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BEEF TRANSLATIONAL GENOMICS: LESSONS FROM THE LITERATURE

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SUMMARY

In the context of animal breeding, "*translational genomics*" can be defined as the adaptation of information derived from genome technologies for animal improvement. It is where the rubber of genomic science meets the road of industry adoption. The oft-underestimated value of DNA-information to assign parentage and identify carriers of recessive genetic conditions has achieved widespread adoption. And while the use of genomic information has proven useful for selection of young bulls in the dairy industry, to date the promise of what could be achieved by genomic information has not matched the reality of what has been delivered to other animal industries. This is due in part to differences in industry structure. Deterministic predictions and experimental observations offer some insights regarding the prerequisites needed to successfully implement genomic selection. Large, densely-genotyped, deeply-phenotyped, multibreed training populations are likely to be required for widespread industry adoption in the beef industry. The development of such populations will require cooperation among breed associations, and international collaborations. There are also economic barriers to adoption due to the segmented nature of the beef industry. Two-way flow of information and market signals between different segments of the beef industry will likely be requisite for adoption. Additionally, value transfer systems will need to be in place so that breeders can be appropriately rewarded for making DNA investments and selection decisions for breeding objectives that benefit the entire commercial production system.

PARENTAGE

DNA information has been used to confirm pedigree or assign parentage for a number of years. Traditionally, highly polymorphic microsatellite markers have been the choice for parentage inference but there is increasing interest in using single-nucleotide polymorphisms (SNP) for this purpose due to their abundance, potential for automation, low genotyping error rates, and relative ease of standardization between laboratories. The low resolving power of biallelic loci means that SNP panels need to include more loci than microsatellite panels to achieve similar discriminatory power. Early panels made up of 36-40 SNP loci were not sufficiently powerful to assign paternity in field situations where factors including variable calf output per sire, large sire cohorts, relatedness among sires, low minor allele frequencies, and missing data often occur concurrently (Van Eenennaam *et al.* 2007b). In the context of a commercial farm setting, it is important to recognize that, as the number or relatedness of putative sires in a multiple-sire breeding group increases, additional markers will be required to maintain single sire assignments at a fixed rate (Pollak 2005). In herds with large numbers of natural service sires in a breeding group, low resolution panels may result in multiple bulls qualifying to a single calf. Given the rapid evolution and precipitous drop in the price of SNP genotyping, having too few SNPs to assign parentage will likely relegate this problem to a concern of the past. Panels of approximately 100 SNP markers developed by the U.S. Meat Animal Research Center (Heaton *et al.* 2002) with an exclusion probability of >99.99% are being commercially offered for ~ $15 in the US, and are being routinely used to assign parentage on some commercial farms. Although it is likely SNP genotyping will be the paternity assignment method of choice in the future, the considerable costs involved in transitioning breed society records and laboratories from microsatellite- to SNP-based parentage assignments remain a barrier to implementation. This is further complicated by the need to decide which of the competing SNP genotyping platforms will ultimately prove to be optimal.

Economic implications. DNA testing for pedigree verification is mandatory for some breeds, and random testing is mandated by others. The obvious value to the breed association is to correct pedigree recording errors. Pedigree errors reduce the rate of genetic gain to below that which is possible and predicted (Israel and Weller 2000). The ability to use DNA to assign parentage also offers the opportunity for breeders to use multi-sire pastures which offer a number of benefits. Having multiple sires present in with a group of cows results in higher fertility, precludes sire failure, and reduces the calving interval. It also minimizes the number of pastures needed, thereby allowing for better pasture management. Additionally, it reduces the labor cost and need to disturb animals at birth, thereby improving both maternal/offspring bonding and worker safety. Finally, it allows for the development of on-farm commercial sire genetic evaluations (Dodds *et al.* 2005).

In New Zealand over 20% of the ram, and 30% of the deer breeding industry are now using DNA-enabled commercial farm sire evaluations (McEwan 2007). McEwan goes on to note that in New Zealand DNA collection is linked to electronic tags, which are being implemented as part of a national identification system. The DNA samplers are labeled with bar codes and this in turn offers the opportunity for all subsequent steps to be automated including the incorporation of the results directly into the appropriate genetic evaluation databases. One of the requirements for widespread adoption of DNA testing technology will likely be the development of systems that simplify DNA collection and seamlessly report data of integral importance to livestock producers.

MONOGENIC TRAITS

In cattle and other species great success has been achieved in identifying genes carrying mutations that cause recessive abnormalities, and developing tests to enable producers to identify carriers. Gene discovery has been achieved using traditional mapping and candidate gene approaches, in addition to genome-wide association studies. It is instructive to compare the situation that faced breeders in the 1950s when faced with "snorter "dwarfism, to that experienced 40 years later when faced with another recessive mutation, Arthrogryposis Multiplex (AM). The recessive mode of dwarfism inheritance in Herefords was determined in the early 1950s, and was ultimately traced back to a bull named St. Louis Lad, who was born in 1899. Breeders had to perform time-consuming and expensive test crosses between potential carrier bulls and known carrier cows to determine carrier status, and in order to eradicate the problem from the national herd entire lines of cattle were eliminated. In contrast, a period of only 4 months elapsed between the time when a notice detailing the need to obtain pedigree information and DNA from cases of "curly calf syndrome" was sent to the Angus Association in late August 2008, and the development of a commercial DNA test by Dr. Jonathan Beever from the University of Illinois in December 2008. The rapid development of this test was made possible by the availability of the bovine genome sequence, and represents one of the most compelling examples of translational genomics in the beef cattle industry.

Economic implications. The chromosomal deletion causing AM occurred in the maternal grandsire of a widely-used Angus bull. This bull was born in 1990 and used widely, and consequently had several thousand registered calves. In the 10 months following the release of the test, the American Angus Association posted the results of tests for AM on about 90,000 cattle. Of these, almost 5,000 bulls and more than 13,000 heifers tested as carriers of AM. However, more than 22,000 bulls and 50,000 heifers tested as free of AM[1]. In the absence of a DNA test, there would be no way to determine the AM-status of animals with affected pedigrees, and in the process of proactively eliminating potential carriers these 72,000 animals would have had to have

[1] Buchanan, D.S. (2010) http://www.ag.ndsu.edu/williamscountyextension/livestock/genetic-defects-in-cattle

been needlessly culled. This benefit dwarfs the costs associated with testing (~US$26 x 90,000 = US$2.4 million), although costs were not insignificant for breeders who had a lot of carriers identified in their herds.

WHOLE GENOME SELECTION

Whole genome selection (WGS) is a form of marker-assisted selection that uses a genome-wide dense panel of markers so that all quantitative trait loci (QTL) are expected to be in linkage disequilibrium (LD) with at least one marker (Meuwissen *et al.* 2001). Deterministic modeling and research results suggest that the accuracy of genomic estimated breeding values (GEBV) is dependent upon the effective population size (N_e) of the breed/species (smaller is desirable), trait architecture (a small number of QTL with large effects is optimal), trait heritability (higher is better), the number of animals phenotyped and markers genotyped in the training population (more of both is better), and relationships between animals in the training and target population (Goddard and Hayes 2007; Goddard 2009; Goddard and Hayes 2009; Hayes *et al.* 2010).

The dairy industry is undoubtedly the poster child of WGS, and industry adoption of the Bovine 50K Illumina iSelect SNP chip (50K) has been swift and pervasive. There are numerous attributes of the dairy industry that make it well suited to WGS. These include a large number of high accuracy progeny test records for training, a clear selection objective returning value to all segments of the industry, the extensive use of a single breed (Holstein) with a low N_e and artificial insemination, centralized genetic evaluation entities with access to both genotypic and phenotypic records for training and retraining. There is an immediate, tangible benefit to the breeding companies funding the genotyping, and that is reducing the cost of progeny testing. The benefits of WGS in the dairy industry come mainly through reducing the generation interval as a result of forgoing young bull progeny testing, and increasing the selection intensity (Pryce *et al*. 2010).

A variety of translational questions regarding the implementation of WGS remain for the both the dairy industry and other animal industries that are contemplating the use of WGS, including:

- How many phenotypic records are required in the initial experiment estimating the effect of chromosome segments?
- How many SNPs are needed to obtain accurate predictions? 50,000; 800,000; whole genome?
- How does the relationship between the training population and the selection candidate affect accuracy?
- How often do chromosome segment effects need to be re-estimated?
- Do predictions work across breeds?
- What is the value generated by the increased accuracy?
- Does this technology change optimal breeding program design?

One of the challenges of applying WGS to beef cattle is improving the accuracy of across-breed predictions. One proposed solution has been to train and validate prediction equations in multibreed populations. When 1,200 Holstein bulls and 400 Jersey bulls genotyped with the 50K chip were combined to form a training population, the resulting accuracies of GEBV in purebred datasets were comparable to, or exceeded, that achieved with a purebred reference population of the same breed (Hayes *et al*. 2009). One explanation for this may be that when training in multiple breeds, only SNPs that are in high LD with the QTL are given an effect in the resultant multibreed prediction equation.

The results of an experiment training and validating in large multibreed beef cattle populations at the U.S. Meat Animal Research Center (USMARC) were recently reported. A Bayesian method was used to predict GEBV for growth and carcass traits. Observed phenotypes from 3358 USMARC cattle representing 8 breeds, and deregressed breeding values from 2063 high accuracy purebred bulls representing 13 breeds were used for training and cross-validation. Accuracies were calculated as the genetic correlation between GEBV and phenotypes within each population.

Removing sires with progeny in the validation population from the training population decreased accuracies, indicating that at least some of the accuracy observed was due to admixture. Relationships between animals in the training and validation populations can cause spurious associations between unlinked loci (Habier *et al.* 2007). Overall, GEBV accuracies ranged from 0.14-0.47 for the 2000 bull-trained predictions and from 0.18-0.32 for the USMARC-cattle trained prediction equations[2].

Across-breed predictions may be improved by the recent availability of very high density (650-770K) SNP panels from Affymetrix (Santa Clara, CA) and Illumina (San Diego, CA). In cattle it has been estimated that SNPs need to be spaced less than 10 kb apart to show consistent LD phase across breeds (de Roos *et al.* 2008). The availability of these very high density panels opens up the possibility of combining data from multiple *Bos taurus* breeds to improve the accuracy of genomic predictions. However, it seems likely that a much greater number (several million) will be needed for SNPs to be in the same LD phase between *Bos taurus* and *Bos indicus* cattle (Goddard and Hayes 2009). Whole genome sequence may offer an approach to identify such markers.

Economic implications. The economics of using DNA information to improve the accuracy of EBVs in the beef industry is complex. The breeding industry is essentially a three-tier system, with the top two tiers being registered herds that supply bulls to the tier below. WGS provide opportunities for influencing the rate of genetic gain in the elite seedstock sector where the use of more expensive genetic improvement technology can be justified based on the increased breeding value of their animals. Unlike the dairy industry, there is less opportunity to decrease the generation interval as many traits can be measured on yearling animals prior to making selection decisions, and as a result progeny testing is not routinely employed. Therefore there is limited opportunity to reduce the generation interval with WGS. However, WGS testing may offer opportunities to improve the accuracy of carcass and maternal trait EBVs in young bulls, and provide some information on economically-relevant traits that have been previously absent from genetic evaluations because they are difficult or expensive to measure (e.g. disease resistance).

Application of technologies to improve genetic gain is an investment which should lead to increased economic returns. Thus, the value of improving accuracy at the time of making selection decisions becomes an important factor in determining which combination of technologies can be applied profitably. We determined the value of improving accuracy using DNA-marker information by modeling a closed beef seedstock herd (Van Eenennaam *et al.* 2011). Selection index theory was used to predict the response to conventional selection based on phenotypic performance records, and this was compared to including information from two marker panels. In one case the marker panel explained a percentage of additive genetic variance equal to the heritability (h^2) for all traits in the breeding objective and selection criteria, and in the other case to half this amount. DNA testing using these hypothetical marker panels increased the selection response between 29-158%. The value of the genetic gain derived from DNA testing ranged from $204-1,119 per test. This included the value associated with selecting replacement bulls for the seedstock herd ($160-836), and the value associated with improving the accuracy of identifying above-average commercial sires ($45-282). However, these values unrealistically assumed that the benefits derived from generating superior bulls were efficiently transferred up the production chain to the seedstock producer incurring the costs of genotyping. Enabling recovery of the costs associated with genetic testing is requisite for the adoption of GWS, and will likely require a change in the structure of the beef industry to include more vertical integration.

Commercial producers may derive value from using DNA information to improve the accuracy of identifying above-average herd sires. However, producers would want this information at the time

[2] Weber, K. L. *et al.* (2011) http://www.intl-pag.org/19/abstracts/P05k_PAGXIX_514.html

of purchase and so testing costs would again be incurred by the seedstock producer, and recouped by an increased price at the time of sale. DNA testing may provide some return by enabling the selection of replacement females based on early predictions of maternal traits, although the value proposition associated with this will be less than for bulls due to the higher number of genetic expressions derived from bulls. The breakeven cost of testing all potential replacement heifers in a self-replacing commercial herd with a replacement rate of 20% using a DNA test with an index accuracy of 0.25 ranged from $3.16 and $3.75 per test, based on Van Eenennaam *et al.* (2011) and assuming that the commercial producer recorded no other data upon which to base heifer selection decisions. This is predicated on the availability of tests with high accuracies for low-heritability maternal traits. The current costs of commercial tests for selection are higher than this (Table 1). In the future, DNA information may be valued for other uses (e.g. marker-assisted management).

Table 1. Cost of commercially-available DNA tests for livestock (as of 1/2011)

Type/Purpose of DNA Test	Species	Cost ($US)
Microsatellite or SNP-based parentage test/Pedigree verification	Cattle	$ 13-25
Genetic Defects/Single gene tests	Cattle	$ 15-100
Illumina Bovine 3K (just genotypes - no prediction equation)/Research	Cattle	$ 38
Illumina Bovine 50K (just genotypes)/Research	Cattle	$150
Affymetrix Bovine 650K (just genotypes)/Research	Cattle	$200
Illumina Bovine 770K (HD) SNP Test (just genotypes)/Research	Cattle	$340
384 SNP Angus Profile (Igenity US/AGI)/Selection	Beef Cattle	$ 65
Illumina Bovine 3K (Pfizer Animal Genetics US)/Selection	Dairy Cattle	$ 45
Illumina Bovine 50K (Pfizer Animal Genetics US/AGI)/Selection	Beef Cattle	$139
Illumina Bovine 50K (Holstein Ass.)/Selection	Dairy Cattle	$150
Illumina Bovine 770K (HD) SNP Test (Holstein Ass.)/Selection	Dairy Cattle	$365
Illumina Bovine 50K (Pfizer Animal Genetics NZ)/Selection	Sheep	$756 (NZ$990)

LOW DENSITY SNP ARRAYS

High-density arrays are currently price prohibitive for many applications and species. There is considerable interest in developing low-density, low cost SNP assays for a variety of purposes including selection of breeding stock in species where individuals have a comparatively low value relative to the cost of high-density arrays, selection of replacement animals on commercial farms, parentage assignment, optimizing mate choice, and marker-assisted management. Two basic approaches can be used to develop low-density arrays. The first involves selecting SNPs that are the most highly associated with the trait of interest in the training data set. This is somewhat analogous to selecting SNP from GWAS studies for marker-assisted selection, and is fraught with the same problems that have been experienced by those studies. In the case of traits that are affected by very many QTL with a small effect, as seems to be the case with most complex traits (Hayes *et al*. 2010), not all QTL will be in LD with markers in the reduced SNP set.

In a study comparing subsets of SNP makers selected from the 50K chip for 9 dairy traits, (Moser *et al*. 2010), few were in common between the different traits, and given that at least 1,000 of the highest ranked SNPs were required to get accurate predictions for each trait, combining the highest ranked SNP for each trait onto a single chip was not seen to be a feasible approach to reducing genotyping costs. The preferred option for Holsteins is to use evenly spaced SNP to infer or impute the sequence of missing SNPs based on the high density genotype of key ancestors (Weigel *et al.* 2009). A hybrid of these two approaches involves selecting a subset of highly ranked SNP within evenly-spaced segments of approximately equal size for imputation (Habier *et al.* 2009; Moser *et al.* 2010). The feasibility of this approach is again dependent on the history of the population, especially the history of its Ne. A small N_e means that LD extends for a long distance and so less SNP will be required to accurately impute the high-density genotype.

COMMERCIAL PRODUCTS

Until relatively recently, commercialized DNA tests for marker-assisted selection in beef cattle targeted only a handful of traits, specifically marbling, tenderness and feed efficiency (Van Eenennaam *et al.* 2007a). Recent tests on the U.S. market target more than 10 traits including growth, maternal, and carcass traits. One of these tests is a 384 SNP panel for Angus cattle (Igenity, Duluth, GA), with accuracies (genetic correlation (r_g) between molecular breeding value (MBV) and trait) in the range of 0.5-0.65 for carcass traits (carcass weight, marbling, longissimus muscle area, and subcutaneous fat depth at 12th rib). Such high levels of accuracy for multiple traits when using a 384 SNP panel contrasts from findings with reduced panels in the dairy industry. There are reports of high accuracy reduced SNP panels being used in company breeding lines (Table 2), although in one case the reduced panel was used for high-density (41K) panel imputation, and in the other case (swine) different SNPs were used in the tests for different traits.

Table 2. Company-reported accuracy estimates of commercial panels for livestock selection

Industry	Trait	# SNPs	Accuracy (r_g) estimate	Country	Breed	Company
Beef	Carcass weight	384	0.54	US	Angus	Igenity[3]
Beef	Backfat thickness	384	0.50	US	Angus	Igenity
Beef	Ribeye area	384	0.58	US	Angus	Igenity
Beef	Marbling score	384	0.65	US	Angus	Igenity
Swine	Scrotal Hernia	96	0.30	US	Cross-bred	Genus/PIC[4]
Swine	Finisher mortality	96	0.30	US	Cross-bred	Genus/PIC
Swine	Total born	196	0.77	US	Cross-bred	Genus/PIC
Chicken	Body Weight	384/41K	0.58	US	Broiler	Aviagen Ltd.[5]
Chicken	Hen house production	imputation	0.60	US	Broiler	Aviagen Ltd.
Beef	Average Daily Gain	50K	0.52-0.58	US	Angus	PAG[6]
Beef	Net Feed Intake	50K	0.30-0.41	US	Angus	PAG
Beef	Dry matter intake	50K	0.28-0.41	US	Angus	PAG
Beef	Tenderness	50K	0.44-0.53	US	Angus	PAG
Beef	Calving Ease (Direct)	50K	0.41-0.57	US	Angus	PAG
Beef	Birth weight	50K	0.51-0.55	US	Angus	PAG
Beef	Weaning Weight	50K	0.53-0.61	US	Angus	PAG
Beef	Calving ease (maternal)	50K	0.53-0.67	US	Angus	PAG
Beef	Milking Ability	50K	0.43-0.68	US	Angus	PAG
Beef	Carcass weight	50K	0.50-0.63	US	Angus	PAG
Beef	Backfat thickness	50K	0.61-0.70	US	Angus	PAG
Beef	Ribeye area	50K	0.49-0.65	US	Angus	PAG
Beef	Marbling score	50K	0.49-0.77	US	Angus	PAG

There are two possible explanations for this discrepancy. The first is that the genetic architecture of these quantitative traits is different in beef cattle, and a limited number of QTL with large effects exist for the genetic variation in these traits. In that case, a smaller number of SNPs associated with these large effect QTLs could explain a significant amount of the genetic variation. The other explanation is that there are relationships between animals in the population that was used for training (high accuracy Angus AI bulls), and the evaluation population

[3] MacNeil, M.D. *et al*. (2010) http://www.kongressband.de/wcgalp2010/assets/pdf/0482.pdf
[4] Deeb, N. *et al*. (2011) http://www.intl-pag.org/19/abstracts/P05n_PAGXIX_606.html
[5] Wang *et al*. (2011) http://www.intl-pag.org/19/abstracts/P05m_PAGXIX_580.html
[6] Pfizer Animal Genetics (2010) https://animalhealth.pfizer.com/sites/pahweb/US/EN/PublishingImages/Genetics%20Assets/HD50K/50K%20Tech%20Summary%204-13-10.pdf

(registered Angus cattle). This is undoubtedly the case, and would likely be the case for most breeds where the training population involves widely-used (i.e. high-accuracy) sires. Markers can predict family relationships between animals, independently of linkage disequilibrium between the markers and QTL (Habier *et al*. 2007). If animals in the training and target populations share DNA segments from a small number of ancestors and are only a few generations apart, a relatively small number of markers will be able to track segments shared between related animals (Moser *et al*. 2010).

Commercial 50K panels have also been released for sheep in New Zealand, and Angus cattle (Pfizer Animal Genetics, Kalamazoo, MI). The advantage of using the 50K panel is that all of the genome wide-markers can be simultaneously used to predict GEBV. The accuracy estimates associated with the U.S. Angus cattle product are higher than would be predicted by deterministic modeling based on the number of phenotypic records used in the training populations. Some estimates involved subsets of the discovery population which may partially explain this observation. It is also unclear whether accuracies were calculated as a simple correlation between the MBV and EBV or estimated in a multivariate genetic model. Lower accuracies were found when this test was calibrated in the Australian Angus population[7], and prediction equations required regional recalibration suggesting the existence of SNP effect x country interaction.

The practical implication of markers picking up family relationships is that the accuracy of marker-based selection will decay over generations within breed. This was demonstrated in German Holstein cattle where the additive-genetic relationships between training and validation animals were found to be a good indicator of accuracy (Habier *et al.* 2010). Effectively this means that the accuracy of prediction equations will decrease as the relationship between the training population and the evaluation population becomes more distant. From the perspective of seedstock breeders, this might not be an issue as elite seedstock typically provide the next generation of selection candidates and so selection candidates will most likely be closely related to the training population. However, such tests are likely to be less accurate across lines of Angus cattle that have few close relatives in the training data set. Practically this means that SNP effects will have to be re-estimated frequently to include data from each generation of selection candidates, although this may create logistical complications for genetic evaluation entities, especially if they do not have access to both the phenotypes and the genotypes or if additional costly phenotyping is required.

OPPORTUNITIES FOR THE FUTURE

The collection of DNA samples for national animal identification purposes offers an opportunity to introduce other DNA-based technologies in a cost-effective manner. It is perhaps the cumulative value derived from using DNA test information for multiple purposes (traceability, parentage, genetic defects, selection, marker-assisted management, product differentiation), in combination with the rapidly-declining cost of genotyping, that will ultimately push the economics of DNA-based technologies over the tipping point towards more widespread industry adoption.

It is becoming increasingly clear that to obtain accurate genomic predictions, it is necessary to train on large numbers of records. Assembling reference populations that are large enough to achieve high accuracy GEBV will be a major challenge for smaller breeds. There are two approaches to dealing with this. One is to combine all the breed data and 50K SNP genotypes across countries (e.g. Hereford). The second approach is to combine all of the data from multiple breeds along with 700K+ (real or imputed) genotypes. This may be the preferred option because haplotype segments with strong LD in crossbred and admixed populations are narrower, and so markers in such segments are expected to have more consistent associations with QTL across the

[7] Animal Genetics and Breeding Unit (AGBU). 2010. Evaluation of Pfizer Animal Genetics HD 50K MVP Calibration. http://agbu.une.edu.au/pdf/Pfizer_50K_September%202010.pdf

training and validation populations. Therefore, the decline of accuracy of WGS over generations that has been observed in simulation studies due to linkage might be slower when admixed or crossbred populations are used for training than when purebred populations are used. This approach has the added advantage in that it might provide an approach to fine map QTL (Goddard and Hayes 2009). The development of large multibreed training data sets may collectively improve the accuracy of WGS above that achievable by any single breed alone, due to the larger combined data set size. The costs involved with obtaining sufficient records for hard-to-measure and low h^2 traits should not be underestimated, and may ultimately thwart the development of some MBVs.

Finally, the value proposition of WGS may shift if the value of genetic gain changes appreciably. This might happen if genomic or other technologies result in the development of high value markets with new product specifications, the introduction of novel traits into the breeding objective possibly driven by new production system requirements, health concerns, or through emerging technologies which enable selection for traits which were previously omitted from breeding objectives due to lack of selection tools. Alternatively, industry structure may evolve to enable the exchange of information and value between the different sectors. For widespread technology adoption, breeders need to be adequately rewarded for making DNA investments and selection decisions for traits that benefit the different sectors of the beef industry.

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