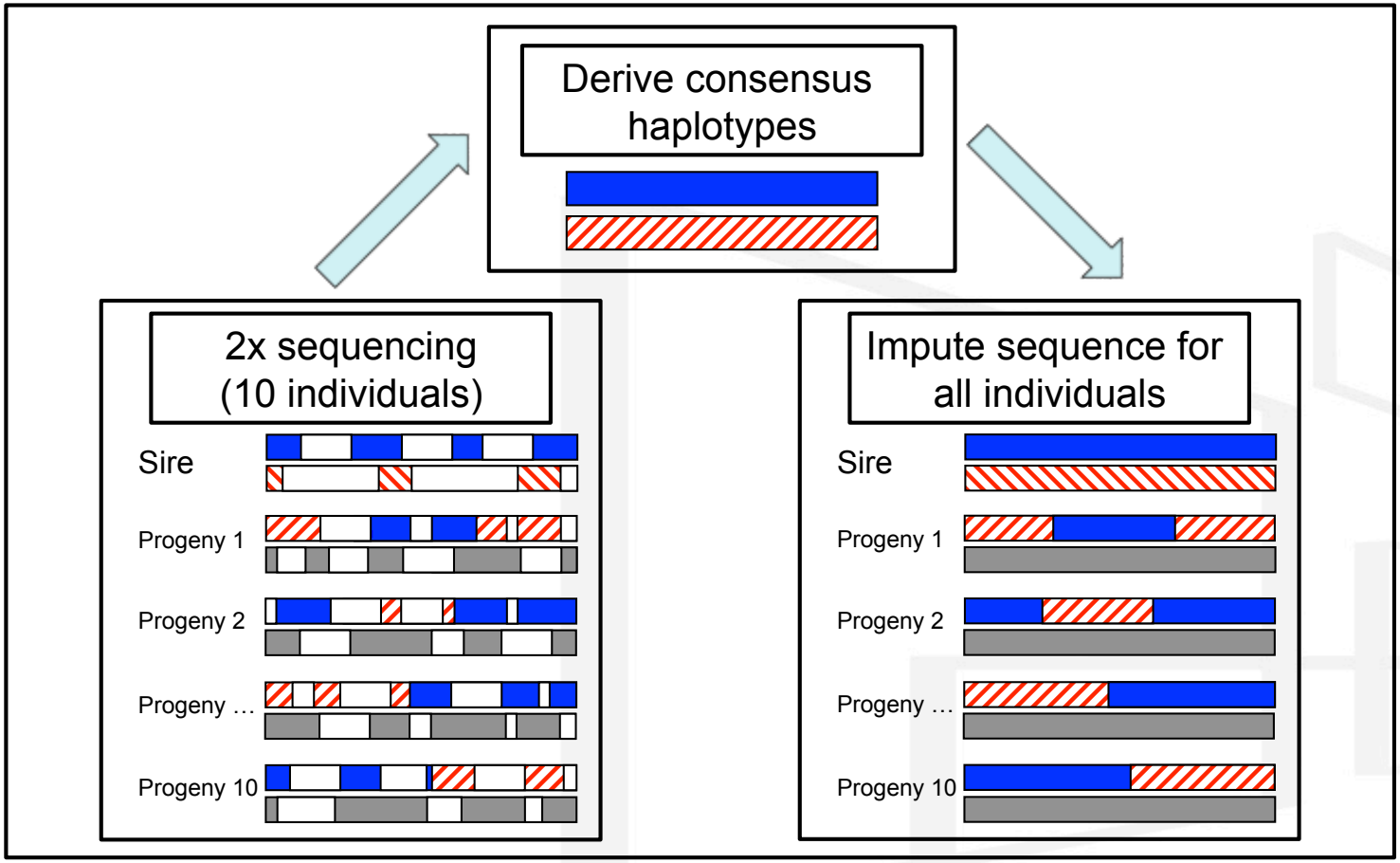
- Imputation
  - » High density information for key individuals (e.g. sire)
  - » Low density information for candidates
  - » Exploit pedigree

- Impute to what density?
  - » cost of sequencing data reducing!
  - » can we get it to $10 /individual with sequencing?

# Sequencing a Population

- ‘Traditional’ sequencing of individuals
  - » 10x or 30x coverage, still expensive
  - » therefore only sequence a few
- Sequencing a population
  - » how best to use total coverage available?
  - » genotyping by sequencing approach, 1x
  - » exploit pedigree and low Ne of livestock
    - » haplotype of key individuals are repeated many times in population
    - » sequence everyone at low coverage
    - » need new generation of imputation tools to cope with probabilistic nature of the sequencing at any locus

# Sequencing a Population



# Sequencing Populations

- Feasible to develop training sets in real populations of 300,000 animals all with sequence information
  - » before the next ISGA?

# The final frontier?

- Feasible to develop training sets in real populations of 300,000 animals all with sequence information
- Two orders of magnitude greater than '1000 Bulls' project in sequence data
- Order of magnitude greater than publically reported training sets for GS
- Will this be the final frontier?
  - » with our finite populations?

# What will final frontier look like?

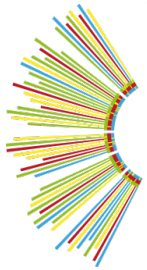

- Will accuracy be 1?
  - » it should be close
  - » if not, why not
    - » what is wrong with our models?
- How many QTN will be detected?
  - » 100's or 1000's?
  - » How much variation do detected QTN explain?


# Challenge of Precision Breeding

- Require to understand genetic correlation
  - » including GxE interactions
- Need to map QTN closely
  - » need sequence data, lots of it
  - » annotation of sequence
- To move from sequence to consequence need to understand expression and regulation
  - » to build the systems biology underling the consequences

# FAANG

- Functional Annotation of ANimal Genomes
  - » new international community consortium
- Target tissues
  - » musco-skeletal
  - » immune tissues
- Assays
  - » DNaseI, FAIREseq, ATAC-seq
  - » histone marks (promoters, enhancers)
  - » Methylation (BS-seq, RRBS)
  - » RNAseq (stranded), CAGE



FAANG
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# Conclusions

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- GS in aquaculture may be particularly beneficial due to sib testing

# Conclusions

- Major expansion of aquaculture genomes and tools emerging, while livestock are in a stage of refinement
- Success of GS is determined by the quality and size of training set
- GS proven to be successful in key livestock species
- GS in aquaculture may be particularly beneficial due to sib testing
- Genomic advances may allow us to boldly go to the final frontier

# Acknowledgements


- Sponsors of the presentation
  - » Red de Excelencia de Biotecnología en Acuicultura
  - » Aquagenomics-Net - Ministerio de Economía y Competitividad
- Sponsors of work presented
  - » EC FP7
  - » Biotechnology and Biological Sciences Research Council, UK
  - » Aviagen, Genus PIC

# Precision Breeding Goals

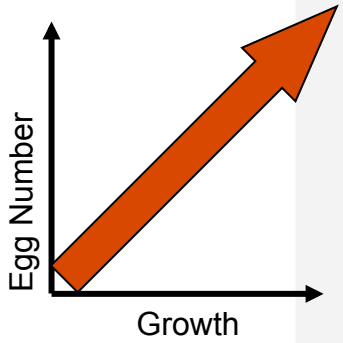
- To increase the scope and precision of predictions of the outcomes of breeding
- To avoid the introduction and advance of characteristics deleterious to animal well-being or, more generally, the well-being of the species
- To manage genetic resources and diversity between and within populations in accordance with the principles set out in the Convention on Biological Diversity

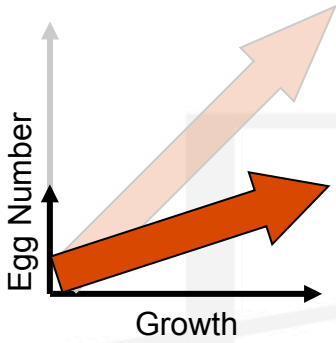
Flint & Woolliams, 2008, Proc.Roy.Soc.B

# Precise Breeding

- Differences in accuracy among traits arise from differences in amount of genetic information
  - » one trait sex-limited, one not
  - » different heritabilities
- Such differences create divergence from gains achieved using economic indices and desired gains

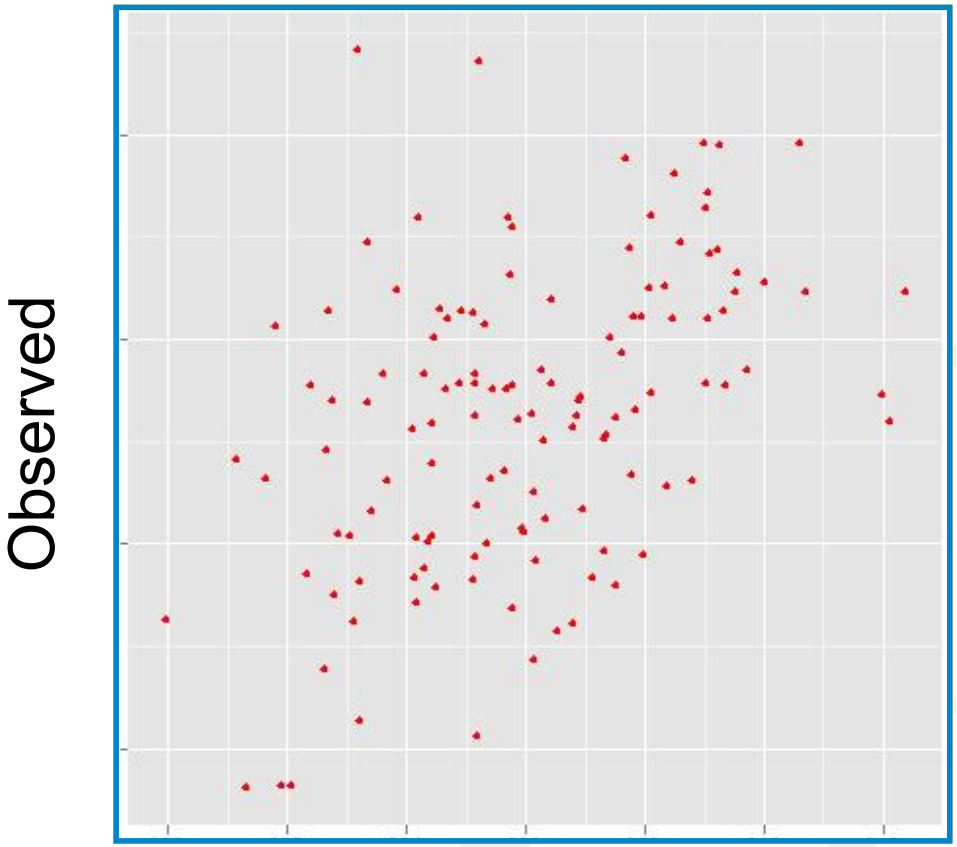
**Desired Gain**




**Achieved Gain**

# Cross Validation: Height




Set 1
r = 0.455

Set 2
r = 0.426

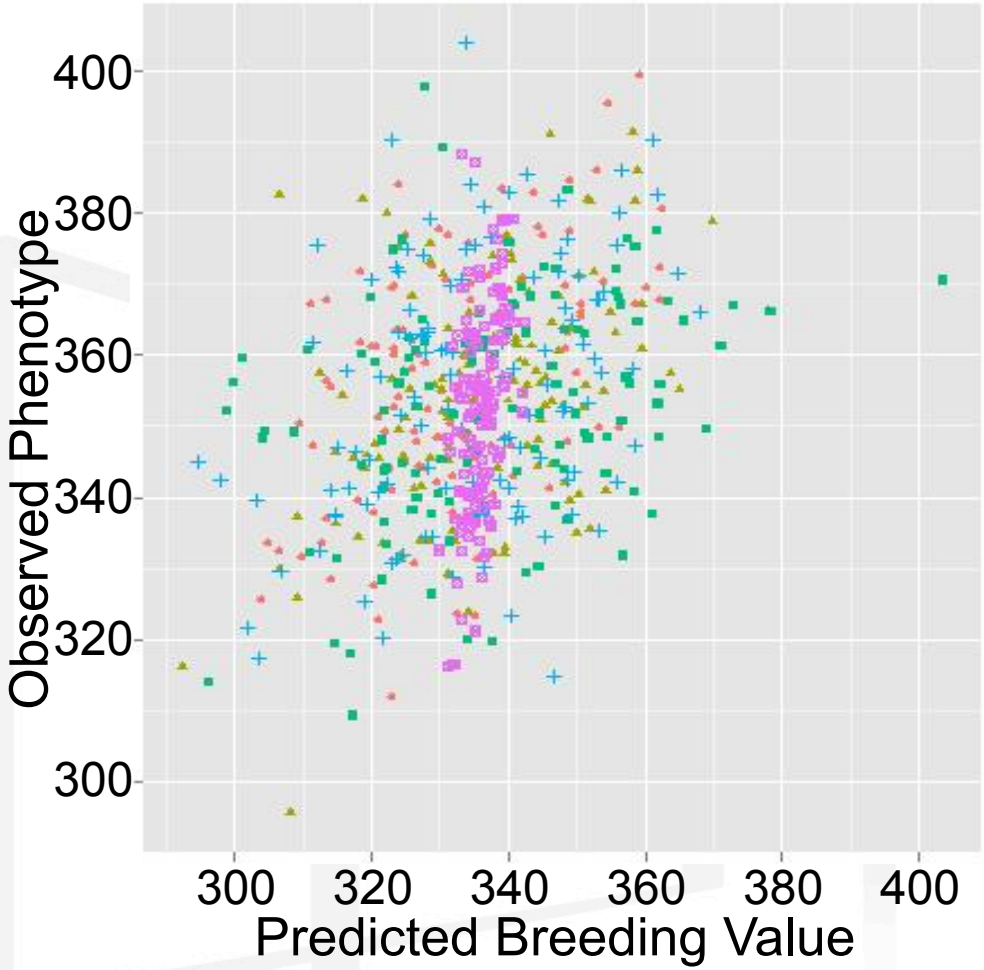
Set 3
r = 0.317

Set 4
r = 0.335

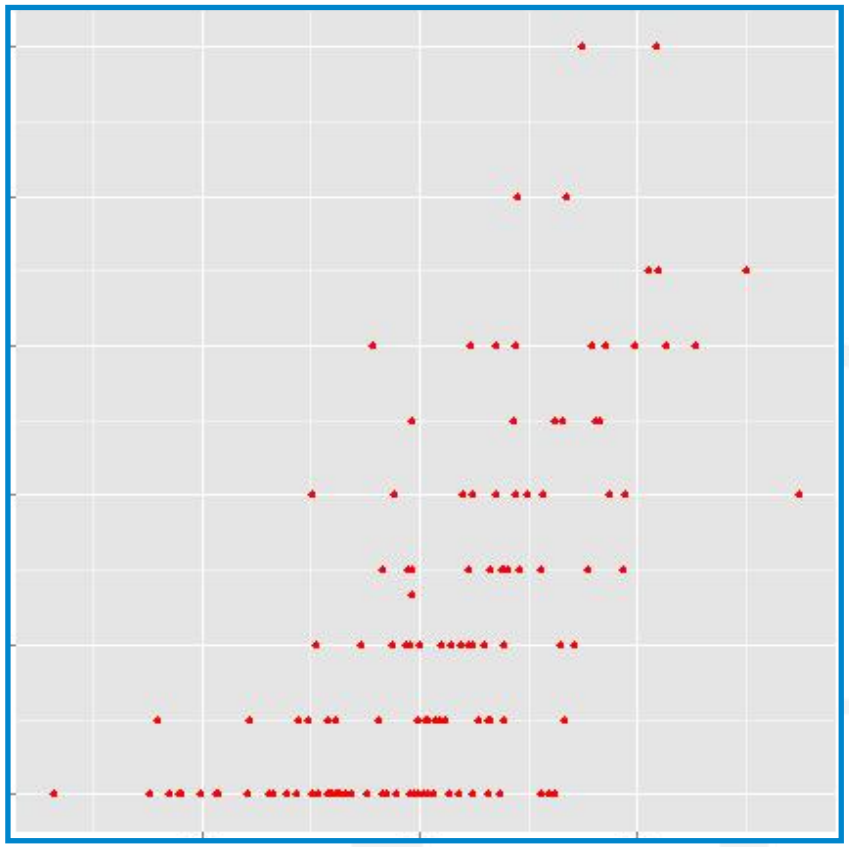
Set 5
r = 0.447

# Prediction of Height

- Accuracy = 0.400
- Max accuracy for predicting phenotype from BV is 0.548
  - » within families
  - » √0.3
- Corrected accuracy = 0.73
  - » from 497 phenotypes

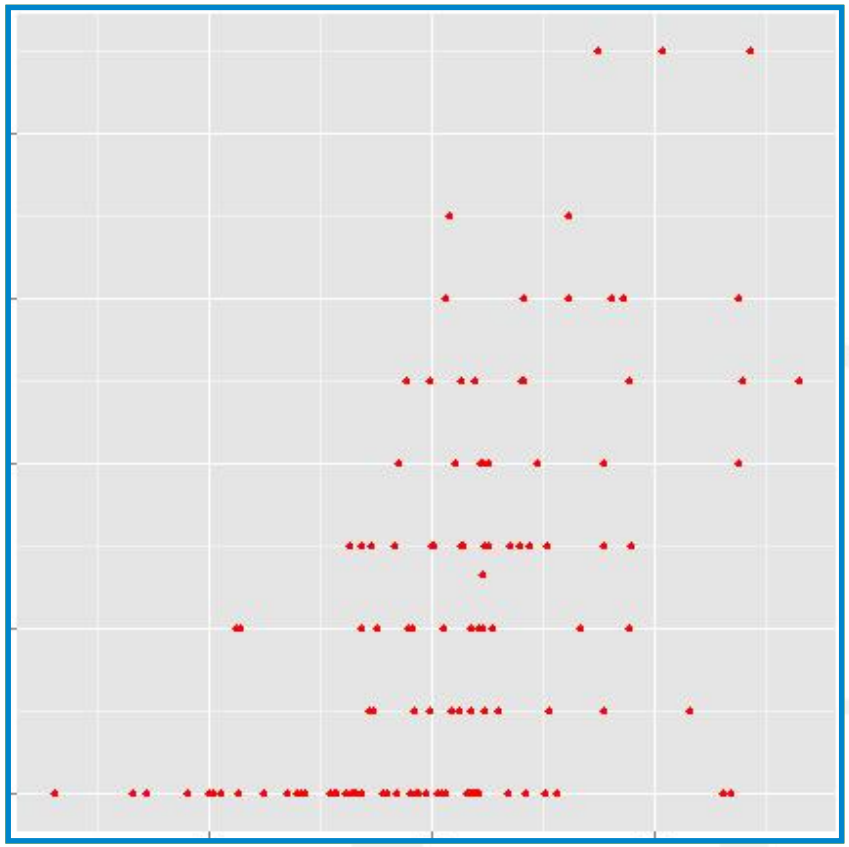


# Cross Validation: Bud Burst




Set 1
r = 0.646

# Cross Validation: Bud Burst




Set 1
r = 0.646

Set 2
r = 0.615

Set 3
r = 0.618

Set 4
r = 0.502

Set 5
r = 0.526

# Prediction of Bud Burst

- Accuracy = 0.581
- Max accuracy for predicting phenotype from BV is 0.632
  - within families
  - √0.4
- Corrected accuracy = 0.92
  - from 497 phenotypes