“Dairy – where biology meets social science”

Alison Van Eenennaam, Ph.D.
Cooperative Extension Specialist
Animal Biotechnology and Genomics
Department of Animal Science
University of California, Davis, USA
Email: alvaneenennaam@ucdavis.edu
Twitter: @BioBeef
Blog: biobeef.faculty.ucdavis.edu
http://animalscience.ucdavis.edu/animalbiotech

“Plant and animal breeders have perhaps the most compelling sustainability story of all time”

Genetic improvement is successful

Greg Botelho

A range of technologies can be used to alter the four components of the breeders’ equation

Genetic change per year = \( \sqrt{\text{Reliability} \times \text{Intensity} \times \text{Genetic Variation}} \)

Generation Interval

reliability = how certain we are about our estimate of an animal’s genetic merit (↑)

selection intensity = function of fraction selected (↑)

genetic variance = [modern biotechnology] (↑)

generation interval = time between generations (↓)

“Artificial insemination was initially a controversial technology”

“In the initial stages of attempting to develop AI there were several obstacles. The general public was against research that had anything to do with sex. Associated with this was the fear that AI would lead to abnormalities. Finally, it was difficult to secure funds to support research because influential cattle breeders opposed AI, believing that this would destroy their bull market.”


“Name the technological innovation”

“It is unknown what long term health consequences may unfold. The studies are not adequate. Furthermore, this will likely not be available or cost effective for small farmers, it will decrease product acceptance and consumption.”

Quote from the introduction of the Pasteurized Milk Ordinance 1924
Crop/species | 2017 total production | 2017 amount needed at 1950's rate | Additional needed |
--- | --- | --- | --- |
Soybeans | 4,391,553,000 BU | 82,591,000 Acres | ~ 120 million Acres |
| (261,493,180,000 lb) | (81,898,546 ha) | (119,769,627,000 kg) |
Corn | 14,604,067,000 Bu | 83,136,000 Acres | ~ 300 million Acres |
| (817,827,752,000 lb) | (33,643,946 ha) | (371,739,887,000 kg) |
Dairy cattle | 215,466,000,000 lbs milk | 9,392,180 head | ~ 31 million head |
| (97,999,010,890 kg) | | |
Broilers | 41,039,000,000 lbs meat | 8,913,000,000 head | ~ 4.4 billion head |
| (18,654,091,980 kg) | | (66.5 billion lbs fed as less efficient FCR) |
History of the main changes in USDA selection indexes for dairy cattle and economics value (%) on traits included in the index

<table>
<thead>
<tr>
<th>Traits included</th>
<th>USDA genetic-economic index (and year introduced):</th>
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<tbody>
<tr>
<td>PEDS</td>
<td>(1971)</td>
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<tr>
<td>MFP</td>
<td>(1976)</td>
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<td>(1994)</td>
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<td>Milk</td>
<td>52</td>
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<tr>
<td>Fat</td>
<td>27</td>
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<tr>
<td>Protein</td>
<td>48</td>
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<tr>
<td>Productive life</td>
<td>27</td>
</tr>
<tr>
<td>Somatic cell score</td>
<td>36</td>
</tr>
<tr>
<td>Udder composite</td>
<td>7</td>
</tr>
<tr>
<td>Feet/legs composite</td>
<td>4</td>
</tr>
<tr>
<td>Body size composite</td>
<td>4</td>
</tr>
<tr>
<td>Daughter pregnancy rate</td>
<td>7</td>
</tr>
<tr>
<td>Calving ability</td>
<td>6</td>
</tr>
<tr>
<td>Cow conception rate</td>
<td>7</td>
</tr>
<tr>
<td>Heifer conception rate</td>
<td>1</td>
</tr>
<tr>
<td>Cow liveability</td>
<td>7</td>
</tr>
</tbody>
</table>

Graph available at: https://queries.uscdcb.com/eval/summary/trend.cfm?R_Menu=HO.d#StartBody

The bovine genome is similar in size to the genomes of humans, with an estimated size of 3 billion base pairs.

The sequencing of the bovine genome allowed for the development of a 50,000 SNP chip, can genotype 50,000 markers at once and identify naturally occurring genetic variation associated with superior performance.

We can use these SNP CHIPS for “genomic” selection?

1000 Bull Genomes Run 6
2703 Sequenced Animals, 11x
~55 Breeds: Dairy, Beef, Dual Purpose, Crosses, Composites
2703 x 11 x 3 billion = 90,000,000,000,000

REFERENCE POPULATION
1,000s animals
– Phenotypes
– Genotypes

Training = estimate the value of every chromosome fragment contributing variation in a population with phenotypic observations

Prediction = the results of training can then be used to develop prediction equations to predict the merit of new animals (e.g. young bulls)
### Millions of Records in dairy database

- **Pedigree records**: 71,974,045
- **Animal genotypes**: 1,035,590
- **Lactation records (since 1960)**: 132,629,200
- **Daily yield records (since 1990)**: 641,864,015
- **Reproduction event records**: 179,559,035
- **Calving difficulty scores**: 29,528,607
- **Stillbirth scores**: 19,567,198

Data from George Wiggins, USDA ARS (7/2015)

### Millions of genotypes in the database

![Graph showing the number of genotypes over time](image)

- Imputed, young
- Imputed, old (young cows included before March 2012)
- Old, <50K, young, female
- <50K, young, male
- <50K, old, female
- <50K, old, male (≥20 bulls)
- ≥50K, young, female
- ≥50K, young, male
- ≥50K, old, female
- ≥50K, old, male

### Genotypes (August 2017)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Bulls</th>
<th>Cows</th>
<th>Total genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holstein</td>
<td>36,933</td>
<td>409,593</td>
<td>1,656,430</td>
</tr>
<tr>
<td>Jersey</td>
<td>5,260</td>
<td>77,714</td>
<td>200,070</td>
</tr>
<tr>
<td>Brown Swiss</td>
<td>6,729</td>
<td>2,633</td>
<td>31,488</td>
</tr>
<tr>
<td>Ayrshire</td>
<td>796</td>
<td>295</td>
<td>7,692</td>
</tr>
<tr>
<td>Guernsey</td>
<td>470</td>
<td>748</td>
<td>3,235</td>
</tr>
<tr>
<td>Crossbred</td>
<td></td>
<td></td>
<td>59,905</td>
</tr>
</tbody>
</table>

Source: National Dairy Database, August 2017

### Genomic selection can help breeders identify animals with superior breeding values at a young age

**Genetic change per year =**

\[
\frac{1}{\text{Reliability}} \times \text{Intensity} \times \text{Genetic Variation} 
\]

**Generation interval** = time between generations

**Reliability** = how certain we are about our estimate of an animal’s genetic merit

**Selection intensity** = function of fraction selected

**Genetic variance** = [modern biotechnology]

### Rate of genetic gain in marketed Holstein bulls has doubled since 2009 genomic selection introduction

![Chart showing rate of genetic gain](image)

- **Average gain: $US50.49/year**
- **Average gain: $US17.72/year**

### What’s a single SNP genotype worth?

- **Pedigree is equivalent to information on ~7 daughters**
- **For protein yield \( h^2=0.20 \), the SNP genotype provides information equivalent to an additional ~12 daughters**

Source: National Dairy Database, August 2017
What’s a single SNP genotype worth?

And for daughter pregnancy rate (h₂ = 0.04), SNP = ~181 daughters

The Genomic Bull

Reference Population

Known genotype and phenotypes

Selection Candidate

Prediction Equation

Genomic breeding value = fₓ₁ + fₓ₂ + fₓ₃ + ... 

Matter genotypes

Selected Breeders

Using genomic breeding values

Lost rBST to the fearmongering ($$)

got hormones? we don’t.

got responsibility? we don’t either!

Our milk results in 7% more methane emissions per glass because we cater to fearmongering about safe technology to increase our sales $$$

Increased methane/unit milk by ~ 7%

Table 1. Effects of rBST use on resource input and waste output (per unit of milk) over the lactation cycle of an average cow

<table>
<thead>
<tr>
<th>Resource Input or waste output per kilogram of milk</th>
<th>Change per unit of milk with rBST use, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resource Inputs</td>
<td></td>
</tr>
<tr>
<td>Net energy for maintenance, MJ</td>
<td>1.73</td>
</tr>
<tr>
<td>Metabolizable protein for maintenance, g</td>
<td>0.82</td>
</tr>
<tr>
<td>Total net energy requirement, MJ</td>
<td>4.79</td>
</tr>
<tr>
<td>Total metabolizable protein requirement, g</td>
<td>77.4</td>
</tr>
<tr>
<td>Feedstuffs per kg dry matter</td>
<td>6.1</td>
</tr>
<tr>
<td>Waste outputs</td>
<td></td>
</tr>
<tr>
<td>Methane, g</td>
<td>26.2</td>
</tr>
<tr>
<td>Manure, kilogram freshweight</td>
<td>1.92</td>
</tr>
<tr>
<td>N excretion, g</td>
<td>5.67</td>
</tr>
<tr>
<td>P excretion, g</td>
<td>5.96</td>
</tr>
</tbody>
</table>

Genetic change per year = \( (\sqrt{\text{Reliability} \times \text{Intensity} \times \text{Genetic Variation}}) \) 

Selectivity = how certain we are about our estimate of an animal’s genetic merit

Selection intensity = function of fraction selected

Genetic variance = modern biotechnology

Generation interval = time between generations

Where does genetic engineering come into the breeders equation?

Mastitis-resistant cows (inflammation of mammary gland)


Genetically enhanced cows resist intramammary Staphylococcus aureus infection

Approved commercially-available Genetically Engineered (GE) food animals

The regulation of genetically engineered (GE) animals in US is by Food & Drug Administration

The Food and Drug Administration’s (FDA) Center for Veterinary Medicine (CVM) evaluates GE animals under the new animal drug provisions of the Federal Food Drug and Cosmetic Act (FDCA). The act defines drugs as “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” The DNA construct in the resulting GE animal is thus a regulated article that meets the drug definition; the GE animal itself is not a drug.

Hierarchical Risk-Based Evaluation (by level)

Does it work?

Is it safe?

Is it durable?

What is its phenotype?

What is its genotype?
**Gene or Genome Editing**

What are we talking about?

- Meganuclease
- Zinc finger TALENs
- CRISPR/Cas9
- Nuclease-induced double-strand break
- Indels = Insertions/Deletions
- Variable length indels
- Precise insertion or modification

**Editing is the Cherry on Top of Breeding Sundae**

Simulation model found accelerated rate of genetic gain (ΔG) when combining genome edits with genomic selection program

- Genome Editing
- Somatic cell nuclear transfer cloning
- Genomic Selection
- Embryo Transfer
- Artificial insemination
- Progeny testing
- Performance recording
- Breed Association

**What is the problem we are trying to solve?**

**Tuberculosis**

CRISPR used in cows to help fight tuberculosis


**Genetic improvement (permanent, cumulative) as a solution to animal disease rather than antibiotics/chemicals**

**What is the problem we are trying to solve?**

Need to manually remove horns from dairy calves to protect human handlers and other animals

https://www.youtube.com/watch?v=Qks_LMmodw
5 bull calves and 1 heifer calf offspring of gene edited (PP) bulls were born in September, 2017 - They are all hornless

January 18th, 2017 FDA draft guidance considers all gene edited animals whose genomes have been “altered intentionally” to be drugs

Are Gene Edited Horn-less calves a drug?
Naturally occurring bovine allele at Polled locus
What is the “new animal drug” in this case?

I am not a drug

Does it make sense to regulate polled dairy calves differently to polled beef calves?

Many applications of genetic technologies, including GE animals align with many sustainability goals including improved animal well-being, efficiency and reduced environmental footprint

Please sign this petition if you agree that:
https://tinyurl.com/DNAisNOTaDRUG
SUMMARY

- Animal breeding programs increasingly utilize a combination of advanced biotechnologies to accelerate the rate of genetic gain.
- There are a number that involve the use of in vitro processes, and many result in genetic modifications that are indistinguishable from the naturally-occurring variation.
- FDA currently regulates GE food animals and requires premarket approval.
- GE animal regulatory burdens to date have been high and associated with unaccountable delay and considerable uncertainty.
- Proposed regulations for gene editing are unworkable and unscientific.
- Ultimately, biotechnologies complement the genetic improvement that can be accomplished using traditional selection techniques and, if breeders are allowed to use them, offer an opportunity to synergistically accelerate genetic improvement in food animal species.

Questions?