

"Developing tools to simplify the use of DNA information in beef cattle breeding"

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United States Department of Agriculture National Institute of Food and Agriculture

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Outline

- Recap: What are we trying to do?
- Lets assume we have success then what?
- Defining a breeding objective
- Management of recessive conditions in breeding programs
- Utilizing genetic and management tools to optimize mate selection decisions
- Anticipated outcomes of USDA reproduction grant



Genotype-Driven Screens for Embryonic Lethals

- Sequence bulls and identify SNPs that are predicted to have a disruptive effect on protein structure (also called causative DNA sequence variants **DSV**)
- Develop chip of DSVs and sequence large number of healthy individuals to identify embryonic lethals
- True embryonic lethals should never be observed in the homozygous state among healthy animals and the resulting departure from Hardy-Weinberg equilibrium should be statistically significant
- Carrier status of the sire and dam should have a negative effect on fertility traits



Missing homozygotes....

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Abstract

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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 \leq 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} ^s 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

If allele frequency of SNP is 50% A: 50%T then expect 25% AA; 50% AT, 25% TT

If see 33% AA and 66% AT then have a case of missing homozygotes (i.e. TT is likely lethal)



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.



Translational questions that remain assuming success

- 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???



What traits need to be improved, and how important are different traits relative to

each other?

Where to Go?

Breeding Objective (Goal of the breeding program)

1957 vs. 2001 chickens





43





85 d.

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Image kindly provided by Dr. Rachel Hawkin, Cobb-Vantress

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Genetic selection to improve bird's health and welfare



Throughout the 1990's and in the new millennium Cobb added additional selection traits related to chicken wellbeing including

- more sophisticated measurements of leg health (e.g. tibial dyschondroplasia (TD) and femoral head necrosis (FHN)),
- walking ability,
- cardiovascular fitness (e.g. ascites),
- skin condition (e.g. foot pad dermatitis), and
- disease resistance.

These trait measurements are now routine parts of Cobb broiler breeding selection programs and include X-ray testing for TD, FHN evaluation, gait assessment, blood oxygen measurement for ascites control and foot pad dermatitis grading. Associated with this, Cobb incidence of TD in pedigree lines decreased, field reports of ascites declined and company regional managers reported reductions in leg problems in each world region.

http://www.cobb-vantress.com/a-better-world/overview/blog/detail/a-betterworld/2012/12/28/genetic-selection-to-improve-bird-s-health-and-welfare



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)



Given this information.....







Which do you think is my dog?



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What emphasis do you think milk yield given in the national US dairy selection index?



1. 0 2. 25% 3. 50% 4. 66% 5. 75% 6. <u>100%</u>





Year that genetic rankings began and emphasis placed on dairy traits in 2010 US national dairy selection indexes

Trait	Year	Emphasis (%)
	begun	
1. Milk yield	1935	0
2. Milk Fat	1935	16
3. Milk Protein	1977	19
4. Calving Ease/Stillbirth	1978/2006	5
5. Udder Shape and Support	1983	7
6. Feet and Leg Conformation	1983	4
7. Body Size/Weight	1983	-6
8. Productive Life/Longevity	1994	22
9. Mastitis Resistance	1994	10
10. Daughter Pregnancy Rate/Fertility	2003	11

Van Eenennaam, A.L. 2013. Genetics and sustainable animal agriculture. Chapter 3 in "Sustainable Animal Agriculture" CABI Publishing. In press.

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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. Van Eenennaam MO 2/12/2013 Animal Genomics and Biotechnology Education







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

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1950. Grand Champion Steer, International, weighing 1025 lbs



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



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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Which trait group should be given the most selection emphasis in US beef cattle production systems?

- 1. Appearance
- 2. Growth
- 3. Reproduction
- 4. Carcass traits
- 5. Depends
- 6. None of above





Need to make sure you are using the right index for your production system

- It is important to understand that in most cases indexes only encompass postweaning and carcass performance. Other factors drive profitability, especially fertility.
- Cow-calf producers keeping replacement heifers and selling calves at weaning should have a relative economic emphasis of 47% on reproduction, 24% on growth, and 30% on carcass traits
- Producers in an integrated system should have a relative economic emphasis of 31% on reproduction, 29% on production, and 40% on carcass traits (Melton, 1995).
- This relative emphasis will depend on how much the value derived from genetic gain in feedlot and carcass traits is shared with the producer in the integrated system.

(*Melton, B. E. 1995. Conception to consumption: The economics of genetic improvement. Proc Beef Improvement Fed 27th Ann Mtg. p 40-87, Sheridan, WY*).



What traits need to be improved, and how important are different traits relative to each other?

Trait

Measurement

Males versus females

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Which traits

• Which animals

Progeny test

•



Breeding

Objective

(Goal of the breeding program)

Image adapted from "Genetic Evaluation and Breeding Program Design" (2011). University of New England, Australia



Estimation of

EPDs (breeding value)

- Phenotypes
- Pedigree
- BLUP
- DNA information

Reproductive Technologies

Artificial insemination

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 Multiple Ovulation/ Embryo Transfer

Selection/Culling/Mate Selection

Based on genetic evaluation

• Balancing the rate of genetic change (ΔG) and inbreeding





\$ INDEXES. Multi-trait selection indexes combine EPDs for several traits into a single economic value.

\$ INDEXES. Multi-trait selection indexes combine EPDs for several traits into a single economic value. The index values are interpreted like EPDs; the difference in index value between two bulls is the expected difference in average dollar value of their progeny, when the bulls are bred to similar cows. Indexes are expressed in dollars per head, and higher indexes mean a higher dollar value per head. An index value only has meaning when it is compared to the index value of another animal of the same breed. In the US indexes are currently calculated for Angus, Charolais, Gelbvieh, Hereford, Limousin, Simmental, and SimAngus bulls.



Example: \$Indexes calculated for Australian Angus animals.

- **Long Fed / CAAB Index** (\$) Estimates the genetic differences between animals in net profitability per cow joined for an example high fertility selfreplacing commercial Angus herd in temperate Australia targeting pasture grown steers with a 270 day feedlot finishing period for the high quality, high marbled Japanese export market. Significant emphasis is placed on marbling and 600 day growth.
- Terminal Index (\$) Estimates the genetic differences between animals in net profitability for an example commercial crossbred herd where *no animals are kept for breeding*. For example using Angus bulls over tropical cows targeting pasture grown steers and heifers with a 100 day feedlot finishing period. Progeny are assumed marketed at 1320 lb live weight at 23 months of age. Emphasis is on growth and carcass yield *with no weighting placed on calving ease, female fertility or milk.*



Long Fed / CAAB Index (\$) - Estimates the genetic differences between animals in net profitability per cow joined for an example high fertility self-replacing commercial Angus herd in temperate Australia targeting pasture grown steers with a 270 day feedlot finishing period for the high quality, high marbled Japanese export market. Significant emphasis is placed on marbling and 600 day growth.

Table 2 - Long Fed / CAAB Index - Profit Drivers



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The range of traits for which BREEDPLAN (Australia) produces EPDs is shown below.

GROWTH

Birth weight Growth - Weaning Growth - Yearling Growth - Final Maternal (Milk) Mature cow weight

BREEDPLAN® TRAITS

FERTILITY

Scrotal size Days to calving Gestation length Calving ease - direct Calving ease - daughter

CARCASS

Carcass weight Fat depth - Rump Fat depth - Rib Retail beef yield Intramuscular fat

OTHER

Net feed intake Docility Flight time Shear force Conformation

Long Fed / CAAB Index (\$) - Estimates the genetic differences between animals in net profitability per cow joined for an example high fertility self-replacing commercial Angus herd in temperate Australia targeting pasture grown steers with a 270 day feedlot finishing period for the high quality, high marbled Japanese export market. Significant emphasis is placed on marbling and 600 day growth.



Table 3 - Long Fed / CAAB Index - EBV Weightings

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Terminal Index (\$) - Estimates the genetic differences between animals in net profitability for an example commercial crossbred herd where *no animals are kept for breeding*. e.g. Angus bulls over tropical cows targeting pasture grown steers and heifers with a 100 day feedlot finishing period. Progeny are assumed marketed at 1320 lb live weight at 23 months of age. Emphasis is on growth and carcass yield *with no weighting placed on calving ease, female fertility or milk.*





COMPARE!!!!!!!! Maternal CAAB index versus Terminal Index





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Develop selection indexes that incorporate agedependent fertility of females (including heifers) in the context of cow-calf and feedlot production with quality and yield grade based marketing of carcass beef. Thus, users of the research results will be provided economically rational emphases for fertility, growth, efficiency, and carcass traits upon which to base selection and mating decisions.



Dr. Mike MacNeil

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"To date, the consideration of reproduction has been cursory in selection indexes used by providers of genetic evaluation to beef breeders and producers. Thus, it is proposed that breeding objectives that explicitly model age-specific reproductive rate as a basis for selection indexes be developed. The indexes will consider the complete life-cycle in a production system that extends from conception to product. Because reproduction is measured late in life relative to the time that selection decisions are made, consideration of phenotypic and molecular indicator traits will be of considerable importance."



When making selection decisions to improve fertility – which group of cattle should selection focus upon?

- - Bulls
 Cows
 Heifers





Genetic composition of the herd: 87% of genetic composition of calf crop is determined by the sires used over the last 3 generations





Maternal grand sires (25%)











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Time line for beef breeding

Bull purchase/selection



Image adapted from "*More Beef from Breeding*" Workshop (2007). Meat and Livestock (MLA), Australia

Progeny born

2015



Progeny slaughtered

2016



2020

Female progeny used for breeding

2018

2019

2017



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2014

2013

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2022

2023

2021



Classic "decision" systems

Targets

Breeding Data **Objective**

Sets of **Rules**

Parameters

Modified from slide kindly provided by Dr. Brian Kinghorn, UNE, Australia Van Eenennaam MO 2/12/2013

Sire use Dams per sire **Avoid inbreeding Trait distributions Avoid genetic defects Reproductive technologies** ...etc.

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Not always attiving at

ACTION



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



American Angus Defect Codes

American Angus - Defect Codes - Windows Internet Explorer

http://www.angus.org/Base/DefectCodes.aspx

Defect Codes

$\Delta \nabla$

- AM Arthrogryposis Multiplex
- CA Contractural Arachnodactyly
- DM Double Muscling
- DW Dwarfism
- HI Heterochromia Irides
- HG Horn Gene
- NH Neuropathic Hydrocephalus
- M1 nt821 Mutation for Double Muscling
- OS Osteopetrosis
- D2 PRKG2 Gene Mutation for Dwarfism
- RT Recessive Trait
- RD Red Gene
- SN Syndactyly
- UB Uncommon Blood
- WT Wild Type Color Gene
- XC Carrier of more than 1 defect
- XF Free of more than 1 defect

- Arthrogryposis Multiplex carrier = AMC
- Arthrogryposis Multiplex free = AMF
- Arthrogryposis Multiplex affected = AMA



Photo used with permission from <u>http://www.angus.org</u>.

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SNPS associated with disorder....

"It will be essential to develop methods that prioritize SNP variants based on the likelihood that they contribute to disease"

- The frequencies of different classes of variations in ten case and ten control human genomes were compared (K. V. Shianna *et al.*, unpublished data).
- There were 383,913 variants (single nucleotide variants and indels) present in at least two cases and no controls.
- However, if testing is restricted to only variants that affect the coding sequence (i.e. missense mutations), this number drops to 2,354
- If testing is restricted to only protein-truncating variants (i.e. nonsense mutations), the number drops further to 152

Cirulli and Goldstein, 2010. Uncovering the role of rare variants in common disease through whole-genome sequencing. Nature Reviews Genetics 11:415. Van Eenennaam MO 2/12/2013 Animal Genomics and Biotechnology Education



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

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If you breed a curly calf carrier cow (AMC) to an curly calf free bull (AMF), what is the chance that the offspring will be stillborn as a result of being curly calf?

1. 0 2. 1/4 (25%) 3. 1/2 (50%) 4. ²/₃ (66%) 5. ³/₄ (75%) 6. 1 **(100%)**

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If you breed a curly calf carrier cow (AMC) to an curly calf free bull (AMF), what is the chance that the offspring will be stillborn as a result of being curly calf?

1.02. 1/4 (25%) 3. 1/2 (50%) $4.\frac{2}{3}(66\%)$ 5. 3/4 (75%) 6. 1 (100%)





Average Long Fed CAAB Index for sires by birth year



Allen, J. M. and C. F. Teseling. 2011. Information empowers – Arthrogryposis multiplex in Angus Australia. Proc. Assoc. Advmt. Anim. Breed. Genet. 19: 135-138.

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Angus Australia provides probability data on animal in database Figure courtesy of Carel Teseling, Angus Australia

Angus Animal Details DOUBLE 0 7 93 F1(AI) EBV Mating Member Sale Files to Semen Search Search Predictor Download Catalogues Catalogues Identifier: CCGF1 Sex: Female Tattoo: CCG F1 (Both Ear) Birth Date: 01/01/2010 Calving Year: 2010 Inventory Season: Autumn Status: Active Register: HBR Genetic Status AMFU, NH25%, CA6% (Click for explanat Sire: B C C BUSHWACKER 41-93 DOUBLE 0 7 EVEREST B51(AI) Dam:

GeneProb used to estimate the probability of every animal in the database being a carrier based on all ancestor and descendant DNA test results

Teseling, C. F., and P. F. Parnell. 2011. The effective management of deleterious genetic conditions in cattle. Proc. Assoc. Advmt. Anim. Breed. Genet. 19: 131-134.

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MateSel Optimised Mating Allocation



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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Mate Sel: 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

inbreeding rate

merit



Finding the right balance

The formal breeding objective Inbreeding 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



<u>Develop software</u> to handle the mutations discovered in this project, and deliver selection and mating recommendations to US beef breeders that exploit this information optimally in competition with other factors of importance (e.g. trait merit, genetic diversity (inbreeding), genetic defects and recessive lethals, logistical constraints, semen costs, etc.)



Dr. Brian Kinghorn

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"Adapt mate selection methodology and develop software that can be used to optimize the rate of genetic gain (using the selection indexes developed by Mike MacNeil) and mate allocation with a key objective being to reduce both the phenotypic expression and allele frequency of the lethals identified in the project. Equally important, this will be carried out in concert with other important issues such as the management of trait merit, genetic diversity, other genetic defects, genome-wide inbreeding, logistical constraints and costs."



Anticipated outcomes of USDA reproduction grant

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



United States Department of Agriculture National Institute of Food and Agriculture



- Multiple-trait selection indexes that include all of the economicallyrelevant traits that influence the profitability of US beef cattle production are integral to this optimization and will be available via the DGVs (DNA sequence variants) produced for the 10,000 participating cows.
 - Indexes provide an economic evaluation of the genetic differences among sires, and an objective method for determining likely differences in the profitability of progeny from different sires conditional on the breeding objective.
 - It is envisioned that the development of the decision support software proposed in this project based on genotype information and economic indexes will provide a platform to facilitate the incorporation of the results of other genomic projects into national cattle evaluation.
 - Decision support software is essential to encourage more widespread industry adoption of DNA technologies by providing a unified approach to appropriately weight the relative economic value of traits in the breeding objective against potential deleterious recessives, and suggest an optimal breeding scheme based on all available information.

QUESTIONS

This project is funded by National Research Initiative 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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More than 98% of the genome does not encode protein sequences, including most intergenic DNA and sequences within introns



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The DNA sequence of a gene can be altered in a number of ways. Gene mutations have varying effects, depending on where they occur and whether they alter the function of essential proteins





Missense mutation (as compared to synonymous) This type of mutation is a change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene.





Nonsense mutation

A nonsense mutation is also a change in one DNA base pair. Instead of substituting one amino acid for another, however, the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.





Insertion

An insertion changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.





Deletion

A deletion changes the number of DNA bases by removing a piece of DNA. Small deletions may remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighboring genes. The deleted DNA may alter the function of the resulting protein(s).

Deletion mutation







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Duplication

A duplication consists of a piece of DNA that is abnormally copied one or more times. This type of mutation may alter the function of the resulting protein.



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Frameshift mutation

This type of mutation occurs when the addition or loss of DNA bases changes a gene's reading frame. A reading frame consists of groups of 3 bases that each code for one amino acid (i.e. codon). A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations.

Frameshift mutation





Microsatellites (SSR)

Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base-pair sequences, and a tetranucleotide repeat is made up of 4-base-pair sequences. This type of mutation can cause the resulting protein to function improperly.

Repeat expansion mutation





"Commercial Heifer Selection Using Genomics"

- What traits are of importance for heifer replacement selection?
- What selection criteria are currently available?
- What traits are genomic predictions available for?
- What is the value of genetic improvement in commercial females?



What traits are of importance for heifer replacement selection?

- Has to be big enough to breed as a yearling
- Has to be phenotypically/structurally sound

THEN IF THERE ARE ANY LEFT – CAN CONSIDER SELECTION

- Reproductive traits are sex-limited, lowly heritable, and some are expressed quite late in life.
 - age at first calving
 - reproductive success
 - replacement rate

i.e. type of traits benefit most from genomics!



Improving the accuracy of genomic selection?

- According to a simulation presented by Meuwissen and Goddard a 40% gain in accuracy in predicting genetic values could be achieved by using sequencing data instead of data from 30K SNP arrays alone.
 Furthermore, by using whole-genome sequencing data, the prediction of genetic value was able to remain accurate even when the training and evaluation data were 10 generations apart: observed accuracies were similar to those in which the test and training data came from the same generation.
- According to the authors, "these results suggest that with a combination of genome sequence data, large sample sizes, and a statistical method that detects the polymorphisms that are informative..., high accuracy in genomic prediction is attainable"

Meuwissen and Goddard, 2010. Accurate prediction of genetic values for complex traits by whole-genome resequencing. Genetics 185(2):623-31.