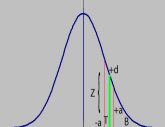


**Where are we going with genomics and genetic improvement?**

**Matt Spangler, Ph.D.**  
Associate Professor of Animal Science/  
Extension Beef Genetics Specialist  
Department of Animal Science  
University of Nebraska – Lincoln, NE

**Alison Van Eenennaam, Ph.D.**  
Cooperative Extension Specialist  
Animal Biotechnology and Genomics  
Department of Animal Science  
University of California - Davis, CA




BIF 6/1/2017

**Quantitative geneticist view of molecular geneticist**

We need to understand what is in the black box

What is the infinitesimal model?

Let's do some more Genome-Wide Association Studies (GWAS)

Does every presentation seriously have to include a Manhattan plot?



**Molecular geneticist view of quantitative geneticist**

Bayes A, B, C, D, E, WTF

I don't care what is in the black box

Does every presentation seriously have to include an equation?

Single Step vs. Bayes whatever

$$P = G + E$$

$$V_P = V_G + V_E$$

$$V_P = V_A + V_D + V_I + V_E$$

Phenotypic Variance = Additive Genetic Variance + Dominant Genetic Variance + Environmental Variance



**This century triggered a DNA avalanche**

DNA TESTING



BIF 6/1/2017

**2003**

**Merial, Quantum sign leptin test pact.(Business Report)**

Publication: Feedstuffs

Publication Date: 04-AUG-03

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SASKATOON, SASK., and DULUTH, GA. -- Quantum Genetics Inc. and Merial Ltd. announced July 23 that they have entered into a global marketing agreement to provide Merial with exclusive rights to market Quantum's new patent-pending DNA test to determine an animal's leptin genotype.

The leptin protein has been demonstrated...

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BIF 6/1/2017

**Igenity L**

**Know. Now.**

**Igenity™ L. Know. Now.**

**Advanced technology. Advanced knowledge.**

What if there was a test that could tell you - in advance - an animal's genetic potential for energy utilization or carcass quality? You'd have the advantage of knowing an animal's potential now, instead of discovering it later through success or failure in the milk string or when the animal goes to market.

Researchers have discovered the specific gene that carries the code for the production of a protein called leptin. Leptin is associated with an animal's potential for appetite and energy utilization, among other things.

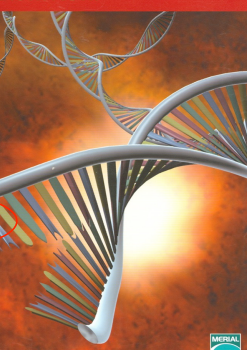
- For dairy cattle this translates directly into maximum dry matter intake (DMI) and peak milk production.
- For beef cattle it relates to days on feed and carcass quality.

The IGENITY™ L Test identifies leptin genotype (L-4\*, L-ct\* or L-cc\*). Now you have another important resource to help you breed, feed, sort, manage and market cattle at an optimum level.

- Leptin is involved in the regulation of feed intake, energy balance, milk production, milk components, marketing scores, puberty, fertility and immune functions.
- Knowing an animal's leptin genotype empowers you to make more informed, strategic management decisions regarding breeding and nutrition.
- The IGENITY™ L Test identifies an animal's leptin genotype at the DNA level, with 100% accuracy.

Market your cattle with the IGENITY L logo system:

- L-4\*
- L-ct\*
- L-cc\*



## A lot of detail about the marker

**Introduction to the Leptin Protein in Cattle**

**Not All Leptin is Created Equal**

**Leptin** is a protein that influences appetite and metabolism energy storage and utilization. Leptin is produced by fat tissue stored by the body as energy reserves. The more fat there is, the higher the leptin concentration (concentration of leptin) in the blood.

High concentrations of leptin normally signal the brain to suppress appetite and slow or inhibit energy for metabolism.

Normal types of leptin are not easily recognized by the brain, so appetite and metabolism are not changed.

The **IGENITY™** L test can identify the genetic variation that determines what type of leptin an animal will produce.

Leptin is involved in a feedback system involving the hypothalamus region of the brain. When leptin receptors register high concentrations of leptin, they send signals to suppress appetite and increase metabolism.

The gene that encodes the code for leptin production has been called the "leptin" gene or "leptin" gene. Location of leptin's association with appetite and metabolism.

When certain is present at the gene site for leptin production, normal leptin results. When leptin is present, it changes the amino acid structure of leptin – changing it.

If an animal has one chromosome with a "C" at the critical site and one containing a "T", then it creates both types of leptin.

The science behind the IGENITY™ L test identifies leptin genotype and provides valuable knowledge for feeding and breeding decisions.

**Leptin Genotype. It pays to know now.**

Identifying leptin genotype and selecting breeding for desired leptin genotype can have a great impact on a dairy or beef operation.

The benefits can extend beyond increased milk production in dairy herds to improved management skills for select culling and transition cow numbers, or beef finishing and marketing strategies.

The beneficial result is that cattle with the L1 genotype receive a "leptin" allele and are predisposed to consume more feed.

**Activity of L-64<sup>TM</sup> Leptin and Receptors**

The L-64<sup>TM</sup> is structurally different and is more difficult for receptors to recognize. As a result, there is no signal to reduce appetite.

L-64<sup>TM</sup> cattle produce both types of leptin – some normal, some difficult to recognize.

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**IGENITY™ L**

Know. Now.

## BOVIGENE

**GeneSTAR™ MARBLING**

GeneSTAR™ Marbling is a DNA genetic marker owned by Bovigen Solutions, LLC, for a major gene (Thymolphilic) associated with marbling. This marker provides beef producers the opportunity to determine an animal's potential for improved marbling more accurately and at an earlier age.

**Marbling Results (% Choice) Difference**

| Yearling | 50% | 62% | 74% | 86% |
|----------|-----|-----|-----|-----|
| Yearling | 50% | 62% | 74% | 86% |
| Cal Fec  | 54% | 41% | 53% | 70% |
| NBCF     | 47% | 54% | 64% | 77% |

In independent trials on over 1500 head, 2 STAR animals produced 10% more choice carcasses than 0 STAR animals. Equally important was the effect that the proportion of carcasses qualifying for premium Choice Grades (25% vs. 10%) in 2 STAR carcasses versus 0 STAR.

This was a study conducted by an independent third party.

**National Beef Cattle Evaluation Consortium.**

**LEGEND**

The results of the GeneSTAR™ tests are reported as:

- 0 STAR - one copy of the desired gene
- 1 STAR - one copy of each form of the gene
- 2 STAR - one copy of the desired gene

**HOW DO I USE THIS IN MY BREEDING PROGRAM?**

Using 2 STARs is the quickest way to influence the presence of these genes in a herd. In addition, selecting 2 STAR females will more quickly increase the frequency of the positive form of the gene. Overall, selecting 2 STAR animals with appropriate EPDs and good structural and blending soundness is the recommended way forward.

**Mating Design**

| Size | Dam | % of Progeny |
|------|-----|--------------|
| 0    | 0   | 100%         |
| 0    | 1   | 50%          |
| 0    | 2   | 100%         |
| 1    | 0   | 50%          |
| 1    | 1   | 25%          |
| 1    | 2   | 50%          |
| 2    | 0   | 100%         |
| 2    | 1   | 50%          |
| 2    | 2   | 100%         |

## One SNP was purported to address multiple traits and explain a lot of genetic variation in quantitative traits – that made sense to some people – especially those with no training in quantitative genetics!

**Now, know more about the genetic potential of your cattle.**

**IGENITY™ L**

Know. Now.

**BOVIGENE SOLUTIONS, LLC**

6/1/2017

## Independent validation of DNA tests

<http://www.nbcec.org/nbcec/>

**National Beef Cattle Evaluation Consortium**

**Commercial genetic test validations**

The purpose of the NBCEC commercial DNA test validation is to independently verify associations between genetic tests and traits as claimed by the commercial genotyping company using phenotypes and DNA from reference cattle populations.

The validation process is a partnership of the owners of DNA and phenotypes (e.g., breed associations) and genomics companies, facilitated by the NBCEC.

**A. L. Van Eenennaam, J. Li, R. M. Thallman, R. L. Quaas, M. E. Dikeman, C. A. Gill, D. E. Franke, M. G. Thomas. 2007. Validation of commercial DNA tests for quantitative beef quality traits. Journal of Animal Science. 85:891-900.**

6/1/2017

## First multi-gene test arrives

**GeneSTAR™ Tenderness**

GeneSTAR™ Tenderness was the first multi-gene test to be commercially available in the beef industry. It combines test results for several markers and genes for the same trait. The test is based, in part, on two genes involved in the post-mortem tenderness process: Calpain and Calpastatin. Calpain is an enzyme which weakens muscle fibers thereby making the fibers more tender. Calpastatin is an enzyme which inhibits the post-mortem tenderness process by inhibiting the effects of Calpain.

**GeneSTAR™ Tenderness Genetic Progeny Difference**

| T1 | T2 | T3 | Star Price |
|----|----|----|------------|
| 0  | 0  | 0  | 1.4        |
| 0  | 0  | 1  | 1.4        |
| 0  | 0  | 2  | 1.4        |
| 0  | 1  | 0  | 1.4        |
| 0  | 1  | 1  | 1.4        |
| 0  | 1  | 2  | 1.4        |
| 0  | 2  | 0  | 1.4        |
| 0  | 2  | 1  | 1.4        |
| 0  | 2  | 2  | 1.4        |
| 1  | 0  | 0  | 1.4        |
| 1  | 0  | 1  | 1.4        |
| 1  | 0  | 2  | 1.4        |
| 1  | 1  | 0  | 1.4        |
| 1  | 1  | 1  | 1.4        |
| 1  | 1  | 2  | 1.4        |
| 1  | 2  | 0  | 1.4        |
| 1  | 2  | 1  | 1.4        |
| 1  | 2  | 2  | 1.4        |
| 2  | 0  | 0  | 1.4        |
| 2  | 0  | 1  | 1.4        |
| 2  | 0  | 2  | 1.4        |
| 2  | 1  | 0  | 1.4        |
| 2  | 1  | 1  | 1.4        |
| 2  | 1  | 2  | 1.4        |
| 2  | 2  | 0  | 1.4        |
| 2  | 2  | 1  | 1.4        |
| 2  | 2  | 2  | 1.4        |

**MATING DESIGN**

As an added test to EPDs, the Mating Design table shows the predictable results which can be obtained through planned breeding decisions utilizing DNA test results from Bovigen.

| Size | Dam | % of Progeny |
|------|-----|--------------|
| 0    | 0   | 100%         |
| 0    | 1   | 50%          |
| 0    | 2   | 100%         |
| 1    | 0   | 50%          |
| 1    | 1   | 25%          |
| 1    | 2   | 50%          |
| 2    | 0   | 100%         |
| 2    | 1   | 50%          |
| 2    | 2   | 100%         |

DNA tests should be considered additional information to be used in conjunction with available performance data for each animal. When comparing two bulls with similar EPDs, GeneSTAR™ GPD results can be used to further evaluate an animal's true genetic potential.

**BOVIGENE COMPANY PROFILE**

Bovigen is an innovative genetic genomics company developing a portfolio of world class DNA tests and solutions for the beef industry through

6/1/2017

Animal Genomics and Biotechnology Education

## I don't know it for a fact – but I just know it is true

**IGENITY™ L**

Know. Now.

**BOVIGENE SOLUTIONS, LLC**

6/1/2017

Animal Biotechnology and Genomics Education

**Now, know even more about the genetic potential of your cattle.**

## 2006

**For Immediate Release**

**Merial Reveals New Multiple-Marker DNA Profile Technology**  
IGENITY MultiMARK™ provides greater confidence in selection and management decisions

South, Ga. – February 20, 2006 – Merial announces an important step forward in genetic testing with the introduction of the beef industry's most comprehensive DNA testing profile – IGENITY MultiMARK™.

By identifying multiple genetic markers, then integrating them into a single profile, IGENITY MultiMARK increases the confidence of selection and management decisions within an operation," says Jim Tate, global beef strategy manager for Merial/IGENITY. "This new approach to DNA testing – unique to IGENITY – helps create greater efficiencies in testing for producers and the industry."

The comprehensive multiple-marker profile approach of IGENITY MultiMARK makes it a significantly cost-effective method for producers to learn more about an animal's genetic potential. "Our goal is to give producers the tools to improve the efficiency and profitability of their operations," Tate says. "By providing a broad range of analyses – and integrating them into profiles that are simple to use and understand – IGENITY MultiMARK allows producers to profile animals for traits that matter most, and to more rapidly improve the genetics of a herd."

Beef testing was the latest DNA technology and a real show toward producing more consistent products that are heavily demanded by consumers. IGENITY MultiMARK helps producers make better-informed decisions, which can open doors to profit opportunities.

Market Assured Selection is the most level of predictability for producers and may actually eliminate some of the guesswork at times," Tate notes. "Producers producers will see these additional options as a means to enhance the tools they already utilize to make breeding, purchasing and other management decisions."

BROOK BUTLER & ASSOCIATES

**Results reported on 1-10 scale**

**The IGENITY profile. Comprehensive. Practical. Powerful.**

**It's easy to understand an IGENITY profile.**

One of the greatest values of the IGENITY profile is that all results are integrated and provided in one single profile, similar to the report shown here.

| IGENITY Profile |    |       |                  |            |                      |                       |             |             |                    |               |             |        |            |
|-----------------|----|-------|------------------|------------|----------------------|-----------------------|-------------|-------------|--------------------|---------------|-------------|--------|------------|
| Animal ID       | MF | Breed | Sample Barcode # | Tenderness | Red/Black Coat Color | Marker Pregnancy Rate | Yield Grade | Ribeye Area | Hot Carcass Weight | Duality Grade | Stayability | BVD-PI | Polled     |
| 701             | M  | -     | nv011507_01      | 10         | ED/ED                | 9                     | 8           | 8           | 8                  | 8             | 8           | POS    | Homozygous |
| 702             | F  | -     | nv011507_02      | 6          | ED/ED                | 3                     | 4           | 6           | 5                  | 7             | 6           | NEG    |            |
| 704             | F  | -     | nv011507_04      | 10         | ED/E                 | 7                     | 3           | 8           | 6                  | 6             | 6           | POS    |            |
| 705             | F  | -     | nv011507_05      | 6          | ED/D                 | 3                     | 4           | 6           | 5                  | 5             | 3           | NEG    |            |

**FEATURES**

- Connects DNA markers where each marker is highly associated with a desirable trait
- Assesses the cumulative effect of all DNA markers associated with a trait
- Results are reported as a Molecular Genetic Value (MGV) which can be used in each animal's genetic selection
- Accuracy can be tested at any age
- Validated in Angus sires and dams in other breeds to enhance accuracy

**BENEFITS**

- The most powerful and complete genetic selection tool currently available for marbling
- Accounts for a significant proportion of total observed genetic variation for marbling
- Results are easy to utilize and incorporate into existing breeding programs
- Can be used to make early selection decisions
- Provides accurate and reliable results for testing and selection of animals

### TRU-MARBLING

One in a series of break-through products that will advance breeding practices in the cattle industry. Tru-Marbling™ is a powerful and comprehensive DNA selection tool that can determine the genetic potential of animals for marbling. In a collaborative research program between Cargill and M&M Genetics, an innovative scientific approach was used to create a DNA-based predictive model for marbling. This model uses a large number of DNA markers to predict the amount of marbling in a carcass. The model is so accurate that it can predict the amount of marbling in a carcass with a confidence level of 95%.

The Tru-Marbling™ is an advanced and revolutionary tool that will allow cattle producers to make early breeding decisions to increase the quantity of carcasses and improve the quality of the carcasses. Tru-Marbling™ has been validated in both commercial crossbred beef cattle populations and in purebred Angus cattle.

The validation in Angus was conducted using samples from the National Cattle Host Project, representing Angus sires and dams. The results showed that Tru-Marbling™ accurately predicted the amount of marbling in a carcass with a confidence level of 95%.

**PROVEN RESULTS**

The Tru-Marbling™ has been validated in both commercial crossbred beef cattle populations and in purebred Angus cattle. The validation in Angus was conducted using samples from the National Cattle Host Project, representing Angus sires and dams. The results showed that Tru-Marbling™ accurately predicted the amount of marbling in a carcass with a confidence level of 95%.

### TRU-TENDERNESS

One in a series of break-through products that will advance breeding practices in the cattle industry. Tru-Tenderness™ is a powerful and comprehensive DNA selection tool that can determine the genetic potential of animals for tenderness. In a collaborative research program between Cargill and M&M Genetics, an innovative scientific approach was used to create a DNA-based predictive model for tenderness. This model uses a large number of DNA markers to predict the amount of tenderness in a carcass. The model is so accurate that it can predict the amount of tenderness in a carcass with a confidence level of 95%.

The Tru-Tenderness™ is an advanced and revolutionary tool that will allow cattle producers to make early breeding decisions to increase the quantity of carcasses and improve the quality of the carcasses. Tru-Tenderness™ has been validated in both commercial crossbred beef cattle populations and in purebred Angus cattle.

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**Results reported as a Molecular Genetic Value (MGV)**

**MOLECULAR GENETIC VALUE (MGV) REPORT**

**NAME:** Legends of the West - Angus Farm

**ADDRESS:** 13417 Trujillo Creek Road, Aguirre, CO 81002

**CONTACT:** Wes Johnson, Foreman

**REPORT DATE:** 09/23/2006

**ORIGINAL REPORT:** 09/23/2006

**CALL ID:** 00003025

**CUSTOMER:** L&M - Legends of the West Angus Farm

**BREED**

Angus

Angus

Angus

Angus

| NAME            | REG #    | TAGS   | SEX | BORN       | SAMPLE    | MARBLING | TENDERNESS |
|-----------------|----------|--------|-----|------------|-----------|----------|------------|
| AF Paul Burman  | 19352178 | AZ-105 | M   | 06/14/2004 | 953681205 | -28.61   | 0.92       |
| AF Casey Jones  | 19352211 | AZ-112 | M   | 05/29/2004 | 953681363 | -19.41   | -3.98      |
| AF Alamo Rising | 19352385 | AZ-146 | M   | 06/19/2005 | 953681405 | 42.19    | -0.75      |
| AF Genomero     | 19352440 | AZ-115 | M   | 12/09/2004 | 953681165 | 10.15    | -4.40      |

**Pfizer Animal Genetics**

1.877.878.0000 www.hovigen.com

## Pfizer Animal Genetics acquired Bovigen – started reporting results as GPD

### Feed Efficiency

GenSTAR GPD Feed Efficiency

| Animal | Feed Efficiency |
|--------|-----------------|
| 1      | 0.15            |
| 2      | 0.15            |
| 3      | 0.15            |
| 4      | 0.15            |
| 5      | 0.15            |
| 6      | 0.15            |
| 7      | 0.15            |
| 8      | 0.15            |
| 9      | 0.15            |
| 10     | 0.15            |

### Tenderness

GenSTAR GPD Tenderness

| Animal | Tenderness |
|--------|------------|
| 1      | 0.15       |
| 2      | 0.15       |
| 3      | 0.15       |
| 4      | 0.15       |
| 5      | 0.15       |
| 6      | 0.15       |
| 7      | 0.15       |
| 8      | 0.15       |
| 9      | 0.15       |
| 10     | 0.15       |

### Quality Grade

GenSTAR GPD Quality Grade

| Animal | Quality Grade |
|--------|---------------|
| 1      | 0.15          |
| 2      | 0.15          |
| 3      | 0.15          |
| 4      | 0.15          |
| 5      | 0.15          |
| 6      | 0.15          |
| 7      | 0.15          |
| 8      | 0.15          |
| 9      | 0.15          |
| 10     | 0.15          |

**384 SNP chip assay**

**The Power of the IGENITY® profile for Angus**

The American Angus Association through its subsidiary Angus Genetics Inc. (AGI), has a vision to provide Angus breeders with the most advanced solutions to their genetic selection and management needs.

1. Dry Matter Intake
2. Birth Weight
3. Mature Height
4. Mature Weight
5. Milk
6. Scrotal Circumference
7. Weaning Weight
8. Yearling Weight
9. Marbling
10. Ribeye Area
11. Fat Thickness
12. Carcass Weight
13. Tenderness
14. Percent Choice (quality grade)
15. Heifer Pregnancy
16. Maternal Calving Ease
17. Direct Calving Ease
18. Docility
19. Average Daily Gain
20. Feed Efficiency
21. Yearling Height

• Anthropometric Markers (AM)  
 • Neutrophilic Hydrocortisol (NH)  
 • Bovine Viral Diarrhea – Persistently Infected (BVDPI)  
 • Coat Color

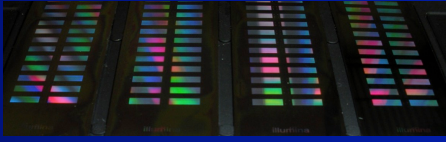
**ANGUS**

2017 BIF Symposium, Athens, Ga.

3

**High-throughput genotyping technology enabled the development of high density "SNP chips"**

The sequencing of the bovine genome allowed for the development of a 50,000 SNP chip – 50,000 DNA markers evenly spaced throughout the genome!



BIF 6/1/2017 Animal Biotechnology and Genomics Education

**Lead Today with 50K**

1. – Calving ease direct
2. – Birth weight
3. – Weaning weight
4. – Yearling weight
5. – Yearling height
6. – Mature weight
7. – Mature height
8. – Dry matter intake
9. – Residual feed intake
10. – Scrotal circumference
11. – Docility
12. – Calving ease maternal
13. – Milking ability
14. – Carcass weight
15. – Fat thickness
16. – Ribeye area
17. – Marbling score
18. – Tenderness

**Results reported as MVP**

Pfizer Animal Health Animal Genetics



**Black Angus Sire G A R Predestined**

Reg. No. 13395344  
Cvark 2121099  
Tasso 5899  
Saves \$25  
Certified \$20  
Sirey 2010170

**EPD**

**GeneStar number**

**MVP PROFILE SCORE**

**G A R Predestined 13395344**

| EPD        | BW   | WW   | YW   | ADG  | DMI  | NFI  | CEM  | MA  | OW   | FAT  | REA  | MS   | TND  | \$B-BMVP |
|------------|------|------|------|------|------|------|------|-----|------|------|------|------|------|----------|
| ACC        | 0.84 | 0.97 | 0.96 | 0.94 | -    | -    | -    | 0.9 | 0.95 | 0.92 | 0.81 | 0.82 | 0.94 | -        |
| EPD % Rank | 30   | 85   | 95   | 95   | -    | -    | -    | 95  | 90   | 4    | 90   | 2    | 1    | -        |
| MVP        | 13   | 1.0  | 27   | -    | 0.45 | 0.97 | 0.04 | 9   | 33   | 100  | 0.07 | 0.00 | 1.12 | -0.42    |
| MVP % Rank | 3    | 70   | 98   | -    | 30   | 90   | 90   | 4   | 1    | 1    | 90   | 1    | 80   | 1        |

**2008 Need to integrate DNA information into National Cattle Evaluation (NCE)**

*"Information from DNA tests only has value in selection when incorporated with all other available forms of performance information for economically important traits in National Cattle Evaluation (NCE), and when communicated in the form of an EPD with a corresponding BIF accuracy.*

*For some economically important traits (e.g. feed efficiency), information other than DNA tests may not be available. Selection tools based on these tests should still be expressed as EPD within the normal parameters of NCE" (Tess, 2008).*

BIF 6/1/2017 Animal Biotechnology and Genomics Education

**Maybe we need quantitative genetics?**



**ΔG**

**EPDs Work**

| Breed     | Regression Coefficient BWT |
|-----------|----------------------------|
| Angus     | 1.06 (0.09)                |
| Hereford  | 1.16 (0.07)                |
| Red Angus | 1.01 (0.14)                |
| Charolais | 1.14 (0.12)                |
| Gelbvieh  | 1.05 (0.14)                |
| Limousin  | 1.11 (0.11)                |
| Simmental | 1.16 (0.14)                |

Kuehn and Thalmman, 2016

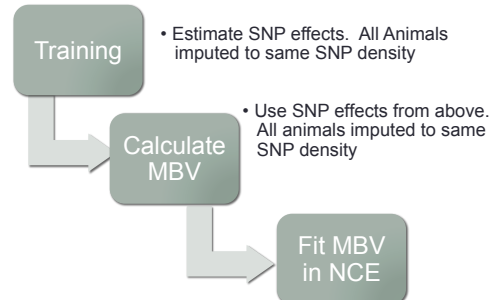
### Disjoined Information Quantitative Genetics Solves the Problem

|       | CE  | BW   | WW  | YW   | MCE | Milk | ME  |
|-------|-----|------|-----|------|-----|------|-----|
| Adj.  |     | 90   | 700 | 1320 |     |      |     |
| Ratio |     | 101  | 107 |      |     |      |     |
| EPD   | 9   | -1.0 | 50  | 90   | 3   | 11   | 0   |
| Acc   | .29 | .37  | .30 | .27  | .18 | .19  | .23 |

|       | YG  | Marb  | BF  | REA  |
|-------|-----|-------|-----|------|
| Adj.  |     | 4.65% | .23 | 12.5 |
| Ratio |     | 106   | 100 | 95   |
| EPD   | .21 | .44   | .05 | -.39 |
| Acc   | .32 | .31   | .33 | .34  |

| DMI | TEND | MARB |
|-----|------|------|
| 7   | 6    | 8    |

### Two-Step Approach



### “Phenotypes” for Training

- Two real choices
- EPD or degressed EPD
  - Allows more power since EPD contains more information than just the animal's own phenotype
  - Limited to the traits that have published EPD for that breed
  - Must account for variable accuracy of EPD
  - Training must mimic the way the EPD was derived
  - Potential for highly selected subset
- Phenotypes
  - Not limited to published EPD
  - Connectedness to larger population may be problematic
  - Less information content

### Estimation of Genetic Parameters

- “Evaluation” Step
- Evaluate genetic correlations using k-folds
  - Use prediction from each fold to evaluate the others
  - Two trait mixed linear model
  - Pool results across folds

### Correlated Trait

- Similar to what has been done before, but now we include MBV

$$\begin{matrix} Y_{MBV} & X_1\beta_1 & Z_1u_1 & e_1 \\ Y_{IMF} & = X_2\beta_2 & + Z_2u_2 & + e_2 \\ Y_{MARB} & X_3\beta_3 & Z_3u_3 & e_3 \end{matrix}$$

MacNeil et al., 2010

### Blending

- Done post evaluation

$$EBV_i = \frac{1-R_i^2}{1-r_g^2R_i^2} MBV_i + \frac{1-r_g^2}{1-r_g^2R_i^2} EBV_i$$

## Increased Accuracy-Benefits

- Mitigation of risk
- Faster genetic progress

$$BV / t = \frac{r_{BV,EBV} i_{BV}}{L}$$

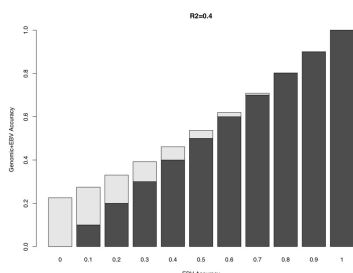
- Increased accuracy does not mean higher or lower EPD!
- Increased information can make EPDs go up or down

## Accuracy

**Table 1.** Approximate number of progeny needed to reach accuracy levels (true  $r$  and the BIF standard) for three heritabilities ( $h^2$ ).

| Accuracy |      | Heritability Levels  |                      |                      |
|----------|------|----------------------|----------------------|----------------------|
| r        | BIF  | h <sup>2</sup> (0.1) | h <sup>2</sup> (0.3) | h <sup>2</sup> (0.5) |
| 0.1      | 0.01 | 1                    | 1                    | 1                    |
| 0.2      | 0.02 | 2                    | 1                    | 1                    |
| 0.3      | 0.05 | 4                    | 2                    | 1                    |
| 0.4      | 0.08 | 8                    | 3                    | 2                    |
| 0.5      | 0.13 | 13                   | 5                    | 3                    |
| 0.6      | 0.2  | 22                   | 7                    | 4                    |
| 0.7      | 0.29 | 38                   | 12                   | 7                    |
| 0.8      | 0.4  | 70                   | 22                   | 13                   |
| 0.9      | 0.56 | 167                  | 53                   | 30                   |
| 0.999    | 0.99 | 3800                 | 1275                 | 700                  |

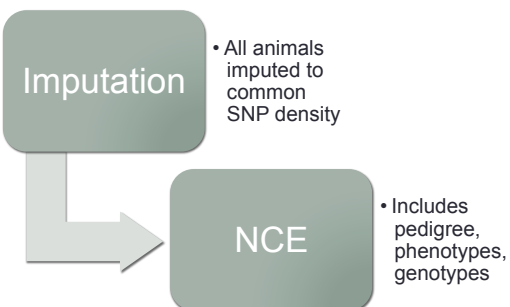
## Impact on Accuracy--%GV=40% BIF Accuracy of < 0.3



## Fall 2016 Status

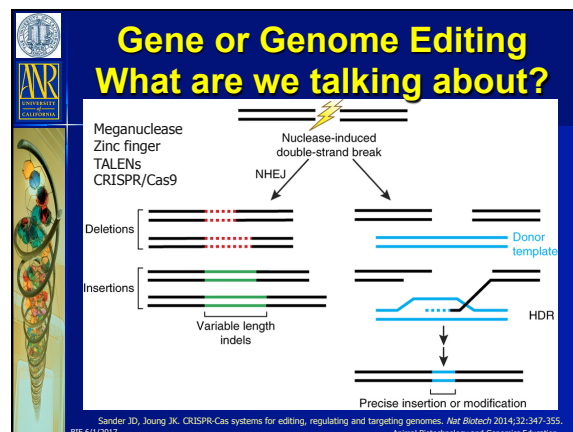
| Breed           | No. Anim | LD Impute | Provider | Method   |
|-----------------|----------|-----------|----------|----------|
| Angus           | 264,656  | Y         | GS, Z    | CORR     |
| Red Angus       | 22,791   | Y         | GS, Z    | BLEND    |
| Hereford        | ~23,000  | Y         | GS       | BLEND    |
| Simmental       | 32,629   | Y         | GS       | BLEND    |
| Limousin        | 3,340    | Y         | GS       | BLEND    |
| Gelbvieh        | 10,162   | Y         | GS       | BLEND    |
| Charolais       | 2,454    | N         | GS       | CORR     |
| Santa Gertrudis | 3,160    | N         | GS       | SS-GBLUP |
| Brangus         | 3,909    | Y         | GS, Z    | SS-GBLUP |

## Single Step Approach



## Single Step (s)

- Two fundamental camps
  - UGA, ssGBLUP—Misztal
  - Theta Solutions/ISU, ss“Hybrid”—Fernando, Garrick, Golden
- Regardless of camp, we are witnessing the first substantial change in NCE software across all breeds.
- No longer trying to make genomic data “fit” current NCE platforms.



Editing is being sold by some as the next silver bullet in breeding programs– that might make sense to some people – especially those with no training in quantitative genetics!

**THOSE WHO DO NOT LEARN FROM HISTORY ARE DOOMED TO REPEAT IT.**

George Santayana  
Spanish Philosopher  
1863-1952

QuoteHD.com

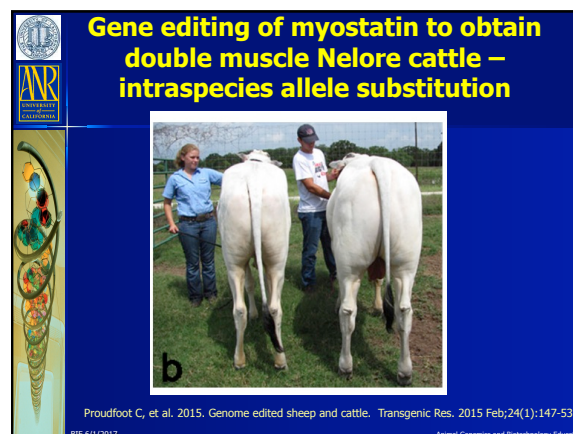
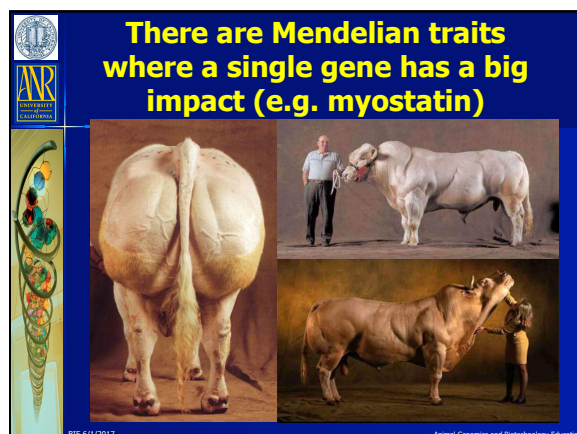
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Editing is the Cherry on Top of Breeding Sundae  
It will be able to introduce useful alleles without linkage drag, and potentially novel genetic variation

**Genome Editing**

- Somatic cell nuclear transfer cloning
- Genomic Selection
- Embryo Transfer
- Artificial insemination
- Progeny testing
- Performance recording
- Development of breeding goals
- Association of like minded breeders

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### Gene Edited Polled Calves

Intraspecies allele substitution of the Celtic allele into the POLLED locus

recombinetics

Carlson DF, Lanco CA, Zang B, Kim E-S, Walton M, et al. 2016. **Production of hornless dairy cattle from genome-edited cell lines.** Nat Biotech 34: 479-81

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Celtic allele (P<sup>C</sup>) corresponding to a duplication of 212 bp (chromosome 1 position 1705834–1706045) in place of a 10-bp sequence = horned (1706051–1706060) at POLLED

Born April 2015

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### Examples of successful gene edited food animal applications

| Species | Target                                        | Targeted Trait/Goal             |
|---------|-----------------------------------------------|---------------------------------|
| Cattle  | Intraspecies POLLED allele substitution       | No horns                        |
|         | Myostatin gene knockout                       | Increased muscle yield          |
|         | Beta-lactoglobulin gene knockout              | Elimination of milk allergen    |
|         | Insertion of lysozyme transgene               | Disease resistance              |
|         | Insertion of lysozyme transgene               | Disease resistance              |
| Chicken | Insertion of SP110 transgene                  | Resistance to tuberculosis      |
|         | Ovalbumin gene knockout                       | Elimination of ovalbumin in egg |
| Goat    | Insertion of Immunoglobulin heavy chain locus | Germline gene editing           |
|         | Myostatin gene knockout                       | Increased muscle growth         |
| Pig     | CD163 gene knockout                           | PRRS Virus Resistance           |
|         | Interspecies RELA allele substitution         | African Swine Fever Resistance  |
| Sheep   | Myostatin gene knockout                       | Increased muscle yield          |
|         | Myostatin gene knockout                       | Increased muscle yield          |

Van Eenennaam, A. L. 2017. **Genetic Modification of Food Animals.** Current Opinion in Biotechnology. 44:27-34.

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### How might gene editing be used in beef cattle breeding?

- Polled/Horned
- Myostatin
- Recessive Genetic Conditions
- Tenderness loci (calpastatin/calpain)
- Disease resistance (e.g. BRD)
- SCD (stearoyl-CoA desaturase)

Editing would synergistically accelerate conventional breeding programs (not replace them!) by precisely bringing in discrete desired genetic variation as needed

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Gene editing **potentially** provides a means by which the discovery of causative SNPs (Quantitative Trait Nucleotides; QTNs) through sequencing projects and the information obtained from various genome wide association studies (GWAS) could be translated into valuable genetic variation for use in animal breeding programs

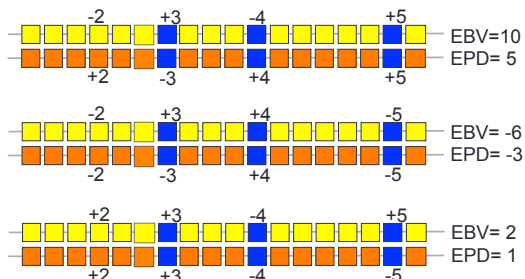
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Maybe we need more quantitative knowledge?

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## EPD at Molecular Level

Slide Courtesy of Dorian Garrick



## Breed Specificity

(Kachman et al., 2013)

| Breed     | Weaning weight MBV |                  |                  |
|-----------|--------------------|------------------|------------------|
|           | Angus              | Hereford         | Limousin         |
| Angus     | <b>0.36±0.07</b>   | 0.14±0.08        | -0.06±0.08       |
| Red Angus | 0.16±0.16          | 0.09±0.16        | 0.25±0.16        |
| Hereford  | 0.04±0.21          | <b>0.42±0.18</b> | 0.27±0.21        |
| Limousin  | 0.02±0.09          | 0.23±0.09        | <b>0.40±0.08</b> |

## Add More SNP?

- Simply adding more SNP does not help.
  - Increase resolution and decrease power
  - Need biological knowledge of added content
- 50K vs HD (80K) (Red Angus Example)
  - Average  $r_g$  = 0.53 and 0.54
  - Looks like it is negligible

## Shift in Direction

- Phenotypic Database→ Standard Panel→ Prediction equation (within population)
- Variants from Sequence→ Phenotypes in Research Population→
  - Variant list to external populations (requires phenotypes to train)
  - Prediction equations to external populations (phenotypes not needed)

## Industry Needs to Actively Participate

- Benefits of GS in beef cattle will not be fully captured until an infrastructure exists for capturing additional ERT
  - Fertility
  - Carcass
  - Disease
- Genotyping only the "best" animals is counterproductive
  - No decision to be made
  - Can lead to bias
- Use the technology to make selection decisions
  - Genotype entire cohort groups

## Weight Trait Project

The WTP is an organized effort to facilitate DNA technology transfer and while at the same time providing a national focus for integration of molecular information into beef genetic evaluation and selection.

## Sequencing

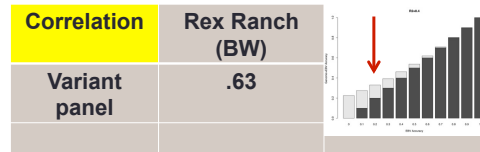
“Categorized” these putative variants by their predicted severity.

| DNA Variant | High Quality |
|-------------|--------------|
| Severe      | 6,513        |
| Moderate    | 89,591       |
| Low impact  | 109,171      |
| Modifiers   | 34.0 million |
| Total       | 34.2 million |

## Validation of Variants

Created a “small” panel of severe variants screened for Birth Weight in the Cycle VII population.

Genotyped > 600 sires from the Rex Ranch for this panel of 185 variants.



## Sequencing Is Just Beginning

- New GGPF250 assay
- Best chance we have at
  - Predicting across populations and transferring information from research populations
    - Birth weight MBV based on 293 variants— $r_g$  ranged between 0.25-0.44
    - Single variant (birth weight)— $r_g$  ranged between 0.17 and 0.34
    - Explaining a limited amount of variation (~10%) can be important for ERT that are sparsely collected (if at all).
  - Developing MAM products
    - An objective, but the highest hanging fruit
    - GxExM

**Melding the Bluppers & Genies**

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