"Implications of Improper Management of Known Genetic Abnormalities"

Alison Van Eenennaam
Animal Genomics and Biotechnology
Cooperative Extension Specialist
Department of Animal Science
University of California, Davis, CA
Ph: (530) 752-7942
alvaneenennaam@ucdavis.edu

This work is being funded by Grant 2013-68004-20364 from the USDA National Institute of Food and Agriculture."

USDA United States Department of Agriculture National Institute of Food and Agriculture

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Outline

- Management of recessive conditions in breeding programs
- Lets assume we have success in identifying "missing homozygotes" – then what?
- Defining a breeding objective
- Utilizing genetic and management tools to optimize mate selection decisions
- Anticipated outcomes of USDA reproduction grant

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Polydactyly

Photo Credit: Schalles, Leipold and McCraw – Beef Cattle Handbook

Slide courtesy of David Buchanan, North Dakota State University

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Mulefoot (syndactyly)

Photo Credit: Schalles, Leipold and McCraw – Beef Cattle Handbook

Slide courtesy of David Buchanan, North Dakota State University

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Marble bone (osteopetrosis)

Photo credit: Schalles, Leipold and McCraw – Beef Cattle Handbook

Slide courtesy of David Buchanan, North Dakota State University

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Protoporphyria (photosensitivity)

Photo Credit: Kent Anderson – North American Limousin Foundation

Slide courtesy of David Buchanan, North Dakota State University

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Hairlessness (hypotrichosis)

Photo Credit: Schalles, Leipold and McCraw – Beef Cattle Handbook

Slide courtesy of David Buchanan, North Dakota State University

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Parrot mouth

Can also be symptom of Marble Bone Disease

Photo Credit: Schalles, Leipold and McCraw – Beef Cattle Handbook

Slide courtesy of David Buchanan, North Dakota State University

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Pulmonary hypoplasia with anasarca (PHA)

Photo Credit: Kaiser and the American Shorthorn Assoc

Slide courtesy of David Buchanan, North Dakota State University

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Tibial Hemimelia (TH)

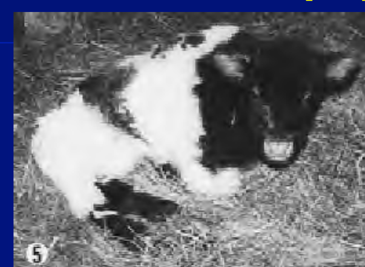

Photo Credit: Marty Ropp – American Simmental Association

Slide courtesy of David Buchanan, North Dakota State University

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Bulldog calf

Photo Credit: Schalles, Leipold and McCraw – Beef Cattle Handbook

Slide courtesy of David Buchanan, North Dakota State University

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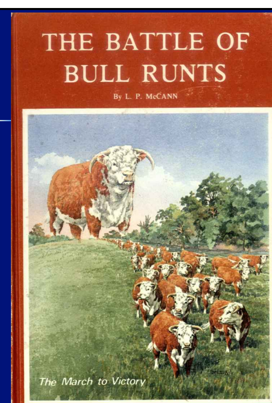

A 1956 survey of Hereford breeders in the USA identified 50,000 dwarf-producing animals in 47 states.

Through detailed pedigree analysis and test crosses, the American Hereford Association, in concert with breeders and scientists, virtually eliminated the problem from the breed. Because carrier status was difficult to prove and required expensive progeny testing, some entire breeding lines were eliminated.

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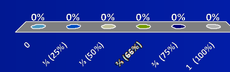
Early extension education about dwarfism explaining carriers and inheritance

Image from Special Collections University Libraries, Virginia Tech: http://spec.lib.vt.edu/imagebase/agextension/boxseven/screen/AGR3618.jpg

If you breed a "carrier" cow (Aa) to a "free" bull (AA), what is the chance that the resulting offspring will be affected (aa)?

1. 0
2. ¼ (25%)
3. ½ (50%)
4. ⅔ (66%)
5. ¾ (75%)
6. 1 (100%)



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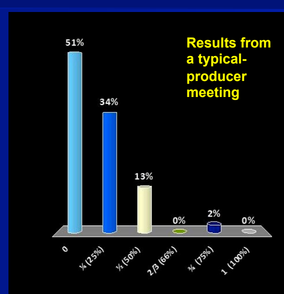

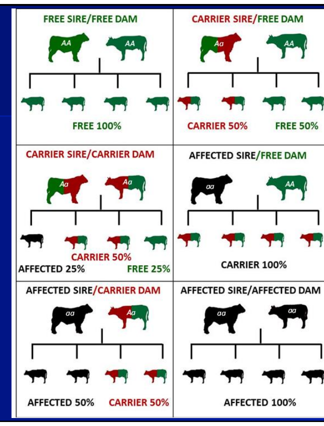

Management Options for autosomal recessive conditions

There are many management options for the control of genetic conditions and the best choice will depend on the needs and requirements of each enterprise. Some of these options include:

- Testing all animals and culling carriers.
- Testing sires and using only free bulls for breeding.

Genetic implications of recessive genetic factors

"*Carrier animals….their overall breeding value worth may outweigh the economic value of carrier status*"

Chalier C. et al. (2008) Highly effective SNP-based association mapping and management of recessive defects in livestock. Nature Genetics 40:449-454

Need to penalize carrier animals appropriately (*not prohibit their use entirely*) and let mate selection software optimize their use in the breeding programs

Management Options for autosomal recessive conditions

There are many management options for the control of genetic conditions and the best choice will depend on the needs and requirements of each enterprise. Some of these options include:

- Testing all animals and culling carriers.
- Testing sires and using only free bulls for breeding.
- Testing all animals and using carriers only in terminal breeding programs or in matings to non-carrier animals and testing their progeny.

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Current codes for Angus

Genetic Condition Codes and Descriptors

The American Angus Association currently recognizes the following genetic conditions:

AM - Arthrogryposis Multiplex	D2 - PRKG2 Gene Mutation for Dwarfism	HG - Horn Gene
CA - Contractural Arachnodactyly	DM - Double Muscling	HI - Heterochromia Irides
DD - Developmental Duplication	DW - Dwarfism	OS - Osteopetrosis
M1 - nt821 mutation for Double Muscling	RD - Red Gene	SN - Syndactyly
NH - Neuropathic Hydrocephalus	WT - Wild Type Color Gene	

The following single letter descriptors appearing after a genetic condition code shall have the following meaning:

P - Refers to a "potential" carrier based on an ancestor known to carry that specific mutation.

F - Refers to an animal tested for one or more genetic conditions and determined to be "free" of that specific mutation.

C - Refers to an animal tested for one or more genetic conditions and determined to be a "carrier" of that specific mutation.

A - Refers to an animal tested for one or more genetic conditions and determined to be a carrier of two copies of that specific mutation. It may or may not exhibit the phenotype associated with that genetic condition.

The following letter designations describe cases in which there is more than one genetic condition present:

XF - Free of more than 1 genetic condition

XC - Carrier of more than 1 genetic condition

XA - Affected of more than 1 genetic condition

RTF - Recessive Trait Free (Produced 35 or more calves from daughters without a genetic defect)

NOTE: The genetic condition codes and descriptors reflect the available, reported genetic condition status of the animal. The Association does not warrant or guarantee that any animal is free of all genetic conditions, whether coded or not coded.

AVOIDANCE OF MATING CARRIER ANIMALS WITH THE SAME GENETIC CONDITION IS AN ESSENTIAL COMPONENT OF MANAGING THE INCIDENCE OF GENETIC CONDITIONS, AS IS THE STRATEGIC USE OF DNA TESTING.

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Weighing carrier status versus merit

G A R Predestined Reg: AAA #13395344 Bull

[DDC-AMF-CAF-M1F-NHF] Click here for info

Sire: B/R New Design 036 AAA #11418151 **Dam:** G A R Ext 4206 AAA #+12716727

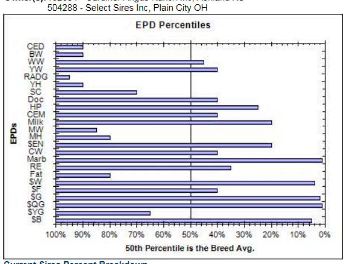
Birth Date: 08/16/1999 **Tattoo:** 5899

Parentage: Blood type, Microsatellite, SNP

Genomic: IG1, IG384, PF50

Breeder: 192604 - Gardiner Angus Ranch Inc, Ashland KS

Owner(s): 192604 - Gardiner Angus Ranch Inc, Ashland KS
504288 - Select Sires Inc, Plain City OH



Current Sires Percent Breakdown

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Translational questions that remain assuming success in finding recessive lethal alleles

- All animals carry recessive genetic conditions – how should "embryonic lethals" be managed
- What is the appropriate penalty to put on embryonic lethals when making mating decisions – how to incorporate into mate selection
- What is the frequency of the embryonic lethals in the target population – if small then less important
- Are appropriate decision support tools available for producers???

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What did the dairy industry do?

J Dairy Sci. 2011 Dec;94(12):6153-61.

Harmful recessive effects on fertility detected by absence of homozygous haplotypes.

VanRaden PM, Olson KM, Null DJ, Hutchison JL.

Animal Improvement Programs Laboratory, Agricultural Research Service, USDA, Beltsville, MD 20705-2350, USA. paul.vanraden@ars.usda.gov

Abstract

Five new recessive defects were discovered in Holsteins, Jerseys, and Brown Swiss by examining haplotypes that had a high population frequency but were never homozygous. The method required genotypes only from apparently normal individuals and not from affected embryos. Genotypes from the BovineSNP50 BeadChip (Illumina, San Diego, CA) were examined for 58,453 Holsteins, 5,288 Jerseys, and 1,991 Brown Swiss with genotypes in the North American database. Haplotypes with a length of ≤ 75 markers were obtained. Eleven candidate haplotypes were identified, with the earliest carrier born before 1980; 7 to 90 homozygous haplotypes were expected, but none were observed in the genomic data. Expected numbers were calculated using either the actual mating pattern or assuming random mating. Probability of observing no homozygotes ranged from 0.0002 for 7 to 10^{-4} [illegible] for 90 expected homozygotes. Phenotypic effects were confirmed for 5 of the 11 candidate haplotypes using 14,911,387 Holstein, 830,391 Jersey, and 68,443 Brown Swiss records for conception rate. Estimated effect for interaction of carrier service sire with carrier maternal grandsire ranged from -3.0 to -3.7 percentage points, which was slightly smaller than the -3.9 to -4.6 percentage points expected for lethal recessives but slightly larger than estimated effects for previously known lethal alleles of -2.5 percentage points for brachyspina and [illegible] percentage points for complex vertebral malformation. Conception rate was coded as a success only if the gestation went to term or the cow was confirmed to be pregnant. Estimated effect of carrier interaction for stillbirth rate based on 10,876,597 Holstein and 25,456 Jersey records was small. Thus, lethal effects may include conception, gestation, and stillbirth losses. Carrier frequency has been >20% for many years for the confirmed defect in Jerseys and is currently 16% for the defect in Brown Swiss. The 3 defects discovered in Holsteins have carrier frequencies of 2.7 to 6.4% in the current population. For previously known defects, map locations and lack of homozygotes were consistent with the literature and lethal recessive inheritance, but numbers of expected homozygotes for some were small because of low frequency. Very large genotypic and phenotypic data sets allow efficient detection of smaller and less frequent effects. Haplotype tests can help breeders avoid carrier matings for such defects and reduce future frequencies.

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Haplotypes Affecting Fertility and their Impact on Dairy Cattle Breeding Programs

Dr. Kent A. Weigel, University of Wisconsin

http://documents.crinet.com/Genex-Cooperative-Inc/Dairy/KWeigel-Haplotypes-Affecting-Fertility.pdf

- The exact genes and their underlying biological roles in fertilization and embryo development are unknown, but it is assumed that the outcome of inheriting the same haplotype from both parents is failed conception or early embryonic loss.
- **The reactive approach of attempting to eradicate every animal with an undesirable haplotype is not recommended in light of their economic impact, and is not practical given the likelihood that many more undesirable haplotypes will be found.**
- Producers should neither avoid using bulls with these haplotypes nor cull cows, heifers, and calves that are carriers, because this will lead to significant economic losses in other important traits.
- Computerized mating programs offer a simple, inexpensive solution for avoiding affected matings, so producers should use these programs and follow through on the mating recommendations.

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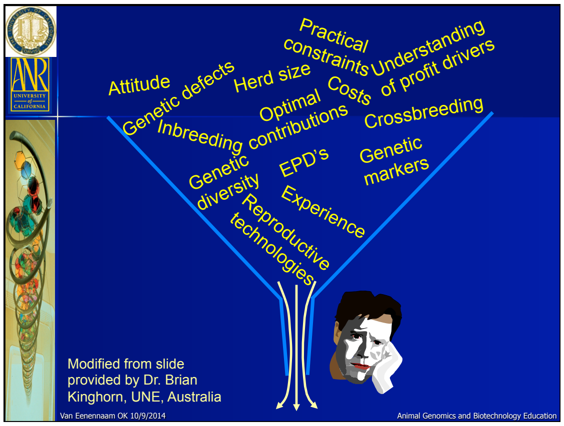
Practical constraints
Understanding of profit drivers
Attitude
Genetic defects
Herd size
Costs
Optimal contributions
Inbreeding
Crossbreeding
Genetic diversity
EPD's
Genetic markers
Experience
Reproductive technologies
Modified from slide provided by Dr. Brian Kinghorn, UNE, Australia
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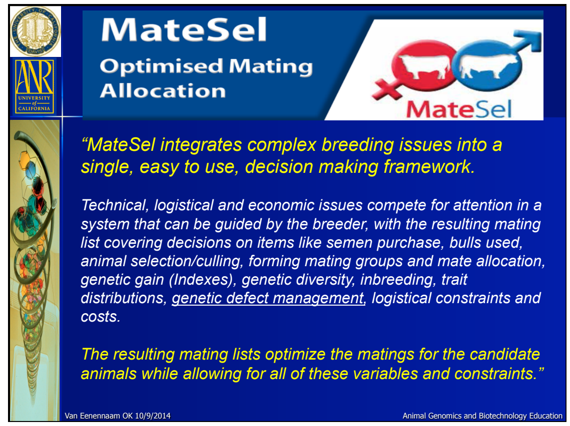
MateSel
Optimised Mating Allocation
MateSel
"MateSel integrates complex breeding issues into a single, easy to use, decision making framework.
Technical, logistical and economic issues compete for attention in a system that can be guided by the breeder, with the resulting mating list covering decisions on items like semen purchase, bulls used, animal selection/culling, forming mating groups and mate allocation, genetic gain (Indexes), genetic diversity, inbreeding, trait distributions, genetic defect management, logistical constraints and costs.
The resulting mating lists optimize the matings for the candidate animals while allowing for all of these variables and constraints."
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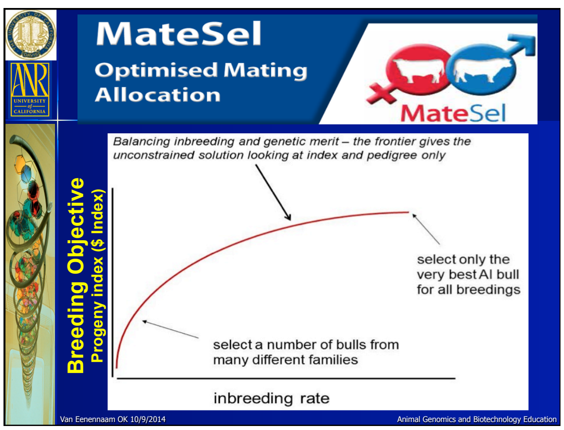
MateSel
Optimised Mating Allocation
MateSel
Balancing inbreeding and genetic merit – the frontier gives the unconstrained solution looking at index and pedigree only
select only the very best AI bull for all breedings
select a number of bulls from many different families
Breeding Objective
Progeny index ($ Index)
inbreeding rate
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Breeding Objective
"A breeding objective need not be economic.
For example, in many companion animal species it is tempting to believe that the breeding objective must be the maintenance of a ridiculous appearance and congenital abnormalities!"
(John Gibson, UNE)
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Historically not all beef cattle breeding objectives have been economic
Photo taken in 1949 at Red Bluff Bull Sale, CA.
Kindly provided by Cathy Maas from Crowe Hereford Ranch, Millville, CA.
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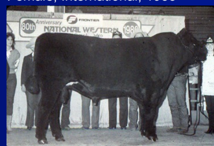
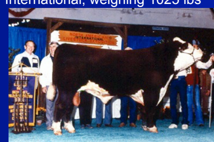
1953. Grand Champion Angus Female, International, 1953

1950. Grand Champion Steer, International, weighing 1025 lbs



1986. "Coblepond New Yorker" weighed 2529 lbs and measured 65 inches tall at 35 mos. (Frame 10) when he was Denver Champion.



1988 Grand Champion Bull, National Polled Hereford Show (frame 10).

Images from Harlan Ritchie's historical review of type https://www.msu.edu/~ritchieh/historical/cattletype.html

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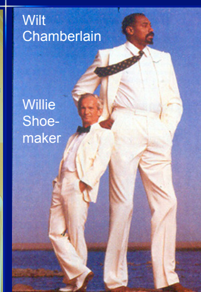
We can make genetic changes in our cattle (and our dogs) - the question is are we making profitable change?



Killed same day at IBP in Iowa: The small female weighed 835 lbs and was extremely fat. The large male weighed 1900 lbs and was very lean.

Images from Harlan Ritchie's historical review of type https://www.msu.edu/~ritchieh/historical/cattletype.html

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Finding the right balance

- **The formal breeding objective**
- **Inbreeding –** (There is an obvious connection between inbreeding and homozygosity)
- **Additional constraints e.g. use no animal with a genetic defect in pedigree**

⬇

Mate selection tool shows you the 'opportunity cost' of imposing non–optimal constraints on mate selection

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Use of Mate Selection Software to Manage Lethal Recessive Conditions in Livestock Populations

- We simulated 100 loci lethal recessive loci into a data set from an US beef herd pedigree consisting of 169 female selection candidates, 85 male selection candidates and 546 ancestor records. Used $Beef as our target index.
- Then used the following two parameters to decide which cows to mate to which bulls:
- **LethalA**: the predicted number of recessive lethal alleles (i.e. Aa) in the progeny **(MINIMIZE CARRIERS)**
- **LethalG**: the predicted number of recessive lethal genotypes (i.e. aa) in the progeny **(MINIMIZE AFFECTED PROGENY)**

Van Eenennaam, A.L., and B. P. Kinghorn. 2014. Use of Mate Selection Software to Manage Lethal Recessive Conditions in Livestock Populations. WCGALP Vancouver, Canada. https://asas.org/docs/default-source/wcgalp-posters/408_paper_9819_manuscript_1027_0.pdf

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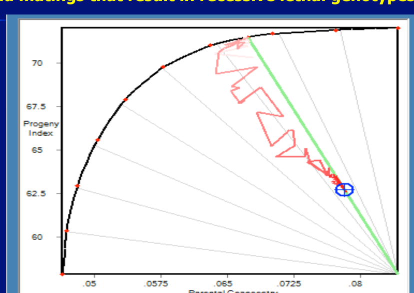
A MateSel run showing considerable decrease in Progeny Index value achievable, with associated increase in parental coancestry (blue circle) when strongly directed to avoid matings that result in recessive lethal genotypes.



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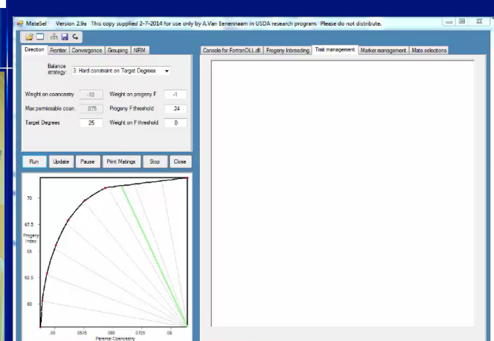
Selection against affected calves (aa) or against carrier calves (Aa)



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CONCLUSIONS

This work is being funded by National Research Initiative Grant 2013-68004-20364 from the USDA National Institute of Food and Agriculture.

- The bottom line is that every animal carries genetic defects and typically breeders do not know what they are or where they are located in the genome.
- Selection against matings that resulted in "aa" homozygote progeny achieved a superior outcome in terms of decreased impact on rate of genetic gain and reduction in progeny lost as compared to selecting against "Aa" carrier progeny.
- Ideally, the economic weighting associated with embryonic loss should be incorporated into the selection index to ensure the optimal compromise in the genetic gain forfeited to reduce embryo mortality.
- The ultimate objective of this research project is to identify lethal recessive alleles and develop tools for the implementation of strategic mating.
- This will help ensure that the carriers are mated strategically to minimize the incidence of affected offspring, while still utilizing their genetics when the value of their merit overrides the discount associated with their carrier status.

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Questions

Alison Van Eenennaam, Ph.D.
Cooperative Extension Specialist
Animal Biotechnology and Genomics
Department of Animal Science
University of California, Davis, USA
alvaneenennaam@ucdavis.edu

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