Moderators: Brian Gerloff, Dale Moore, Dee Whittier, Steve Smalley, John Wenz, Martey Masterson, Nathan Keefer

Feeding the World through Improved Animal Health and Genetic Selection

Holly L. Neibergs, *PhD*
Washington State University, Department of Animal Sciences, PO Box 646353, Pullman, WA 99164-6353
509-335-6491, Email: neibergs@wsu.edu

Abstract

Animal health is a complex interaction of the genetics of the individual, the environment in which they live, and the management practices that influence the animal's pathogen exposures. To efficiently maximize production and meet the increasing global demand for meat and dairy protein, cattle health must be improved. The use of genetic selection to choose cattle that are less susceptible to disease has not been extensively explored. The availability of new genetic tools makes the identification of loci associated with disease more efficient and provides an opportunity to use genomic selection to increase the rate of genetic gains in production and health traits. The genetic gains from these advances have begun to be realized in the dairy industry. This review discusses the potential for improvement in cattle production and health through genetic selection as a means of meeting the global demands for beef and dairy protein for human consumption.

Résumé

La santé animale est une interaction complexe entre la génétique de l'individu, son environnement et le stress auquel il est exposé, et le type de régie qui influence son exposition aux pathogènes. Afin de maximiser la production efficacement et de rencontrer la demande globale toujours croissante pour la viande et les protéines laitières, la santé des bovins doit être améliorée. L'utilisation de la sélection génétique pour choisir des bovins moins susceptibles aux maladies n'a pas été explorée en détail. La disponibilité de nouveaux outils génétiques permet d'identifier plus facilement les loci associés à la maladie et donne une chance à la sélection génomique d'accroître le taux de gain génétique pour les caractéristiques associés à la production et à la santé. Les gains génétiques découlant de ces percées commencent tout juste à être reconnus par l'industrie laitière. Cette analyse discute du potentiel d'amélioration de la production et de la santé des bovins par l'entremise de la sélection génomique afin de rencontrer la demande globale pour la viande et les protéines laitières de consommation humaine.

Introduction

Global demand for beef is on the rise. Cattle futures have jumped to record highs as demand for beef is strong in the midst of dwindling cattle supplies. Since the United States cattle inventory peaked in 1975, total cattle inventory has declined by 38.3 million animals (29%) which has fueled increased cattle prices.[39] This year alone, cattle have increased over 25% in value and cattle prices are expected to remain robust in the foreseeable future.[38]

Along with the higher demand for beef has come a growing global demand for dairy products. United States dairy exports of dry ingredients have increased by 75% over this period in 2010.[36] This increase is notable in that the United States exported dairy products in 2010 worth $3.7 billion, a 63% increase over 2009 and just short of the all-time record of $3.8 billion exported in 2008. Much of the increase in exports has been fueled by the heightened Asian demand for United States dairy products, which is projected to continue.[36]

The ability to provide beef and dairy products for human consumption hinges upon efficient production. Cattle are not able to produce meat or dairy protein efficiently without being healthy, well cared for and well managed. Animal health begins with the genetic background of the animal to resist, fight, and tolerate pathogens and extreme environmental conditions. The increased density of cattle on feed and in dairies provides opportunities to identify cattle that are resistant to disease and to further identify management practices that aid in preventing disease. The interplay of the genetic background of cattle with modern veterinary and management tools is beginning to be studied more closely. These studies have been made possible by new technologies and resources that were not previously available. Because of these previous limitations, genetic selection as a means of improving animal health has been largely overlooked. The aim of this review is to assess how new genetic tools may facilitate improved animal health through genetic selection.

Genetic Selection in the Absence of Molecular Information

Francis Galton addressed how to select for genetic traits that could not be placed into discrete classes. His approaches are considered to be the foundation upon which modern statistical genetics is based.[5,35] These principles have been expanded, and it has become accepted that the expression of quantitative (continuous) traits is typically influenced by genetic and environmental factors due to genetic variation consistent with Mendelian expectations.[20] Breed associations and businesses that sell semen for artificial insemination have devoted a great deal of time and resources identifying the genetic components of variances in traits that are in demand in beef and dairy cattle. The aim of these groups is to identify how much of the variation within a cattle population is due to genetic causes and how much is due to environmental causes. Once this is estimated through the heritability of the trait, then specific sires may be evaluated for their genetic worth by estimating the probability that the sire will positively contribute toward a desirable trait in their offspring. An increase in environmental variability serves to decrease the response to selection by decreasing the heritability of the trait, whereas a uniform environment will aid in increasing the heritability and thus the response to selection.

Animal breeding programs are founded on the principle that an individual's phenotype provides a window into the animal's underlying value at the molecular level. The accuracy of this principle and of the predictive models that estimate the breeding values of individual animals depends on the heritability of the trait, if differences in the trait result in a difference in the ability of the animal to survive and reproduce, and the accuracy of the measurement of the trait. Estimates of breeding values are commonly used as a means of predicting which individuals will contribute the best gene variants to the next generation. The breeding value is the genetic component of a dam or sire that is potentially transmitted to the offspring. Estimates of breeding values are known as EBV. As only half of the genetic information from a sire or dam is actually transmitted to the offspring, sometimes the progeny difference (PD), as it is termed in beef cattle, or transmitting ability (TA), as it is termed in dairy cattle, is a more useful measure of the genetic value of an individual. The progeny difference or transmitting ability of an individual animal is half of its breeding value. Predictions of progeny differences or transmitting abilities are referred to as expected progeny differences (EPDs), predicted differences (PDs) or progeny transmitting abilities (PTAs). Sire summaries are often populated by estimated breeding values, expected progeny differences or estimated transmitting abilities and have been used for decades in the selection of sires. These values must be taken in context of the genetic background of the animal (breed) and the environment in which the trait was measured. Estimates for breeding values, progeny differences or transmitting abilities have been based on progeny testing of the sires. Progeny testing has the disadvantages of taking several years to complete, is expensive, and only about 12% of the bulls tested graduate into the proven bull line-up.[10] The advantage of progeny testing is that it accurately assesses a sire's genetic worth for both qualitative and quantitative traits.

The effectiveness of this approach in the dairy industry may be measured by the total amount of milk produced in the United States by year and the subsequent total number of cows required to produce the milk. Total milk production in 1940 in the United States was approximately 107.8 billion lb (49 billion kg) produced by an estimated 70 million cows.[25] In contrast, the estimated total milk yield in 2005 was 171.6 billion lb (78 billion kg) which was produced from only nine million cows.[25] Although production traits have been successfully targeted and selected for, health traits have been largely ignored unless they were the result of a congenital disorder that was generally the result of a single gene mutation.

Marker Assisted Selection

Genetic anomalies that result in congenital disorders, such as bovine leukocyte adhesion deficiency (BLAD), have been identified and used to reduce their incidence. Bovine leukocyte adhesion deficiency is a recessive disorder identified in Holstein cattle that results in an affected animal's white blood cells failing to attach to the endothelium. This attachment is critical for the subsequent migration of the white blood cells to the site of infection to destroy invading pathogens. Because of this failure, calves with BLAD suffer from recurrent respiratory and gastrointestinal bacterial infections that result in death. The mutation in the CD18 gene was identified and has been used to select for cattle that will not produce a BLAD calf.[31] Bovine leukocyte adhesion deficiency is inherited as an autosomal recessive disorder that has been reduced in Holsteins due to the effectiveness of marker assisted selection against the causal mutation in CD18.

Marker assisted selection is the use of a DNA variant to predict the phenotype an animal will possess. Soller was one of the first to suggest that animals could be pre-selected based on the use of DNA markers before progeny test information was available.[32] Marker assisted selection is most useful in traits that are difficult or costly to measure, or that occur late in life when an animal is well into its reproductive life.

The accuracy of marker assisted selection depends on whether or not the marker is the cause of the phenotype.[9] If the marker represents the causal mutation (such as with BLAD), then the marker will be accurate 100% of the time. Often, the marker does not represent the causal mutation but is in linkage disequilibrium with the causal mutation. Linkage disequilibrium represents the non-random distribution of alleles (variant forms of DNA) into gametes at meiosis. When one DNA variant tends to segregate at meiosis with another DNA variant, the two variants are exhibiting linkage disequilibrium because they are not assorting independently. When the level of linkage disequilibrium between DNA variants is very high, then one variant can be highly predictive of the other variant. Unfortunately, linkage disequilibrium levels change over time (as the number of meioses increase) and are affected by population size, inbreeding, and the architecture of different breeds. So the predictive value of a marker for marker assisted selection in one breed may differ in another breed. The degradation and differences in linkage disequilibrium across breeds detract from the utility of marker assisted selection. To account for these differences in linkage disequilibrium, studies to determine the linkage disequilibrium in different breeds of cattle are very important.

In dairy cattle, marker assisted selection has been successfully used to select for milk traits (milk yield, fat content, protein, and cheese production) as well as productive life, fertility, dairy form and somatic cell scores. Marker assisted selection used to evaluate young dairy bulls before progeny testing has been shown to increase the rate of genetic gain by 20 to 30%.[18,28] A comparison of markers and traditional evaluations for 589 Holstein AI bulls was recently reported.[37] In all cases, the percent reliability of the PTA increased from 2 to 9% with the addition of the marker information.[37] Marker assisted selection has been used commercially for production traits in beef cattle such as meat tenderness, marbling, subcutaneous fat thickness, ribeye area, heifer pregnancy rate, docility, average daily gain and many other traits for a number of years.

Marker assisted selection is arguably the most helpful when incorporated into a molecular profile that can be combined with traditional EPD and PTA selection tools to enhance the precision of the selection.[34] For animals with no or very few offspring, marker assisted selection can improve the accuracy of the EPD or PTA and provide information on traits that would not otherwise be possible. This is particularly useful when producers want to purchase unproven bulls as herd sires, as the accuracy of prediction of the value of the bull increases with the combination of the pedigree data and the DNA testing information. Pearson correlation estimates between true and predicted breeding values were improved in simulations of animals with marker information, as compared to conventional data alone.[34] However, when even a few records were available for the trait in addition to the marker information, the combined information provided a more accurate prediction of the breeding value than the marker information alone.

Marker assisted selection has not been widely adopted to improve animal health, but has been used to select against mastitis. The opportunity for response to genetic selection for mastitis was recognized as early as 1960. Records kept on bulls in Norway identified that the daughter of the three bulls with the worst PTAs for mastitis resistance had twice the mastitis frequency of daughters of bulls with the best PTAs for mastitis.[17] In Scandinavian countries, livestock health records are recorded routinely by attending veterinarians. This practice has enabled the incorporation of national health records into selection indexes to maintain desirable levels of fertility and mastitis while improving production.[24]

A key component to the success of national health recording systems is the standardizing and recording of traits. For example, the response to selection for animals that are resistant to mastitis will vary by whether clinical mastitis is directly measured, or if somatic cell counts are used as an indirect measure, or if a combination of somatic cell counts and clinical mastitis is used as an index for genetic selection. Selection based on clinical mastitis records is 43% more efficient than the indirect measurement of somatic cell counts or scores.[40] The choosing of the phenotype to use for a health trait and how it will be measured is very important, and should remain consistent across and within countries. The absence of standardized health records and definition of disease weakens the efficiency of selection. In the United States, marker assisted selection has been used to slow the increase in incidence of mastitis through indirect measurement of somatic cell counts in milk.[1] The selection against mastitis and yield traits is difficult as genetic correlations between them range from -0.03 to 0.32 when all lactations are considered.[39] Because selection for yield traits has the tendency to increase mastitis, the reduction of incidence of mastitis is unlikely unless selection for yield traits is moderated. It is a more realistic goal to try to slow the incidence of disease through selection and best management practices than to reduce the disease when it is negatively associated with milk traits.

The choice of what criteria will be used for diagnosis of disease is also important. The diagnostic tools available for bovine paratuberculosis are examples where the ability to diagnose the disease will affect the ability to study the disease as well as to identify the loci associated with the disease. The sensitivity of the fecal culture diagnostic test differs from the sensitivity of the ELISA for *Mycobacterium* subspecies *avium paratuberculosis,* both of which are used for clinical testing.[44] The loci that have been found to be associated with animals that are fecal-positive, ELISA-positive or tissue-positive differ, emphasizing the importance of consistent diagnostics and definitions for disease.[13,22,29,45]

The definition of disease is of particular importance in diseases with a range of symptoms or a multitude of pathogens responsible for the disease. Bovine respiratory disease (BRD) exhibits both of these characteristics. To identify loci associated with this disease, it is critical to clearly define the disease through a set of clinical signs and to identify the pathogens involved through diagnostic testing. The identification of the loci associated with susceptibility to specific pathogens assists in understanding the pathogenic process, as well as allowing selection for animals that are less susceptible to disease. Initial work was conducted to identify if a broad definition of BRD and one of the pathogens responsible for BRD, bovine viral diarrhea (BVD) virus, shared the same loci for susceptibility. It was found that the same large genomic regions were identified, but with further interrogation additional loci were identified for the narrow definition of BVD persistent infection.[23,46] Further evaluations of the loci associated with susceptibility to BRD are under way in beef and in dairy cattle with a high density panel of markers. The diagnosis of individual pathogens will be incorporated into this analysis so that the interaction of the host and pathogen may be determined.

Identifying and characterizing the loci associated with infectious disease is often daunting. Complex diseases are affected by many genes as well as the environment. When searching for loci associated with a polygenic disease, the use of marker panels with very high density can become critically important because high density panels are more likely to capture genetic information for all genes. Currently, two high density marker panels are available to conduct genome-wide genetic studies. The Illumina (San Diego, CA) HD BeadChip with over 770,000 SNPs and the Affymetrix (Fremont, CA) BOS 1 Array with 648,000 SNPs will facilitate genetic studies for complex disease because they will better represent the genome of cattle, particularly in the diverse beef breeds.

The genetics of complex health traits, such as resistance to infectious disease, have not been well characterized or selected for. The failure to identify the genetics of these traits has largely been due to the lack of well characterized populations of animals with disease and also inadequate genetic and financial resources. To tease out the genetic components of these traits, consideration and control of management practices, the environment and pathogen exposure are critical. Genetic resources that are now available to identify the genetics of complex disease began with the Human Genome Project.

Animal agriculture has greatly benefitted from the methods and technologies developed as part of the Human Genome Project and its expansion into animal models. Cattle have benefitted from the sequencing of their genome and the identification of DNA variants across cattle breeds that can be exploited to identify genetic regions associated with complex traits.[2,3] The availability of these resources has enabled the research community to begin to tackle complex traits and to integrate molecular (DNA variant) information into their selection tools.

Genomic Selection

Marker assisted selection has matured from an initial offering of very few markers that explained little of the genetic variation to marker panels with tens to hundreds of thousands of markers with the potential to explain much more of the genetic variation. In a recent study, it was reported that the use of marker panels increased the selection response between 29 to 158% above the response obtained when incorporating conventional selection information only.[42] This was equivalent to a gain of performance that ranged in value from $89 to $565 per commercial beef bull and $5,332 to $27,910 per AI bull.

Genomic selection or whole genome selection is a form of marker assisted selection that utilizes many DNA markers that represent the whole genome of the individual. This form of selection relies on linkage disequilibrium, just as marker assisted selection does. The advantage of genomic selection is that it has the potential to explain a much greater proportion of the genetic variance of a trait because of the greater number of markers.

The use of genomic information in combination with prediction equations is termed genomic estimated breeding value (GEBV).[21] Meuwissen *et al* used a simulation model to estimate that the accuracy of GEBV for potential breeding animals could be as high as 0.85 when haplotypes (regions of the genome inherited as a block) were used.[21] The actual improvement in GEBV was not as high in young Holstein bulls tested with single markers (not haplotypes) but did provide an improvement over pedigree information alone.[43] Young Holstein bulls were used to determine the reliability of genomic predictions for five yield traits, five fitness traits, and 16 conformation traits along with net merit with a marker panel of over 38,000 SNPs. When averaged across all traits, combined genomic predictions had reliabilities that were 23% greater than with parent information alone.[43] This improvement in accuracy has led to the rapid adoption of genomic selection by dairy artificial insemination companies.[6] This tool holds the promise of increasing genetic gains for dairy production traits by up to 70%.[19] Health traits could also realize significant increases in genetic gains. For example the heritability for BRD has been estimated to be 0.48 on a continuous scale.[32] If the genomic breeding values are as high as the square root of the heritability, as Van der Werf suggests, genomic selection could increase the response for breeding animals that were less susceptible to BRD by 69%.[41]To implement genomic selection, a reference population must first be tested. This involves compiling a data set of a moderate number of cattle with phenotypes that have been genotyped with a large number of SNP.[11] From this data set, prediction equations will be computed and validated in a new independent training population of cattle. The prediction equation incorporates genotypes from the training population and predicts breeding values from them.[11] To combine conventional EBV and GEBV, a selection index may be used to combine the two data together for use. For animals with conventional EBV that have not been genotyped or do not have the same markers genotyped, a second method is to infer the genotypes to calculate GEBV.

Genomic selection has been predicted to have a dramatic impact on the selection of cattle by facilitating and increasing the accuracy of selection of complex traits, like health traits, in cattle. A simulation has shown that genomic selections can double the rate of genetic gain.[7] This is due to the improved rate of genetic gain for complex traits, but it also accounts for the reduction in generation interval that would result from selection of cattle at an early age. The early age of selection is possible as soon as the calves are born if progeny testing is not required. This reduces the cost of choosing sires and provides the opportunity to increase selection intensity for replacement heifers. It has been estimated that the reduction in cost of operating dairy breeding companies would be 92% if genomic selection was used instead of traditional progeny testing.[27]

Genomic selection's use of a denser composite of genome-wide markers to predict the effects of many genes is a better approach for selection of complex traits than marker assisted selection, which uses fewer markers. Resistance or susceptibility to infectious disease is typically due to many genes, and so is more suited to genomic selection with a dense marker panel. The ability to select for animals without phenotypic information or progeny data is of particular value with disease traits and traits that are costly, difficult to obtain or that occur late in life. Ongoing research to identify loci associated with complex traits, such as feed efficiency and susceptibility to BRD, with the use of high density SNP panels in reference populations of different breeds will provide opportunities to use genomic selection for these important traits to benefit the cattle industry. These cattle research populations have resulted from the formation of consortiums of scientists, producers, and industry stakeholders so that several thousand animals may be evaluated to identify loci associated with these traits, and to provide GEBV for these traits to the industry. Large cattle populations will be characterized, as recent studies have found that an increase in Holstein bulls in the reference population from 1151 to 3576 resulted in a linear increase in the gain in coefficient of determination of GEBV, emphasizing the importance of a large reference population for the study of complex traits.[43] The use of crossbred populations has been shown to increase the accuracy of GEBV for multiple breeds when tested using simulation data.[7] The use of crossbred beef populations has been recommended to increase the accuracy of GEBV when the breeds are not too diverse and a sufficient density of markers is available.[15,26] In addition to the large dairy population, crossbred and purebred beef populations will also be studied for BRD to encompass the diversity of the beef industry.

A major challenge to the implementation of genomic selection is the availability of reference populations of multiple breeds with genotypic and phenotypic information.[12] Some progress has been made in the collection of these populations. The assembly by the USDA of a reference population of over 6,700 dairy bulls with genotypes on 50,000 SNPs has led to an accuracy of genomic breeding values for young dairy bulls of greater than 0.8.[6] Efforts with smaller reference populations have yielded results with somewhat lower accuracies in Australia, New Zealand, and the Netherlands.[14] An additional challenge for genomic selection is identifying whether the marker effects will have to be re-estimated continuously or periodically from new reference populations as genetic progress is made and linkage disequilibrium changes over generations.

Conclusions

The use of new genetic tools such as GEBV will enhance our ability to produce more meat and dairy products for the growing global human population. Selection is, however, only part of the answer. The integration of selection programs with the best management practices for the unique environments in which cattle are raised will be critical for the successful rise in cattle productivity. The value of best management practices coupled with selection will only be implemented if it is cost-effective. Studies that evaluate genetic selection and best management practice must incorporate economic studies to determine their economic efficiency by comparing the value in added productivity with the cost of selection tools and management expenses.

To maximize the transition of these technologies to the cattle industry, our present and future livestock professionals must be introduced to GEBV and best management practices. The costs and financial rewards for utilizing these technologies need to be shared vertically through the cattle industry. If the costs are not paired with the financial incentives for producing better animals, progress will not be made. Outreach, continuing education programs, and changes in didactic college curricula to reflect new approaches to animal health and production will be necessary to educate the livestock industry. These efforts are well under way, and are already reflected in changes in sire summaries in the dairy and beef sectors.

Beginning in 1994, the addition of traits that were not associated with yield was incorporated into selection indexes. Since then, conformation, daughter pregnancy rate, service sire ease, and daughter calving ease have been added for dairy sire summaries. Economic weights for non-production traits have increased from 0 to 45%.[30] In beef, non-production traits such as heifer pregnancy rate, stayability, maternal calving ease, and docility have been added as a result of marker information in sire summaries. Non-production traits for health and feed efficiency will be one of many traits added to genomic selection indexes after ongoing studies are completed. The improved selection indexes applied to potential sires and dams will result in improved production, animal welfare, and economic returns. In this way, the use of new genetic selection tools will facilitate the increasing demand to feed the world with fewer, more efficient animals.

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