Impact of New Genomic Technologies on Herd Improvement and the Dynamics of Replacement Programs

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Outline

• How does genomics work?
• How accurate are the genomic predictions?
• Is there a way to reduce genotyping costs?
• Are some applications cost-effective today?
• What new applications will be developed?

Bovine Genome Sequence

30 pairs of chromosomes
3 billion base pairs (potential SNPs)

Single Nucleotide Polymorphism

“SNP Chips”

Also Illumina 3K, LD (6.9K), HD (778K), and Affymetrix HD (620K) SNP chips
Example SNP
(located at 2,153,905 base pairs on chromosome 13)

“AA” (genotype AA)  “AB” (genotype AG or GA)  “BB” (genotype GG)

Code = 0  Code = 1  Code = 2

SNP Genotype of Elevation
(part of chromosome 1)

Reference Population

Old Animals with Phenotypes

“AA”  Code = 0
“AT”  Code = 1
“TT”  Code = 2

Estimating SNP Effects

Slope of the line indicates the estimated SNP effect, which is the change in PTA protein per extra copy of a given SNP allele.

Manhattan Graph of SNP Effects

Height of the “dot” indicates the expected gain in PTA milk from inheriting one extra copy of the favorable SNP allele (match with genotype of a new calf).

Genomic PTA (GPTA) for a Young Calf

Reference Population of Older Animals

Estimated SNP Effects

Genotype New Calf using Blood or Hair Sample
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Cooperative Dairy DNA Repository

19,000 bulls with DNA samples in the CDDR

National Genetic Evaluation Program

6 million daughter performance records at USDA-AIPL

USDA-AIPL Validation Study

<table>
<thead>
<tr>
<th>Training Data (2004)</th>
<th>HOL</th>
<th>JER</th>
<th>BSW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulls with progeny</td>
<td>4,422</td>
<td>1,149</td>
<td>472</td>
</tr>
<tr>
<td>Cows with records</td>
<td>947</td>
<td>212</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>5,369</td>
<td>1,361</td>
<td>512</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testing Data (2009)</th>
<th>HOL</th>
<th>JER</th>
<th>BSW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulls with no progeny</td>
<td>2,035</td>
<td>388</td>
<td>150</td>
</tr>
</tbody>
</table>

Gains in Reliability, by Trait

<table>
<thead>
<tr>
<th>Trait</th>
<th>HOL</th>
<th>JER</th>
<th>BSW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime Net Merit</td>
<td>24%</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Milk Yield</td>
<td>26%</td>
<td>6%</td>
<td>17%</td>
</tr>
<tr>
<td>Fat Yield</td>
<td>32%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Protein Yield</td>
<td>24%</td>
<td>2%</td>
<td>14%</td>
</tr>
<tr>
<td>Fat %</td>
<td>50%</td>
<td>36%</td>
<td>8%</td>
</tr>
<tr>
<td>Protein %</td>
<td>38%</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>Productive Life</td>
<td>32%</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>Somatic Cell Score</td>
<td>23%</td>
<td>3%</td>
<td>17%</td>
</tr>
<tr>
<td>Daughter Pregnancy Rate</td>
<td>28%</td>
<td>7%</td>
<td>18%</td>
</tr>
<tr>
<td>Final Score</td>
<td>20%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Udder Depth</td>
<td>37%</td>
<td>20%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Picking the Right Calf with Genomics

<table>
<thead>
<tr>
<th>Family</th>
<th>Holstein</th>
<th>Jersey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Brothers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best Genomic PTA in November 2004 = Best Progeny Test PTA in January 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>86/126 (66%)</td>
<td>24/34 (71%)</td>
</tr>
<tr>
<td>3</td>
<td>5/30 (50%)</td>
<td>5/8 (63%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal Half Brothers</th>
<th>Family</th>
<th>Holstein</th>
<th>Jersey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Genomic PTA in November 2004 = Best Progeny Test PTA in January 2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>138/210 (66%)</td>
<td>28/41 (68%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>43/66 (65%)</td>
<td>10/16 (62%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12/26 (46%)</td>
<td>3/8 (38%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5/12 (42%)</td>
<td>2/3 (67%)</td>
<td></td>
</tr>
</tbody>
</table>
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• Are some applications cost-effective today?
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What about Commercial Females?

• At current prices, the 50K and HD chips are limited to applications involving males and elite females
• A chip with 300 to 3000 selected or equally spaced SNPs might deliver a substantial portion of the gain for a fraction of the price
• Applications may include: parentage discovery, selection among replacement heifers, preliminary screening of potentially elite young bulls and heifers, and genomic mating programs

Recombination

SNPs pass from one generation to the next in chunks (haplotypes), not independently

What is Genotype Imputation?

Aocdrnig rscheearch at Cmabrigde Unervtisy, it don't mtaer in wahn oredr the ltteerz in a wrod are, the oly iprmootnt thng is taht the frist and lsat ltteer be at the rghit pclaethe. The rset can be a toatl mses and you can stll raed it wouhht a porbelm. Tlhs is bcuseae the huamm mnid deos not raed ervry ltteer by istlef, but the wrod as a wlohe.

• Your brain can do this after you learn a language
• Imputation algorithms can do this after they learn which haplotypes are present in the reference population

Accuracy of Imputed Genotypes

• Use 50K genotypes of 2,542 Jersey bulls, cows, heifers, and calves born in 1953-2006 as the reference panel for building haplotypes
  ➔ “Training Set”

• Mask and impute genotypes for 20, 40, 80, 90, 95, 98, or 99% of SNPs in 604 Jersey bulls, cows, heifers, and calves born in 2007-2009 to evaluate the accuracy of genotype imputation
  ➔ “Testing Set”

AI Bulls and Elite Cows

• Genomic proofs became official in January 2009
• Genomic evaluations for young bulls now have reliability similar to early first-crop evaluations
• AI organizations are marketing hundreds of genome-tested 2, 3, or 4 year-old bulls: You should use these bulls, but use fewer units per individual bull to mitigate risk
• Genotypes are often required for bull dams or other animals that are being marketed
Accuracy of Imputed Genotypes

- We need about 3,000 SNPs to impute 50K genotypes correctly.

Accuracy of Imputed PTAs: Milk

- Reference PTA with No Masked Genotypes
- Reference PTA with No Masked Genotypes
- PTA with Imputation of Masked Genotypes

Accuracy of Imputed PTAs: Protein %

- Reference PTA with No Masked Genotypes
- Reference PTA with No Masked Genotypes
- PTA with Imputation of Masked Genotypes

Accuracy of Imputed PTAs: Fertility

- Reference PTA with No Masked Genotypes
- Reference PTA with No Masked Genotypes
- PTA with Imputation of Masked Genotypes

Accuracy of Imputed PTAs

- Use 50K genotypes and 2006 phenotypes for 1,446 Jersey bulls with progeny in May 2006 as reference animals to build haplotypes and estimate SNP effects → "Training Set"
- Mask and impute 93, 96, 98, or 99% of SNPs in 316 Jersey bulls with progeny in April 2009, compute genomic PTAs from imputed SNPs and evaluate accuracy of the predictions → "Testing Set"
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Strategies for Genotyping Females

- Test the whole herd
- Screen potentially elite animals for marketing
- Screen potentially inferior animals for culling
- Screen animals “at risk” for selection or culling

Which is the Best Heifer?

University of Wisconsin Dairy Herd

Heifer 6347

Net Merit $5
Genomic PTA for Milk Yield

Selection of Replacement Heifers

University of Wisconsin Dairy Herd

Average REL
27% before testing
65% after testing

Superior Genetics

Potential Bulls

0 40 80 120 150

Net Merit $5

Do you really want these heifers, or their offspring, in your herd?
Design of Simulation Study

- 1000-cow herd plus replacement heifers
- Replicated 100 times
- Selection for lifetime net merit (NMs)
  - mean = $45, standard deviation = $198
- Genetic trend in PTA = +$28 per year
- Error rate in sire identification = 15%
- Cost of 3K genomic test = $40 per animal

Reliability without / with Genomics

<table>
<thead>
<tr>
<th>Age Group</th>
<th>3K + No Pedigree</th>
<th>3K + Sire Known</th>
<th>3K + Full Pedigree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves &lt; 12 mo of age</td>
<td>0.00 / 0.48</td>
<td>0.22 / 0.58</td>
<td>0.35 / 0.62</td>
</tr>
<tr>
<td>Yearlings 12-24 mo of age</td>
<td>0.00 / 0.49</td>
<td>0.23 / 0.59</td>
<td>0.36 / 0.63</td>
</tr>
<tr>
<td>Milking cows 2 yr of age</td>
<td>0.20 / 0.55</td>
<td>0.24 / 0.61</td>
<td>0.42 / 0.64</td>
</tr>
<tr>
<td>Milking cows 3 yr of age</td>
<td>0.22 / 0.58</td>
<td>0.38 / 0.63</td>
<td>0.47 / 0.66</td>
</tr>
<tr>
<td>Milking cows 4 yr of age</td>
<td>0.24 / 0.60</td>
<td>0.42 / 0.64</td>
<td>0.52 / 0.68</td>
</tr>
<tr>
<td>Milking cows 5 yr of age</td>
<td>0.25 / 0.61</td>
<td>0.45 / 0.65</td>
<td>0.55 / 0.69</td>
</tr>
<tr>
<td>Milking cows 6 yr of age</td>
<td>0.26 / 0.62</td>
<td>0.47 / 0.66</td>
<td>0.57 / 0.70</td>
</tr>
<tr>
<td>Milking cows 7 yr of age</td>
<td>0.27 / 0.63</td>
<td>0.48 / 0.66</td>
<td>0.58 / 0.70</td>
</tr>
</tbody>
</table>
### What’s the Best Strategy?

- Genotyping is most informative for animals with missing or incorrect pedigrees and animals that don’t yet have performance data.
- Whole-herd genotyping may be cost effective if pedigree and performance data are unavailable.
- Pre-sorting animals by pedigree values and testing the subset that are “at risk” for selection or culling may be preferred if accurate pedigrees are available.

### Outline

- How does genomics work?
- How accurate are the genomic predictions?
- Can we use genomics on commercial farms?
- Are some applications cost-effective today?
- What new applications will be developed?

### Managing Inbreeding

<table>
<thead>
<tr>
<th>Registration Number</th>
<th>Pedigree-Based Inbreeding Estimate</th>
<th>% Heterozygous SNPs on Genom Chip</th>
</tr>
</thead>
<tbody>
<tr>
<td>JEAUS00115954478</td>
<td>18.6%</td>
<td>28.3%</td>
</tr>
<tr>
<td>JEAUS00115486672</td>
<td>17.4%</td>
<td>29.8%</td>
</tr>
<tr>
<td>JEAUS00087046018</td>
<td>14.1%</td>
<td>34.4%</td>
</tr>
<tr>
<td>JEAUS00114624440</td>
<td>14.0%</td>
<td>34.1%</td>
</tr>
<tr>
<td>JEAUS00115011391</td>
<td>14.0%</td>
<td>39.3%</td>
</tr>
<tr>
<td>JEAUS00087181563</td>
<td>13.0%</td>
<td>36.5%</td>
</tr>
<tr>
<td>JEAUS00115752423</td>
<td>12.6%</td>
<td>36.2%</td>
</tr>
<tr>
<td>JEAUS00114669078</td>
<td>12.5%</td>
<td>39.4%</td>
</tr>
<tr>
<td>JEAUS00087072713</td>
<td>12.2%</td>
<td>34.5%</td>
</tr>
<tr>
<td>JEAUS00115458806</td>
<td>12.2%</td>
<td>34.1%</td>
</tr>
</tbody>
</table>
Selecting for New Traits

- Measurement of traits like feed intake, hormone levels, immune function, etc. is not possible on tens of thousands of progeny test daughters each year
- These traits can be measured in a reference population of 5,000 to 20,000 cows on experimental farms or collaborating commercial farms
- The resulting SNP effect estimates can be matched with genotypes of young bulls and heifers on other farms for use in selection and management decisions

Summary: Example Herd Protocol

1. Submit hair or blood cards when heifer is 9-10 months of age
2. If GPTA for Lifetime Net Merit > $600, flush once and then breed to the best available AI bull based on recommended pedigree mating
3. If GPTA for Lifetime Net Merit is $400-600, breed to the best available AI bull using sexed semen
4. If GPTA for Lifetime Net Merit is $200-400, breed to the best available AI bull using conventional semen
5. If GPTA for Lifetime Net Merit is $75-200, use as recipient for a fresh embryo or frozen embryo (if fresh is unavailable), or breed to an AI bull in the 80th percentile (if fresh and frozen are unavailable)
6. If GPTA for Lifetime Net Merit is < $75, breed to an AI bull in the 80th percentile and sell as a short-bred heifer

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