

Management of lethal recessive alleles while optimizing genetic gain in beef cattle

Lindsay R. Upperman

Department of Animal Science, University of California, Davis 95616

Introduction

Management of inbreeding is an important focus for animal breeders because inbreeding can lead to reduced biological fitness of a population, also known as inbreeding depression. High levels of inbreeding resulted during the formation of British cattle breeds, such as Angus and Hereford, causing less genetic diversity when compared to other breeds. Inbreeding has the most profound negative impact on traits associated with female stayability and reproduction including the total number of calvings through life, calf weight at 3 months of age, longevity, and number of calves produced up to 7 years. As such, inbreeding has a significant impact on maternally-based traits in beef cattle. One reason inbreeding negatively impacts fertility is that it increases the likelihood that common recessive loss of function alleles at essential genes will be inherited from carrier sire by carrier dam matings. Such recessive lethal alleles have been documented in dairy cattle breeds, and ongoing sequencing projects are seeking to identify them in beef cattle breeds. Although fertilization rates in beef cattle are estimated to be around 90%, average calving rate to a given service is closer to 55%, suggesting a 35% embryonic or fetal mortality rate. If some portion of this loss is due to known homozygous recessive loss of function alleles at essential genes, mate selection could be employed to avoid heterozygous carrier matings. As the number of known recessive genetic conditions increases within a breed, it becomes increasingly difficult to avoid carrier matings. To date the beef cattle industry's approach to deleterious recessive alleles has been to overtly avoid the use of carrier animals, irrespective of the genetic merit of the animals involved. In fact, some breed associations will not allow carrier animals to be registered, leading to the removal of carrier animals from breeding populations regardless of their polygenic genetic merit. This approach is unlikely to be

an optimal strategy from the perspective of genetic improvement. It is probable that in some cases the overall breeding value of carrier animals outweighs the economic penalty of their carrier status. Now is an opportune time to examine and review the progress that has been made in understanding and selecting for female fertility in beef cattle, and ultimately consider the management options that are available to minimize the impact of recessive lethal conditions on beef cattle genetic improvement programs.

Review of Literature

The Cattle Industry

The cattle industry is one of the most important industries in the United States (U.S.), ranking first nationally in agricultural commodities production value at \$59.9 billion, surpassing corn production value for the past two years (USDA, 2016). It accounts for \$78.2 billion dollars (21 percent) of the \$377 billion dollars of total cash receipts produced from agricultural commodities in the U.S. (USDA, 2016). Beef production encompasses a range of operations which span from cow-calf systems that utilize pasture for grazing to feedlots that focus on grain finishing for slaughter, making this a highly-specialized industry. Beef cattle producers currently manage approximately 92 million head of cattle (USDA, 2016), with 31.2 million of those being beef cows and 6.4 million beef heifers. Thirty two percent of heifers were kept as replacement females, the highest beef heifer replacement rate that has been observed since 1995 (NCBA, 2016; USDA, 2016). Replacement females are the next generation of cows, so increasing numbers within the cattle inventory should allow for superior genetics to be incorporated into a herd (Diskin and Kenny, 2014).

Cow and Heifer Efficiency

Cows and heifers are an important part of the beef industry as they play a crucial role in converting low-quality forage to a high-quality protein source for human consumption (Diskin and Kenny, 2014). Within cow-calf operations, female reproductive efficiency is a key component for profitability. Optimization of female efficiency encompasses factors such as genetics, nutrition, body condition score,

fertility, and health (Diskin and Kenny, 2014). Cow reproductive efficiency is influenced by a female's age at puberty and pregnancy, days of post-partum anestrus, and lifetime production (Burns et al., 2010; Diskin and Kenny, 2014). Additionally, females are expected to establish and maintain pregnancies shortly after calving (Berry et al., 2014).

Beef Female Reproduction

The failure of a cow to become pregnant can cost a producer around \$165 per cow exposed in a breeding season (Lamb et al., 2008). Approximately 4.5% of the beef cow herd is culled each year due to the failure to become pregnant (Bellows et al., 2002). Females can fail to become pregnant for various reasons, including being prepubescent at breeding, anestrous, inadequate nutrition, disease, genetics, or traumatic events (Lamb et al., 2008). Of the females who become pregnant, average fertilization rates are around 90% (Diskin and Morris, 2008). Despite these high fertilization rates, associated calving rates average 55%. This suggests that embryo or fetal mortality occurs in approximately 35% of pregnancies between fertilization and calving (Diskin and Morris, 2008).

Embryo Mortality

Several studies have documented the occurrence of embryo mortality as shown by the differences in fertilization and subsequent calving rates (Burns et al., 2010; Diskin and Sreenan, 1980; Dunne et al., 2000; Warnick and Hansen, 2009). Embryo mortality can occur at different days of gestation. Early embryo mortality (EEM) refers to mortalities that occur between fertilization and day 24 of gestation (Burns et al., 2010), which is when the fully elongated conceptus starts implantation to the endometrium (Lonergan et al., 2016). Late embryo mortality (LEM) refers to mortalities that occur between days 25 and 45 of gestation, which is when the process of differentiation toward organ development occurs. The majority of studies suggest that 75-80% of all embryo mortalities are EEM (Burns et al., 2010). Diskin and Sreenan (1980) found that 44% of embryo mortalities occurred at day 12 and 34% at day 16. Another study found embryo loss following artificial insemination was 32% at day 14 and 24% at day 30 (Dunne et al., 2000). Conversely, Warnick and Hansen (2009)

reported increased embryonic mortality (61%) after 34 days when compared to embryonic mortality before 34 days (16%). Furthermore, females who didn't produce a calf in the past one or two breeding seasons had a higher incidence of abnormal conceptuses (Warnick and Hansen, 2009). Collectively, these studies imply that most embryo mortalities happen after day 12 of gestation but are also still possible up to and after day 34.

Factors Affecting Embryo Mortality

Embryo mortality can be caused by a variety of genetic and environmental factors throughout development (Burns et al., 2010). Genetic factors include chromosomal defects, individual genes, or genetic interactions, whereas environmental factors include nutrition, age, climate, infectious diseases, or hormonal imbalances (Van Raden and Miller, 2006; Perkel et al., 2015). For instance, female cattle with three follicular waves compared to two follicular waves, were found to have smaller and younger follicles which produce less estradiol, and this has been shown to be associated with reduced rates of conception (Ahmad et al., 1997; Keith Inskeep, 2001). Infectious causes of embryo mortalities include Campylobacteriosis, Trichomoniasis and Bovine Viral Diarrhea Virus, which can lead to a harsh uterine environment for the embryo (Clark et al., 1986; Houe, 1999; Kirkland and MacKintosh, 2006; Burns et al., 2010). An example of a genetic cause of embryo loss is a known mutation in the interferon-tau gene. Decreased expression of interferon-tau in the blastocyst allows for luteolysis of the corpus luteum (Burns et al., 2010) which interferes with maternal recognition of the embryo and resets the estrus cycle, causing loss of the pregnancy (Mathialagan and Roberts, 1994). Chromosomal abnormalities, which can cause hereditary conditions or diseases, can also influence embryo survival (King, 1985). For example, the 1/29 Robertsonian chromosomal translocation present in several beef breeds has been suggested as a cause of reduced fertility in both cattle sexes (Gustavsson, I. 1979). It is possible to manage these environmental and genetic factors that affect embryo mortality through operation-specific considerations and by managing the levels of inbreeding, respectively.

Inbreeding

Factors that affect embryo mortality, such as inherited diseases, can be compounded by inbreeding, or the mating of close relatives such as daughters and sires. Increased levels of inbreeding have been found in British cattle breeds, including dairy breeds as well as beef breeds such as Angus and Hereford, when compared to other continental beef breeds or *Bos indicus* breeds (Purfield et al., 2012). Inbreeding depression, which occurs when identical alleles are passed down to offspring by a common ancestor, can decrease the biological performance or fitness of certain traits (Carrillo and Siewerdt, 2010), with reproduction traits being more sensitive to inbreeding than growth or carcass traits (Parland et al., 2007; Carolino and Gama, 2008). The reproductive traits most impacted by inbreeding are total number of calves produced in a cow's lifetime and calf weight at 3 months of age, followed by female longevity and number of calves produced up to 7 years (Carolino and Gama, 2008). Gonzalex-Recio et al. (2007) found that increased inbreeding values also had detrimental effects on fertility. Females with greater than 25% inbreeding had lower pregnancy rates and higher dystocia rates when compared to low or non-inbred females (Gonzalex-Recio et al., 2007). Although inbreeding has an undesirable effect on reproductive phenotypes as observed in the above studies, it can also play a role in the genetic components of reproduction.

Genetic Causes of Embryo Mortality

Inbreeding depression results in two main effects at the gene level (Carrillo and Siewerdt, 2010). The first is a decrease in the number of heterozygous individuals, which affects the genetic diversity within the population. The second is an increase in detrimental outcomes, including embryonic lethality, due to homozygosity at certain loci (Carrillo and Siewerdt, 2010).

A number of different alleles that affect cow fertility have been identified in both beef and dairy cattle. In dairy cattle, four loci associated with embryo mortality, along with three strong candidate causation mutations, were identified in Holstein, Monteliearde, and Normande breeds (Fritz et al., 2013). Another study of 337 Holstein Friesian cows found three possible recessive lethal alleles in selectin genes that are

required for embryo implantation and placental development (Chen et al., 2017). Additionally, more than 400 candidate loss of function (LOF) alleles were identified in a study of 6,300 Belgian beef and 35,000 New Zealand dairy cattle. Testing of 200 candidate offspring from carrier sire by carrier dam matings identified nine mutations that resulted in significant depletion of homozygotes, providing evidence that these alleles were true LOF variants (Charlier et al., 2016). Similarly, Hoff et al. (2017) identified seven loci with haplotypes that were not observed in the homozygous form in Angus beef cattle, suggesting these loci as possible candidates for LOF alleles. These studies suggest that a large number of LOF alleles impacting fertility may be present in various cattle populations.

Female Selection Traits

Although reproductive traits are of vital importance to the beef industry, only a limited number of effective selection tools for genetic improvement of reproduction are currently available (reviewed by Van Eenennaam, 2013). Instead, traits such as days to calving, calving interval, longevity, stayability, pregnancy rate, first-service conception rate, scrotal circumference, age at puberty, postpartum interval, length of the estrus cycle immediately prior to breeding, days to first breeding, heifer pregnancy rate, size of the ovulatory follicle, and the total number of follicles in the ovary are commonly used as indicator traits or markers of fertility (Van Eenennaam, 2013). In order to select the best females within a breed, producers utilize expected progeny differences (EPDs), predictions of performance of an individual's future progeny, for given traits.

Currently in the U.S. beef cattle industry, female-based EPDs typically include: heifer pregnancy, calving ease maternal, maternal milk, herds, daughters, mature weight, and mature height. The American Hereford Association also includes udder suspension and teat size (American Hereford Association, 2017). Most other beef breeds, such as Gelbvieh, Charolais, Red Angus, and many others, have similar female selection criteria within their breed pedigree databases (Red Angus Association of America, 2017; American Gelbvieh Association, 2017; American International Charolais Association, 2017). Several U.S. breed associations are implementing a total-herd reporting system by actively recording data from all the females in a herd each year,

thus enabling the development of better genetic evaluations of reproductive traits. However, direct selection on single traits can lead to unfavorable consequences for reproduction or growth. Ideally tools that allow for selection of multiple traits would be optimal (Davis, 1983; MacNeil, 1985).

Economic Selection Indexes

Further complicating selection for improved reproduction, is that reproductive and health traits often have negative genetic correlations with growth traits. Significant increases in livestock production and growth have been accomplished with the currently available genetic selection tools, (Rauw et al., 1998; Berry et al., 2014). However, increased production efficiency can negatively impact reproductive or health traits, ultimately affecting future production (Rauw et al., 1998; Berry et al., 2014).

One tool producers can use for selection on multiple traits is an economic selection index. An economic selection index is the combination of multiple traits based on their degree of importance toward the breeding objective, which allows for improved performance for all of the selected traits (Berry et al., 2017). Hazel (1943) developed selection index methodology for optimized multiple trait selection. Multiple-trait selection indexes can be developed to optimize profit given a specific breeding objective, with different traits being assigned an economic weight based upon their contribution to profit. Economic index rankings are equivalent to the term “fitness” in wild populations, with the highest ranked individual being the “fittest”, or most profitable, according to the breeding objective and therefore a desirable parent for a given production system. With classical index selection, the breeding objective determines the targeted direction of genetic change for the traits, weighted by their respective market values (MV). This market value is the economic value per unit increment in the trait (e.g. \$/unit liveweight). The breeding goal (H), or aggregate genotype, can be represented in the following equation:

$$H = MV_1 EBV_1 + MV_2 EBV_2 + \dots + MV_n EBV_n;$$

where EBV_i is the additive genetic value of trait i , and MV_i is the market value (also known as economic value) of trait i , defined by the change in profit of a unit change in the trait i (Hazel, 1943). A multi-trait selection index combines EPDs for the selected traits into one economic value (Van Eenennaam, 2013). For example, when looking at differences in index values between two bulls that are bred to similar cows, the expected difference in dollar value is the result of the average of their progeny, which is comparable to an EPD. Index values are conveyed in dollars per head of the progeny, with a higher value resulting in more dollars per head for the given progeny. However, due to selection indexes being calculated from EPDs within a breed, these values can only be compared to other individuals within the same breed. Today, indexes are calculated for cattle breeds such as Angus, Charolais, Gelbvieh, Hereford, Limousin, Simmental, and SimAngus (Van Eenennaam, 2013).

Unfortunately, most of the calculated indexes within beef breeds are for growth and carcass performance (Van Eenennaam, 2013). Yet, profitability within a given breeding objective can be based on other factors, including fertility. One study showed that improvements in fertility could be up to 4-fold more important than carcass trait improvements (Melton, 1995), while another study showed that fertility traits are 3 times more important than carcass traits within a cow-calf operation that markets progeny at weaning (Aby, 2016). This study also suggested that of the fertility traits, stillbirth was the most significant followed by age at first calving, calving interval, twinning frequency, and calving difficulty (Aby, 2016). Conversely, Gutierrez et al. (2002) found that age at first calving was a more reliable trait for selection for improved fertility than calving date and calving interval. However, these are only a few of the numerous studies that have looked at the relative importance of fertility in cow-calf production systems. Roughsedge et al. (2005) reviewed a number of studies in other countries that observed the ratio of relative weightings in phenotypic standard deviation units for reproductive: growth: carcass traits (Table 1).

Table 1: Ratios of relative weightings in phenotypic standard deviation units for reproductive: growth: carcass traits in different countries. Modified from Van Eenennaam, 2013.

<u>Country</u>	<u>Reproductive:Growth:Carcass</u>	<u>References</u>
Australia	6:2:1 and 3:2:1	Van Eenennaam, 2013; Roughsedge et al., 2005
Canada	4:1:1	Van Eenennaam, 2013; Roughsedge et al., 2005
New Zealand	2:1	Van Eenennaam, 2013; Roughsedge et al., 2005
Ireland	9:3:1, 8:3:1 and 9:4:6	Van Eenennaam, 2013; Roughsedge et al., 2005
Norway	3:1	Aby, 2016

These data suggests that globally most breeding objectives tend to place a higher economic emphasis on reproductive traits over growth or carcass traits, especially when the objective is focused on herd replacements. Thus, more emphasis should be placed on selection for reproductive traits within U.S. selection indexes. However, growth and carcass traits can make an equal contribution to the breeding objective when the objective is retained ownership of the progeny (Roughsedge et al., 2005). In a system where producers sell calves at weaning and therefore derive no direct value from carcass traits, the emphasis placed on traits other than reproduction and growth depends on the value of genetic progress in carcass performance that is shared with the cow-calf producer.

Since ultimately all traits are important to the beef cattle supply chain, incorporation of both carcass traits and female reproduction traits in an all-purpose selection index would provide the best scenario for general breeding objectives (MacNeil et al., 1985). The all-purpose indices that do exist in for US beef cattle breeds all include calving ease (direct and maternal), and some measure of carcass merit. They do not include more than one or two EPDs (Stayability, Heifer Pregnancy, Scrotal Circumference, Days to Conception) associated with fertility (Bullock, 2017). For example, the Hereford Association has a baldy maternal index (BMI\$) and a Brahman influence index (BII\$), which indicates the use of Hereford bulls on Angus or Brahman-

based cow herds, respectively. These indexes include only scrotal circumference as a fertility indicator trait.

Other countries have incorporated several reproductive traits into maternal indexes. Evans et al. (2007) reported a calving traits index in Irish cattle which incorporated calving difficulty, gestation length, and calf mortality. Another index called “milk & fertility” included traits such as cow survival, calving interval, days to first calving, maternal calving difficulty, maternal weaning weight, and cull cow carcass weight (Evans et al., 2007). A recent economic selection index was also proposed for a maternal-based dam line including traits of stayability, heifer pregnancy, direct and maternal calving ease, and direct and maternal weaning weight (MacNeil, 2016).

In order to utilize such a maternal-based index, EPDs or indicator traits with genetic correlations to objective traits would be required, and the availability of such data varies by breed. Currently, very few U.S. beef breeds have an EPD for stayability e.g. Gelbvieh (Bullock, 2017). The use of stayability in the above maternal index for the Angus breed which does not currently publish a stayability EPD, would require estimates of the current AAA EPD traits with stayability, meaning that the genetic correlations between stayability and the other traits would need to be obtained from literature estimates. It is difficult to find these estimates because 1) stayability has many different definitions, and 2) usually the definition forces independence of traits (i.e. $r = 0$). For example, the Canadian Hereford Association has reported a negative genetic correlation between weaning weight direct and stayability of -0.22 , whereas no correlation was found between milk or weaning weight maternal and stayability (Canadian Hereford Association, 2015). Heifer pregnancy and stayability genetic correlations have not been reported in the literature for *Bos taurus* cattle; however, in Nellore cattle, a *Bos indicus* breed, a genetic correlation of 0.64 was found for stayability and heifer pregnancy with a low residual correlation of -0.08 , suggesting no major environmental effects were common to both traits (Van Melis et al., 2010). This positive correlation suggests that heifer pregnancy EPDs could be used as an alternative to stayability to select for longevity in *Bos indicus* females but further studies are needed to confirm a similar correlation in *Bos taurus* (Van Melis et al., 2010).

Management Strategies

Selection index calculations traditionally do not incorporate the effect of specific alleles that result in embryonic or fetal mortality, as most selection indices assume that traits have a linear relationship with profitability (Bullock, 2017). The management of recessive lethal conditions became an important factor in cattle breeding in the 1950s as a result of dwarfism (McCann, 1974), and more recently as a result of an increased number of cases of Arthrogryposis Multiplex (AM), a recessive genetic condition in Angus cattle where affected animals die before or soon after birth. A DNA test was developed to identify individuals that carry this recessive lethal allele (Beever, 2008). In the Australian Angus population, DNA test results and pedigree information were used to calculate the probability that a non-tested animal was an AM carrier using the software program GeneProb (Kerr and Kinghorn, 1996; Kinghorn 1997). These results were then interpreted and made public on the Australian Angus website. Along with this program, the association designed educational programs to help members understand how to identify and manage recessive lethal alleles. By incorporating these practices, producers decreased their use of AM sires, thus decreasing the carrier individuals within the Australian Angus population (Allen and Teseling, 2011).

Although this example shows that the reduction of recessive lethal alleles is possible, complete elimination of these alleles may be more difficult (Charlesworth and Willis, 2009), thus continued long term management is necessary. Allen et al. (2011) modeled the impact of a sire who carries a recessive lethal genetic condition. Random mating herds that use an occasional carrier sire had a low occurrence of homozygous affected calves (less than 1%). However, within a self-replacing herd, where carrier females may stay in the herd for around 20 years, consistent management is required to avoid recessive lethal conditions (Allen et al., 2011).

Almost a decade ago, Charlier et al (2008) suggested that using high-density SNP panels to accelerate the identification of certain mutations that cause defects within livestock populations would allow for immediate management within breeding practices (Charlier et al., 2008). One of the important considerations in managing recessive alleles is the frequency of the recessive allele in the population. Hoff et al. (2017) found a high minor allele frequency of 7.8% for the lethal recessive allele of the GEMIN2 gene

(BTA21); six other LOF alleles were also found at additional loci at comparable frequencies. Similarly, Charlier et al. (2016) found nine lethal mutations with minor allele frequencies ranging from 1.2% to 6.6%. Furthermore, Cole et al. (2016) reviewed current studies which reported allele frequencies for several recessive haplotypes found in dairy cattle within the U.S. genomic evaluation system (Table 2):

Table 2: Reported allele frequencies for recessive haplotypes in both dairy and beef cattle. Modified from Cole et al., 2016.

<u>Breed</u>	<u>Frequency (%)</u>	<u>Functional/Gene Name</u>	<u>References</u>
Aryshire	13.0	PIRM/UBE3B	Cooper et al., 2014; Venhora et al., 2014
Brown Swiss	6.67	Unknown	VanRaden et al., 2011
	7.78	<i>TUBD1</i>	Schwarzenbacher et al., 2016
	2.19	SDM/ <i>SPAST</i>	Hafner et al., 1993; Thomsen et al., 2010
	3.61	SMA/KDSR(<i>FVT1</i>)	El-Hamidi et al., 1989; Krebs et al., 2007
	1.56	Weaver/ <i>PNPLA8</i>	McClure et al., 2013; Kunz et al., 2016
Holstein	2.76	Brachyspina/ <i>FANCI</i>	Agerholm et al., 2006; Charlier et al., 2012
	1.92	<i>APAF1</i>	Adams et al., 2012
	1.66	Unknown	VanRaden et al., 2011; McClure et al., 2014
	2.95	<i>SMC2</i>	Daetwyler et al., 2014; McClure et al., 2014
	0.37	<i>GART</i>	Fritz et al., 2013
	2.22	<i>TFB1M</i>	Cooper et al., 2013; Schütz et al., 2016
	0.25	BLAD/ <i>ITGB2</i>	Shuster et al., 1992
	1.37	CVM/ <i>SLC35A3</i>	Agerholm et al., 2001
	0.01	DUMPS/ <i>UMPS</i>	Shanks et al., 1984

Jersey	12.10	CWC15	Sonstegard et al., 2013
	1.3	Unknown	VanRaden et al., 2014
Angus	7.8	GEMIN2	Hoff et al., 2017

MateSel

As bovine resequencing efforts expand, it is likely that tens, if not hundreds, of recessive conditions will be identified in cattle populations. Computerized mate selection programs offer an efficient approach to manage large numbers of recessive genetic conditions in a breeding population. Mate selection is the process of choosing the optimal sire and dam combination based on the predicted genetic merit of the progeny for a given breeding objective (Allaire, 1980; Kinghorn, 2011). This can be done virtually to compare different mating scenarios and the genetic progress expected in each mating pair. Mate selection decisions must take into consideration the culling of individuals, purchase of semen or embryos, sire availability, inbreeding considerations and possible genetic conditions (Kinghorn, 2011).

Kinghorn (2011) developed a mate selection program called MateSel which optimizes the rate of genetic gain towards a given breeding objective while also holding inbreeding to a user defined level and handling the logistical details such as limiting the utilization of certain sires, for instance poor calving ease bulls, to within female groups of an older productive age. The program allows producers to simulate mating decisions and interactively constrain different variables to observe the impact of such constraints on the rate of genetic progress. This program offers the opportunity to compare and contrast different approaches to the management of recessive conditions in cattle. It visually displays how progress towards the stated breeding objective is impacted by the breeder or breed association decisions to avoid the use of carrier sires, as compared to specifically avoiding the mating of carrier sires by carrier dams through mate allocation to avoid producing homozygous affected calves (Kinghorn, 2011).

Management – Short vs. Long Term

Computerized mate selection programs, such as MateSel, can help breeders decrease inbreeding accumulation, thus increasing the overall efficiency of animal

production systems (Weigel and Lin, 2000). A study by Koenig and Simianer (2006) concluded that optimization tools allow for the management of inbreeding without any simultaneous loss in genetic gain. They suggested that the use of mating programs would be the best for short term management of inbreeding on a farm; however, in the long term, more focus needs to be on controlling relationships of incoming young herd sires entering the breeding population (Koenig and Simianer, 2006). Another study by Liu et al. (2015) reviewed the utilization of different programs to control inbreeding, while also factoring in different numbers of loci that affect a trait. They found that regardless of how many loci were affecting the trait, the programs used were able to control inbreeding and produce a higher level of genetic progress over both short and long term time frames (Liu et al., 2015). Ultimately, these studies indicate that both short and long term management of inbreeding and recessive alleles is possible, but long term management may be more difficult without the use of computer programs.

Conclusions/Implications

Female reproductive efficiency is an important factor contributing to beef production and overall profitability. Ongoing sequencing projects are likely to identify an increasing number of recessive LOF alleles at essential genes that result in embryonic mortality when inherited in the homozygous condition. This will make it increasingly complicated for breeders to consider all of the potential carrier sire by carrier dam matings when making breeding decisions. Computer software programs offer an approach by which breeders can choose appropriate mate allocations. Mate allocation can be used to optimize the rate of genetic progress towards an economic index while also avoiding same-locus carrier matings that result in homozygous affected offspring. Mate selection software is likely to become increasingly important to manage both inbreeding and recessive genetic conditions, especially as assisted reproductive techniques offer further opportunities to increase the intensity of selection of genetically superior seedstock.

References:

- Åby B, Vangen O, Sehested E, Aass L. 2010. The economic importance of fertility traits in beef cattle. In Wageningen Academic Publishers, editor, Book of Abstracts of the 61st Annual Meeting of the European Association for Animal Production. Wageningen Academic Publishers, The Netherlands. p. 145-150.
- Adams, H.A., T. Sonstegard, P.M. VanRaden, D.J. Null, C. Van Tassell, and H. Lewin. 2012. Identification of a nonsense mutation in APAF1 that is causal for a decrease in reproductive efficiency in dairy cattle. Plant Anim. Genome XX Conference, San Diego, CA, abstr. P0555.
- Agerholm, J.S., C. Bendixen, O. Andersen, and J. Arnbjerg. 2001. Complex vertebral malformation in Holstein calves. J. Vet. Diagn. Invest. 13:283–289 doi: 10.1177/104063870101300401
- Agerholm, J.S., F. McEvoy, and J. Arnbjerg. 2006. Brachyspina syndrome in a Holstein calf. J. Vet. Diagn. Invest. 18:418–422. doi: 10.1177/104063870601800421
- Ahmad, N., E. Townsend, R. Dailey, and E. Inskeep. 1997. Relationships of hormonal patterns and fertility to occurrence of two or three waves of ovarian follicles, before and after breeding, in beef cows and heifers. Anim. Reprod. Sci. 49(1):13-28. doi: 10.1016/S0378-4320(97)00057-2
- Allen, JM, and CF Teseling. 2011. Information empowers – Arthrogryposis multiplex in Angus Australia. Proc. Assoc. Advmt. Anim. Breed. Genet. 19:135-138
- Allen, JM, PF Parnell, and C.F. Teseling. 2011. Managing deleterious genetic conditions at the herd level. Proc. Assoc. Advmt. Anim. Breed. Genet. 19:139-142
- American Angus Association. 2017. EPD and \$Value Definitions. <http://www.angus.org/Nce/Definitions.aspx>. (Accessed 15 May 2017.)
- American Gelbvieh Association. 2017. EPD Info – American Gelbvieh. <http://www.gelbvieh.org/genetic-technology/epd-info/>. (Accessed 15 May 2017.)
- American Hereford Association. 2017. Udder scores. <http://www.hereford.org/member-services/herd-management-tools/udder-scores/>
- American International Charolais Association. 2017. American International Charolais Association EPD. http://charolaisusa.com/members/genetic_evaluation.html. (Accessed 15 May 2017.)
- Beever, J.E. 2008. http://www.angus.org/NAAB_release.pdf. (Accessed 15 May 2017.)

- Bellows, D. S., S. L. Ott, and R. A. Bellows. 2002. Review: Cost of Reproductive Diseases and Conditions in Cattle. *The Professional Animal Scientist* 18(1):26-32. doi: 10.15232/s1080-7446(15)31480-7
- Berg, D. K., J. van Leeuwen, S. Beaumont, M. Berg, and P. L. Pfeffer. 2010. Embryo loss in cattle between Days 7 and 16 of pregnancy. *Theriogenology* 73(2):250-260. doi: 10.1016/j.theriogenology.2009.09.005
- Berry, D. P., S. Conroy, T. Pabiou, and A. R. Cromie. 2017. Animal breeding strategies can improve meat quality attributes within entire populations. *Meat Sci.* doi: 10.1016/j.meatsci.2017.04.019
- Berry, D., E. Wall, and J. Pryce. 2014. Genetics and genomics of reproductive performance in dairy and beef cattle. *Animal* 8(s1):105-121.
- Bullock, D., D. Brown, and L. Keenan. 2017. The Power of Economic Selection Indices to Make Genetic Change in Profitability. *Proceedings of the Beef Improvement Federation 49th Research Symposium and Annual Meeting, Athens (GA): 2017. In press.*
- Burns, B. M., G. Fordyce, and R. G. Holroyd. 2010. A review of factors that impact on the capacity of beef cattle females to conceive, maintain a pregnancy and wean a calf- Implications for reproductive efficiency in northern Australia. *Anim. Reprod. Sci.* 122(1-2):1-22. doi: 10.1016/j.anireprosci.2010.04.010
- Canadian Hereford Association. 2015. EPD Averages Tools and Trends Fall 2015. http://www.hereford.ca/3_cattlebusiness/EPD%20Averages%20Tools%20and%20Trends%20Fall%202015.pdf. (Accessed 15 May 2017.)
- Carolino, N., and L. T. Gama. 2008. Inbreeding depression on beef cattle traits: estimates, linearity of effects and heterogeneity among sire-families. *Genet. Sel. Evol.* 40(5):511-527. doi: 10.1051/gse:2008018

- Carrillo, J. A., and F. Siewerdt. 2010. Consequences of long-term inbreeding accumulation on preweaning traits in a closed nucleus Angus herd. *J. Anim. Sci.* 88(1):87-95. doi: 10.2527/jas.2009-1897
- Charlesworth, D., and J. H. Willis. 2009. The genetics of inbreeding depression. *Nat. Rev. Genet.* doi:10.1038/nrg2664
- Charlier, C., J.S. Agerholm, W. Coppieters, P. Karlskov-Mortensen, W. Li, G. de Jong, C. Fasquelle, L. Karim, S. Cirera, N. Cambisano, N. Ahariz, E. Mullaart, M. Georges, and M. Fredholm. 2012. A deletion in the bovine *FANCI* gene compromises fertility by causing fetal death and brachyspina. *PLoS ONE* 7:e43085.
- Charlier, C., W. Coppieters, F. Rollin, D. Desmecht, J. S. Agerholm, N. Cambisano, E. Carta, S. Dardano, M. Dive, and C. Fasquelle. 2008. Highly effective SNP-based association mapping and management of recessive defects in livestock. *Nat. Genet.* doi: 40(4):449-454.
- Charlier, C., W. Li, C. Harland, M. Littlejohn, W. Coppieters, F. Creagh, S. Davis, T. Druet, P. Faux, F. Guillaume, L. Karim, M. Keehan, N. K. Kadri, N. Tamma, R. Spelman, and M. Georges. 2016. NGS-based reverse genetic screen for common embryonic lethal mutations compromising fertility in livestock. *Genome Res.* doi: 10.1101/gr.207076.116
- Chen, X., S. Zhang, Z. Cheng, J. S. Cooke, D. Werling, D. C. Wathes, and G. E. Pollott. 2017. Polymorphisms in the selectin gene cluster are associated with fertility and survival time in a population of Holstein Friesian cows. *PLOS ONE* 12(4):e0175555. doi: 10.1371/journal.pone.0175555
- Clark, B. L., J. H. Dufty, and I. M. Parsonson. 1986. The frequency of infertility and abortion in cows infected with *Tritrichomonas foetus* var. brisbane. *Aust. Vet. J.* 63(1):31-32. doi: 10.1111/j.1751-0813.1986.tb02873.x
- Cooper, T.A., G.R. Wiggans, D.J. Null, J.L. Hutchison, and J.B. Cole. 2014. Genomic evaluation, breed identification, and discovery of a haplotype affecting fertility for Ayrshire dairy cattle. *J. Dairy Sci.* 97:3878–3882. doi: 10.3168/jds.2013-7427
- Cooper, T.A., G.R. Wiggans, P.M. VanRaden, J.L. Hutchison, J.B. Cole, and D.J. Null. 2013. Genomic evaluation of Ayrshire dairy cattle and new haplotypes affecting fertility and stillbirth in Holstein, Brown Swiss and Ayrshire breeds. *Amer. Dairy*

- Sci. Assoc.–Amer. Soc. Anim. Sci. joint annual meeting, Indianapolis, IN, July 9, poster T206.
- Daetwyler, H.D., A. Capitan, H. Pausch, P. Stothard, R. van Binsbergen, R.F. Brøndum, X. Liao, A. Djari, S.C. Rodriguez, C. Grohs, D. Esquerré, O. Bouchez, M.-N. Rossignol, C. Klopp, D. Rocha, S. Fritz, A. Eggen, P.J. Bowman, D. Coote, A.J. Chamberlain, C. Anderson, C.P. Van Tassell, I. Hulsegge, M.E. Goddard, B. Guldbbrandtsen, M.S. Lund, R.F. Veerkamp, D.A. Boichard, R. Fries, and B.J. Hayes. 2014. Whole-genome sequencing of 234 bulls facilitates mapping of monogenic and complex traits in cattle. *Nature Genet.* 46:858–865. doi: 10.1038/ng.3034
- Davis, M. E., J. J. Rutledge, L. V. Cundiff, and E. R. Hauser. 1983. Life Cycle Efficiency of Beef Production: II. Relationship of Cow Efficiency Ratios to Traits of the Dam and Progeny Weaned. *J. Anim. Sci.* 57(4):852-866.
- Diskin, M. G., and D. A. Kenny. 2014. Optimising reproductive performance of beef cows and replacement heifers. *Animal* 8(s1):27-39. doi: 10.1017/S175173111400086X
- Diskin, M. G., and D. G. Morris. 2008. Embryonic and early foetal losses in cattle and other ruminants. *Reprod. Domest. Anim.* 43 Suppl 2:260-267. doi: 10.1111/j.1439-0531.2008.01171.x
- Dunne, L. D., M. G. Diskin, and J. M. Sreenan. 2000. Embryo and foetal loss in beef heifers between day 14 of gestation and full term. *Anim. Reprod. Sci.* 58(1-2):39-44. doi: 10.1016/S0378-4320(99)00088-3
- El-Hamidi, M., H.W. Leipold, J.G.E. Vestweber, and G. Saperstein. 1989. Spinal muscular atrophy in Brown Swiss calves. *J. Vet. Med. A.* 36:731–738. doi: 10.1111/j.1439-0442.1989.tb00786.x
- Evans, R. D., T. Pabiou, A. Cromie, F. Kearney, and B. Wickham. 2007. Genetic Improvement in the Irish Suckler Beef Herd: Industry Expectation and Experience so far. *Interbull Bulletin.* 36:7
- Fritz, S., A. Capitan, A. Djari, S. C. Rodriguez, A. Barbat, A. Baur, C. Grohs, B. Weiss, M.

- Boussaha, D. Esquerre, C. Klopp, D. Rocha, and D. Boichard. 2013. Detection of haplotypes associated with prenatal death in dairy cattle and identification of deleterious mutations in GART, SHBG and SLC37A2. PLoS One 8(6):e65550. doi: 10.1371/journal.pone.0065550
- Gonzalez-Recio, O., E. Lopez de Maturana, and J. P. Gutierrez. 2007. Inbreeding Depression on Female Fertility and Calving Ease in Spanish Dairy Cattle. J. Dairy Sci. 90(12):5744-5752. doi: 0.3168/jds.2007-0203
- Gutiérrez, J. P., I. Álvarez, I. Fernández, L. Royo, J. Diez, and F. Goyache. 2002. Genetic relationships between calving date, calving interval, age at first calving and type traits in beef cattle. Livest. Prod. Sci. 78(3):215-222. doi: 10.1016/S0301-6226(02)00100-8
- Hafner, A., E. Dahme, G. Obermaier, P. Schmidt, and G. Dirksen. 1993. Spinal dysmyelination in new-born Brown Swiss x Braunvieh calves. J. Vet. Med. B 40:413-422. doi: 10.1111/j.1439-0450.1993.tb00158.x
- Hazel, L. N. 1943. The genetic basis for constructing selection indexes. Genetics 28(6):476-490.
- Hoff, J. L., J. E. Decker, R. D. Schnabel, and J. F. Taylor. 2017. Lethal Haplotypes and Candidate Causal Mutations in Angus Cattle. bioRxiv doi: 0.1101/125203
- Houe, H. 1999. Epidemiological features and economical importance of bovine virus diarrhoea virus (BVDV) infections. Vet. Microbiol. 64(2-3):89-107. doi:10.1016/S0378-1135(98)00262-4
- Gustavsson, I. 1979. Distribution and effects of the 1/29 Robertsonian translocation in cattle. J. Dairy Sci. 62(5):825-835. doi: 10.3168/jds.S0022-0302(79)83334-2
- Keith Inskeep, E. 2001. Factors that Affect Embryonic Survival in the Cow, Factors Affecting Calf Crop: Biotechnology of Reproduction. CRC Press. p. 255-279. doi: 10.1201/9781420040838.ch19
- Krebs, S., I. Medugorac, S. Röther, K. Strässer, and M. Förster. 2007. A missense mutation in the 3-ketodihydrosphingosine reductase *FVT1* as candidate causal mutation for bovine spinal muscular atrophy. Proc. Natl. Acad. Sci. USA 104:6746-6751. doi: 10.1073/pnas.0607721104

- Kerr, R. J., and B. P. Kinghorn. 1996. An efficient algorithm for segregation analysis in large populations. *J. Anim. Breed. Genet.* 113(1-6):457-469. doi: 10.1111/j.1439-0388.1996.tb00636.x
- King, W. A. 1985. Intrinsic embryonic factors that may affect survival after transfer. *Theriogenology* 23(1):161-174. doi: 10.1016/0093-691X(85)90080-9
- Kinghorn, B. P. 1997. An Index of Information Content for Genotype Probabilities Derived from Segregation Analysis. *Genetics* 145(2):479-483.
- Kinghorn, B. P. 2011. An algorithm for efficient constrained mate selection. *Genet. Sel. Evol.* 43(1):4. doi: 10.1186/1297-9686-43-4
- Kirkland, P. D., and S. G. MacKintosh. 2006. Ruminant Pestivirus Infections, part 1 Diagnostic Overview Aust. NZeal. Stand. Diagn. Proc. p 1-30.
- Koenig, S., and H. Simianer. 2006. Approaches to the management of inbreeding and relationship in the German Holstein dairy cattle population. *Livest Sci.* 103(1-2):40-53. doi: 10.1016/j.livsci.2005.12.009
- Kunz, E., S. Rothhammer, H. Pausch, H. Schwarzenbacher, F. Seefried, K. Matiasek, D. Seichter, I. Russ, R. Fries, and I. Medugorac. 2016. Confirmation of a non-synonymous SNP in *PNPLA8* as a candidate causal mutation for Weaver syndrome in Brown Swiss cattle. *Genet. Sel. Evol.* 48:21. doi: 10.1186/s12711-016-0201-5
- Lamb, G. C., C. Dahlen, V. R. G. Mercadante, and K. Bischoff. 2008. What is the Impact of Infertility in Beef Cattle? In: I. F. A. S. University of Florida Extension (ed.), Gainesville, Florida.
- Liu, H., T. H. E. Meuwissen, A. C. Sørensen, and P. Berg. 2015. Upweighting rare favourable alleles increases long-term genetic gain in genomic selection programs. *Genet. Sel. Evol.* 47(1):19. doi: 10.1186/s12711-015-0101-0
- Lonergan, P., T. Fair, N. Forde, and D. Rizos. 2016. Embryo development in dairy cattle. *Theriogenology* 86(1):270-277. doi:10.1016/j.theriogenology.2016.04.040
- MacNeil, M. D. 2016. Value of genomics in breeding objectives for beef cattle. *Revista Brasileira de Zootecnia.* 45(12): 794-801. doi: 10.1590/s1806-92902016001200010

- MacNeil, M. D., L. V. Cundiff, C. A. Dinkel, and R. M. Koch. 1985. Genetic Correlations of Reproductive and Maternal Traits with Growth and Carcass Traits in Beef Cattle. In: U. o. Nebraska-Lincoln (ed.) Digital Commons, Lincoln, Nebraska.
- Mathialagan, N., and R. Roberts. 1994. A role for cytokines in early pregnancy. *Indian J. Physiol. Pharmacol.* 38(3):153-162.
- McCann, L P. *The Battle of Bull Run: Overcoming Dwarfism*, Published by the author, Kansas City, MO. 1974. Print.
- McClure, M., E. Kim, D. Bickhart, D. Null, T. Cooper, J. Cole, G. Wiggans, P. Ajmone-Marsan, L. Colli, E. Santus, G.E., Liu, S. Schroeder, L. Matukumalli, C. Van Tassell, and T. Sonstegard. 2013. Fine mapping for Weaver Syndrome in Brown Swiss cattle and the identification of 41 concordant mutations across NRCAM, PNPLA8 and CTTNBP2. *PLoS One* 8:e59251. doi: 10.1371/journal.pone.0059251
- McClure, M.C., D. Bickhart, D. Null, P. VanRaden, L. Xu, G. Wiggans, G. Liu, S. Schroeder, J. Glasscock, J. Armstrong, J.B. Cole, C.P. Van Tassell, and T.S. Sonstegard. 2014. Bovine exome sequence analysis and targeted SNP genotyping of recessive fertility defects BH1, HH2, and HH3 reveal causative mutation in *SMC2* for HH3. *PLoS ONE* 9:e92769.
- Melton BF. Conception to consumption: the economics of genetic improvement. In: *The Proceedings of the Beef Improvement Federation 27th Research Symposium and Annual Meeting*. Sheridan (WY): 1995. p. 40–87.
- National Cattlemen’s Beef Association. 2016. *Beef Industry Statistics - Beef USA*. <http://www.beefusa.org/beefindustrystatistics.aspx> (Accessed May 22 2017).
- Parland, S. M., J. F. Kearney, M. Rath, and D. P. Berry. 2007. Inbreeding Effects on Milk Production, Calving Performance, Fertility, and Conformation in Irish Holstein-Friesians. *J. Dairy Sci.* 90(9):4411-4419. doi: 10.3168/jds.2007-0227
- Perkel, K. J., A. Tscherner, C. Merrill, J. Lamarre, and P. Madan. 2015. The ART of selecting the best embryo: A review of early embryonic mortality and bovine embryo viability assessment methods. *Mol. Reprod. Dev.* 82(11):822-838. doi: 10.1002/mrd.22525

- Purfield, D. C., D. P. Berry, S. McParland, and D. G. Bradley. 2012. Runs of homozygosity and population history in cattle. *BMC Genet.* 13:70. doi: 10.1186/1471-2156-13-70
- Red Angus Association of America. 2017. EPD Averages & Ranges (Spring 2017) _ Red Angus Association of America. <http://redangus.org/genetics/epd-averages>. (Accessed 15 May 2017.)
- Rauw, W. M., E. Kanis, E. N. Noordhuizen-Stassen, and F. J. Grommers. 1998. Undesirable side effects of selection for high production efficiency in farm animals: a review. *Livest. Prod. Sci.* 56(1):15-33. doi: 10.1016/S0301-6226(98)00147-X
- Roughsedge T, Amer PR, Thompson R, et al. Development of a maternal breeding goal and tools to select for this goal in UK beef production. *Animal science (Penicuik, Scotland)* 2005;81:221-232.
- Schütz, E., C. Wehrhahn, M. Wanjek, R. Bortfeld, W.E. Wemheuer, J. Beck, and B. Brenig. 2016. The Holstein Friesian lethal haplotype 5 (HH5) results from a complete deletion of *TFB1M* and cholesterol deficiency (CDH) from an ERV-(LTR) insertion into the coding region of *APOB*. *PLoS ONE* 11:e0154602. doi: 10.1371/journal.pone.0154602
- Schwarzenbacher, H., J. Burgstaller, F.R. Seefried, C. Wurmser, M. Hilbe, S. Jung., C. Fuerst, N. Dinhopf, H. Weissenböck, B. Fuerst-Waltl, M. Dolezal, R. Winkler, O. Grueter, U. Bleul, T. Wittek, R. Fries, and H. Pausch. 2016. A missense mutation in *TUBD1* is associated with high juvenile mortality in Braunvieh and Fleckvieh cattle. bioRxiv doi: 10.1101/041921.
- SelectSires.2017.Terminology.<http://www.selectsiresbeef.com/index.php/beefreources/term>. (Accessed 15 May 2017.)
- Schwarzenbacher, H., J. Burgstaller, F.R. Seefried, C. Wurmser, M. Hilbe, S. Jung., C. Fuerst, N. Dinhopf, H. Weissenböck, B. Fuerst-Waltl, M. Dolezal, R. Winkler, O. Grueter, U. Bleul, T. Wittek, R. Fries, and H. Pausch. 2016. A missense mutation in *TUBD1* is associated with high juvenile mortality in Braunvieh and Fleckvieh cattle. bioRxiv doi: 10.1101/041921.

- Shanks, R.D., D.B. Dombrowski, G.W. Harpestad, and J.L. Robinson. 1984. Inheritance of UMP synthase in dairy cattle. *J. Hered.* 75:337–340. doi: 10.1093/oxfordjournals.jhered.a109951
- Shuster, D.E., M.E. Kehrli Jr., M.R. Ackermann, and R.O. Gilbert. 1992. Identification and prevalence of a genetic defect that causes leukocyte adhesion deficiency in Holstein cattle. *Proc. Natl. Acad. Sci. USA* 89:9225–9229.
- Sonstegard, T.S., J.B. Cole, P.M. VanRaden, C.P. Van Tassell, D.J., Null, S.G. Schroeder, D. Bickhart, and M.C. McClure. 2013. Identification of a nonsense mutation in *CWC15* associated with decreased reproductive efficiency in Jersey cattle. *PLoS ONE* 8:e54872. doi: 10.1371/journal.pone.0054872
- Thomsen, B., P.H. Nissen, J.S. Agerholm, and C. Bendixen. 2010. Congenital bovine spinal dysmyelination is caused by a missense mutation in the *SPAST* gene. *Neurogenetics* 11:175–183. doi: 10.1007/s10048-009-0214-0
- USDA, N. A. S. S. 2016. Overview of the United States Cattle Industry (June 2016). <http://usda.mannlib.cornell.edu/usda/current/USCatSup/USCatSup-06-24-2016.pdf> (Accessed 19 May 2017.)
- Van Eenennaam, A. L. 2013. Considerations related to breed or biological type. *Vet Clin North Am Food Anim Pract* 29(3):493-516. doi: 10.1016/j.cvfa.2013.07.012
- Van Melis, M. H., J. P. Eler, G. J. Rosa, J. B. Ferraz, L. G. Figueiredo, E. C. Mattos, and H. N. Oliveira. 2010. Additive genetic relationships between scrotal circumference, heifer pregnancy, and stayability in Nellore cattle. *J. Anim. Sci.* 88(12):3809-3813. doi: 10.2527/jas.2009-2127
- VanRaden, P. M., and R. H. Miller. 2006. Effects of Nonadditive Genetic Interactions, Inbreeding, and Recessive Defects on Embryo and Fetal Loss by Seventy Days. *Journal of Dairy Science* 89(7):2716-2721. doi: 10.3168/jds.S0022-0302(06)72347-5
- VanRaden, P., D. Null, J. Hutchison, D. Bickhart, and S. Schroeder. 2014. Jersey haplotype 2 (JH2). Changes to evaluation system (August 2014). Council on Dairy Cattle Breeding.

- VanRaden, P.M., K.M. Olson, D.J. Null, and J.L. Hutchison. 2011. Harmful recessive effects on fertility detected by absence of homozygous haplotypes. *J. Dairy Sci.* 94:6153–6161. doi: 10.3168/jds.2011-4624
- Venhoranta, H., H. Pausch, K. Flisikowski, C. Wurmser, J. Taponen, H. Rautala, A. Kind, A. Schnieke, R. Fries, H. Lohi, and M. Andersson. In frame exon skipping in *UBE3B* is associated with developmental disorders and increased mortality in cattle. *BMC Genomics* 15:890. doi: 10.1186/1471-2164-15-890
- Weigel, K., and S. Lin. 2000. Use of Computerized Mate Selection Programs to Control Inbreeding of Holstein and Jersey Cattle in the Next Generation. *J. Dairy Sci.* 83(4):822-828. doi: 10.3168/jds.S0022-0302(00)74945-9