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## INVITED PAPERS

### 1. GENOMIC SELECTION TO IMPROVE LIVESTOCK PRODUCTION IN DEVELOPING COUNTRIES WITH A FOCUS ON INDIA

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#### Abstract

Global livestock production has increased substantially during the last decades, in both number of animals and productivity. Meanwhile, the human population is projected to reach 9.6 billions by 2050 and most of the increase in the projection takes place in developing countries. Rapid population growth will increase the demand for food as well as animal products, particularly in emerging economic giants like India. Moreover, the urbanization has considerable impact on patterns of food consumption in general and on demand for livestock products, in particular and the increased income growth led to more expenditure on livestock products. Since livestock production in developed countries has well adopted livestock genomic selection tools to improve both productivity and quality of animal products, opportunities to increase productivity in developing countries via genomic tools/selection have not been fully explored. The future of livestock breeding focuses on both product quality and productivity, animal welfare, disease resistance and reducing environmental pollution. Among the breeding tools, molecular genetics and genomics and modern reproductive techniques such ovum-pick up and in vitro production (OPU-IVP) of embryos will have a considerable impact in the future. This paper attempts to provide basic concepts of using genomic tools for livestock production with the focus on genomic prediction and selection methods and discuss about the potential application of genomic selection to increase livestock productivity, to enhance the disease resistance, fertility, resource use and the ability to adapt to climate changes. The paper also highlights the potential of genomic selection to overcome these challenges in India and other developing countries.

#### Introduction to genomic tool and genomic selection

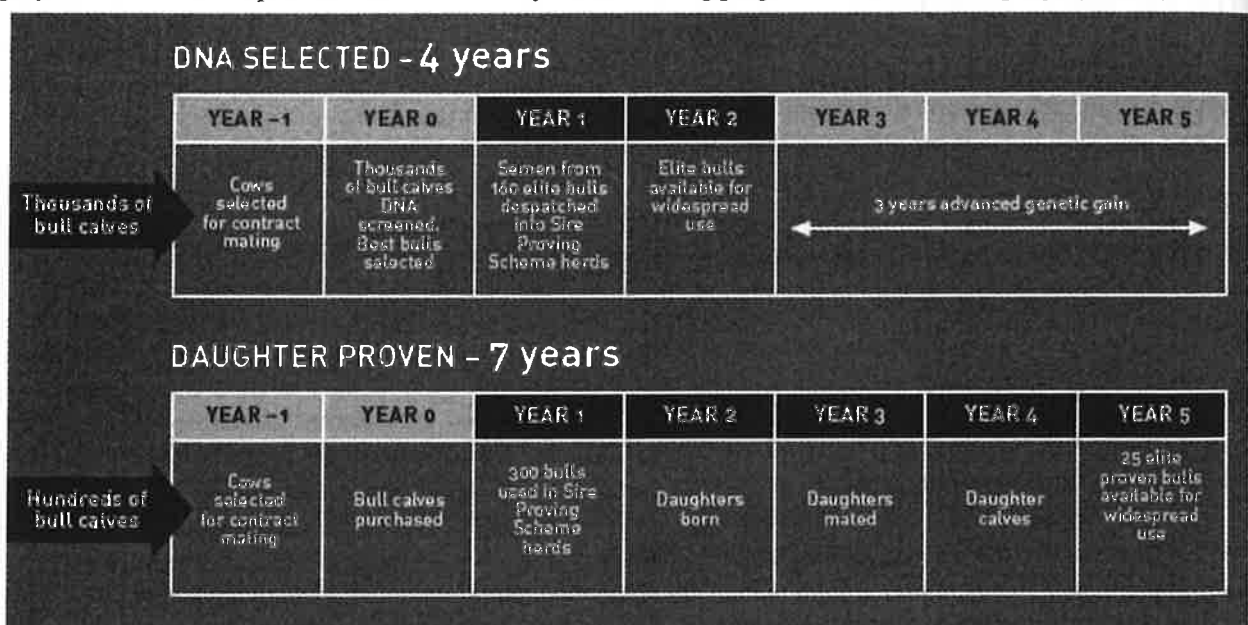
##### Application of molecular genetics in livestock before genomic prediction

The application of molecular genetics to animal breeding started in the 1970's, scientists used the DNA markers to detect genes or genomic regions that control traits of interest. Then, these identified genes or markers allowed breeders to make improvements using marker-assisted selection as part of their overall improvement programme (Kadarmideen et al. 2006). Many genes have been identified for different production traits in livestock species, for instance *Halothane (HAL)*, *estrogen receptor (ESR)* and *Melanocortin 4 receptor (MC4R)* in the pig; *DGAT1 diacylglycerol O-acyltransferase 1 (DGAT1)*, *Growth hormone receptor (GHR)*, *Melanocortin 1 receptor (MC1R)*, and *calpastatin (CAST)* in cattle (Rothschild and Plastow 2014). To identify causal genes/markers for traits of interest, many quantitative trait loci (QTL) have been detected. To date (January, 2015), more than 12,000 QTL have been identified in cattle and pigs and around 4,000 QTL for chicken (<http://www.animalgenome.org/cgi-bin/QTLdb/index>). However, the implementation of QTL information in breeding programs has been rarely successful because of several reasons. Many QTL have not been functionally validated, so it is difficult to use them in practice. Moreover, these QTL have explained very small proportion of the variation in the traits, often the highest phenotypic variation explained by a single QTL is only a few percentage of total variance. Since many complex traits (especially the production traits) are controlled by a large number of QTL, it has not only made it difficult to identify the causative variants for a given trait, but also limited use of these causal variants or QTL in the breeding program. The use of significant markers of a marker assisted selection method is unlikely to improve genetic gain (Goddard and Hayes 2009).



## Principle of Genomic prediction

High-throughput genomic technologies, especially high-throughput SNP genotyping methods were commercially available for several years (commercial SNP chips exist for cattle (750,000SNPs), pigs (60,000SNPs), dogs (250,000SNPs), sheep (56,000SNPs), horses (55,000SNPs) and chickens (600,000SNPs). This has led to increased adaptation of genomic/sequencing technologies in the livestock sector, particularly in the area of animal genetics and breeding. In the context of animal breeding, perhaps a genomic prediction / selection was the biggest change that resulted as a consequence of adaptation of high-throughput genotyping technologies in the livestock sector. Genomic selection refers to making breeding decisions based on genomic estimated breeding values (GEBVs) that are computed by estimating SNP effects from prediction equations (Meuwissen et al. 2001). These SNP effects are normally estimated from a reference population consisting of a subset of animals with both SNP genotypes and phenotypes for traits of interest. Estimated SNP effects are then used to determine the merit of other genotyped animals that are not yet phenotyped. Two major advantages of genomic selection compared with traditional selection based on pedigree and phenotype alone are (i) it can select animals accurately early in life using their GEBVs from genomic predictions, (ii) it can also predict phenotypes that are very difficult or expensive to measure, including but not limited to fertility, meat quality, disease resistance, methane emissions, and feed conversion (Hayes et al. 2013). In dairy cattle, for example, dairy bulls are traditionally selected following progeny testing, because genetic merit for milk production of a bull can only be accurately evaluated through the milk production of his daughters. From the time dairy bulls' daughters are born, reach puberty, get inseminated, get pregnant, give birth to a calf and complete a full lactation (first lactation heifers), it can take anywhere between 5-7 years depending on the country (in tropics it takes more time) (Figure 1). It comes with enormous costs as well as time for each bull to be progeny tested. Although progeny testing results in accurate selection, genomic selection can reduce the generation interval by at least two years as we can pre-select the young bulls to be either progeny tested for the milk production or used directly in the breeding programmes without ever progeny testing.



**Figur 1: Generation interval using genomic prediction compared to traditional methods (daughter proven)**  
(Adapted from [http://www.licnz.com/genomic\\_selection\\_dna\\_.cfm](http://www.licnz.com/genomic_selection_dna_.cfm)).

The first option can save costs and increase accuracy and the second option dramatically increases costs, time and increase accuracy of selection. It is stated increase in genetic gain or income is 60%-120% compared to traditional methods of progeny testing (Schaeffer 2006; Pryce and Daetwyler 2012).

## Methods of Genomic prediction

Genomic prediction models vary based on several assumptions regarding the variance of traits of interest. Genomics best linear unbiased prediction (GBLUP) is a prediction method that assumes that all markers contribute to the additive

genomic variance. This method is similar to the traditional BLUP method applied for in animal breeding for over 20 years, except that a genomic relationship matrix replaces the numerator relationship matrix computed from the pedigree information. Another method called Random regression BLUP (Meuwissen et al. 2001) assumes SNP effects are randomly distributed, and is considered equivalent to GBLUP (Goddard et al. 2011). Single-step BLUP (ssBLUP) jointly analyzes phenotypes and genotypes of all animals in one step (Aguilar et al. 2010). Inclusion of all animals (with and without genotypes) results in the better correction of genomic preselection effects; and consequently provides more accurate estimation of GEBVs. Several Bayesian approaches have been used for genomic prediction, and these methods assume a prior knowledge about distribution of SNP effects influencing a trait. BayesA assumes that all SNPs have an effect, but each SNP has a different variance that is assumed to be equivalent to a scaled inverse- $\chi^2$  prior (Meuwissen et al. 2001). The BayesB and BayesC $\pi$  assume that each SNP has either an effect of zero or non-zero with probabilities  $\pi$  and  $1-\pi$ , respectively (Habier et al. 2011). Gianola et al. (Gianola et al. 2006) introduced semi-parametric methods (reproducing kernel Hilbert spaces (RKHS) regression) for whole-genome analysis of quantitative traits. Genomic prediction accuracy gets better as the trait heritability and the reference population used for calculating GEBVs increases. Overall, genomic prediction methods are improving, especially with advent of whole genome sequence data from next generation sequencing. At present, the difference between performances of different methods is marginal for most traits because they are controlled by many QTLs with small effect sizes. Genomic BLUP and its single step extension that includes non-genotyped animals (ssBLUP), remain the most commonly used methods.

### **Genomic selection to improve livestock in developing countries with a focus on India**

Genomic tools in general and genomic prediction or genomic selection, in particular significantly improve livestock production and the theoretical background in animal science (Kadarmideen 2014), however, its application to developing countries have been limited. The constraining factors are lack of nation-wide or state-wide phenotype and pedigree recording/keeping schemes across all dairy farms (or sheep or pig farms), the type of livestock production systems (often small holder systems in India with a few exceptions), co-ordinated use of breeding animals, formal genetic evaluation centers for entire state or nation in addition to many other factors such as the funding for livestock keepers, infrastructure, human resources and so on. The livestock production system in developing countries varies by the geographic and climate conditions. Genomic prediction can focus small holder farmers to reduce hunger and poverty or to medium size farm to quickly improve the productions. Livestock is an important subsector of agricultural production system in India. It plays major role in the national economy as well as in socioeconomic development of millions of rural households spread across more than 600,000 villages (Pattnaik et al. 2012). The overall contribution of livestock sector to the agricultural growth domestic product (GDP) is 24–32% and to national GDP is 4–6% (Pattnaik et al. 2012).

### **Potential of Genomic selection to improve production/reproduction traits**

Perhaps, improving production/reproduction and health traits are among the most important task for livestock production in developing countries since the productivity of livestock is far below potential. With genomic prediction in cattle, the sire with higher genomic breeding values can be selected for use in Artificial insemination (AI) or to produce the embryos for transfer (via either conventional embryo transfer (ET) or via OPU-IVP ET programs). However, it is necessary to consider the physical infrastructure such as devices to store sperm, embryos, AI tools and transportation services. In pigs, Akanno et al. (Akanno et al. 2014) showed accuracies of GEBVs in the range of 0.30 for number born alive to 0.86 for backfat in the validation population which is better than pedigree-based approach in a simulation to mimic pig populations in developing countries. In another study, the authors also suggest that the high density SNP chip can help improve the indigenous pig populations with low linkage disequilibrium and combination of genomic selection with repeated backcrossing of crossbreds to exotic pigs in developing countries promises to rapidly improve the genetic merit of the commercial population (Akanno et al. 2013). The authors showed that clear opportunities to improve production traits in pig breeds. The potential of improving genetic merit by genomic selection for beef cattle in Latin America is also highlighted by (Montaldo et al. 2012). We developed the GIFT project (Genomic Improvement of Fertilization traits in Danish and Brazilian Cattle) to help improve fertilization traits in Brazil cattle (<http://gift.ku.dk>) as an example to implement the genomic prediction in developing countries. The GIFT project conducts quantitative genetics and animal breeding research on important attributes or traits related to OPU and in vitro production (IVP) of embryos. These embryos undergo “genomic selection” thus an animal is already pre-selected using an embryo stage based on their genotypes! Thus contributing dramatically to reducing generation interval and to profitability of

OPU-IVP operations in the Brazilian and Danish cattle industry. The GIFT project operates in the state of São Paulo to identify high genetic merit donor cows and recipient heifers with higher pregnancy rates via Genome-Wide Association Studies and genomic selection for OPU-IVP and pregnancy traits in several thousands of Brazilian cattle. In Denmark, transcriptomic experiments using RNA sequence profiles of OPU-IVP recipient cows are conducted to identify differentially expressed genes and gene regulatory networks in maternal-conceptus tissues in recipient cows that do and do not maintain pregnancy.

Regarding to the situation in India, the milk production (both in cattle and buffaloes) have significant impact on the economy, the genomic improvement for these traits needs to be highly prioritized. India has the highest number of live cattle in the world with around 214,350,000 stocks in 2012 (<http://faostat.fao.org>). Genomic prediction can be used to identify best bulls and cows for milk production (milk, fat, protein yield) and milk quality (milk self-life extending lactoperoxidase thiocyanate systems, healthy Solids Not Fat etc.), reproduction (insemination success, calving rates etc.) in each community. This bull or cow can be used for mating and/or to produce semen for AI. The distribution of semen to small holders across many many villages is encouraging therefore there is a high possibility that genomic selection can be achieved successfully even within villages.

### **Potential of Genomic selection to improve disease resistance/tolerance**

Livestock disease is one of the major concerns for livestock breeders because of its impact on economics, its transmission to other species, potential to affect human and its cause to animal welfare concern. Genomics of disease resistance has been reviewed in many studies across different species (Yáñez et al. 2014; Lunney 2007; Bishop and Morris 2007). Bishop and Woolliams (Bishop and Woolliams 2014) indicated focus on major endemic diseases included bovine tuberculosis and paratuberculosis in pigs and nematode infections in sheep. Kadarmideen et al. (Kadarmideen et al. 2011) and Ali et al. (Ali et al. 2013) have shown that bovine tuberculosis in African Zebu cattle have genetic basis and that certain SNPs, microsatellite markers and candidate genes such as NRAMP1 gene polymorphisms can be used in marker assisted selection schemes to reduce the incidence or increase resistance to bovine tuberculosis, particularly in Zebu cattle. This in combination with existing genetic diversity in disease resistance in developing countries in Africa that we have reported earlier (e.g. (Flury et al. 2009) it can certainly help genetic improvement of disease resistance. Many studies have shown that the animal species in developing countries are less susceptible to common disease than exotic animals. For instance, Zanga et al. (Zanga et al. 2003) showed that indigenous pigs are better adapted to local production conditions and environments and less susceptible to common disease exotic pigs in Zimbabwe. Selection for disease resistance based on DNA technologies is possible and can be done by either marker assisted selection or genomic prediction. Genomic prediction have been showed its potential application for Tuberculosis resistance in dairy cattle (Tsairidou et al. 2014), for porcine reproductive and respiratory syndrome virus infection in pigs (Boddicker et al. 2014) or for newcatles disease in chicken (Liu et al. 2014). In India, Sekar et al. (Sekar et al. 2011) interviewed that experts and showed that controlling Tuberculosis diseases among the highest priorities among other zoonotic disease. In India, higher incidence of tuberculosis in buffaloes as compared to cattle has been estimated on the basis of tuberculin (Shukla and Singh 1972). A report have shown that 60 per cent of the total 520,000 cattle in the Kerala State were partially or fully affected by the tuberculosis disease and almost all crossbred cattle were suffering with tuberculosis (<http://en.engormix.com/MA-dairy-cattle/news/india-bovine-alarms-health-t539/p0.htm>). Since estimated a heritability for TB resistance of  $0.18 \pm 0.04$  (Brotherstone et al. 2010), it can be removed by a breeding program. Genomic selection for TB resistance therefore is important task to sustainable development of livestock production in India. Tick infestation is another common ecto-parasitic infection in Indian cattle. In tropical part of Northern Australia, we (O'Neill et al., (2010) demonstrated greater genetic variation (high heritability) exists in tick resistance in Indian derived tropical composite breeds such as Brahman cattle. There are also many other cattle diseases such as infectious bovine keratoconjunctivitis for which we reported substantial genetic variation (Ali et al. 2012) and hence a potential for genomic selection. Another disease can be important is Foot-and-mouth disease, which remains a serious threat to the livestock populations. Especially in India, with 528 million foot-and-mouth disease (FMD) susceptible animals, primarily cattle and buffaloes of India, where the disease is endemic. However, there have been no report how genetically determined FMD is and hence it may be worthwhile to make a population genetic study on FMD.

## Potential of Genomic prediction to improve heat stress, climate resilience and methane emission

Around 55% of India population directly or indirectly depends on the climate sensitive agriculture sector (Ahmad et al. 2011). Livestock production is the driving force to climate change (green house gas) but also very sensitive to climate change. Climate change is not only affecting feed supply, increased drought, changes in disease prevalence and increased incidence of heat stress (Rothschild and Plastow 2014) but also brings many new disease germs for livestock (Singh et al. 2011). Rothschild and Plastow (Rothschild and Plastow 2014) indicated that long-term genetic solutions are needed to identify genomic signatures of selection related to heat stress. In tropical part of Northern Australia, we (O'Neill et al., (2010) demonstrated greater genetic variation (high heritability) exists in heat stress or tolerance in Indian derived tropical composite breeds such as Brahman cattle. Therefore, it offers an opportunity to study the level of genetic variation in heat tolerance and drought tolerance among Indian breeds and use the better animals in genomic selection. In practice, several studies have found individual genes or genomic regions associated with mechanisms to combat climate issues (Liao et al. 2013). The review by (Hayes et al. 2013) indicate the possibility of genomic selection for resistance to heat stress. Hayes et al. (Hayes et al. 2009) report the accuracy of genomic prediction for tolerance to heat stress was moderate at 0.37, which much higher than accuracy based on pedigree information (0.16). Breeding for methane emission might be difficult because it is more expensive to measure (compared to other production traits) although the trait is moderately heritable. However, selection for improved feed efficiency can lead to reductions in methane emissions (Hegarty et al. 2007). Selection for improved feed efficiency can also help to reduce the nitrogen/phosphorous emission in pigs (Saintilan et al. 2013) and enhance sow performance to tropical climate condition (Renaudeau et al. 2014). In our study on pigs, we reported substantial genetic variation in feed efficiency in pigs (Do et al. 2013). However, the problem will be to design an effective breeding program for climate change or resource use efficiency. As mentioned by (Naskar et al. 2012) breeding for climate change adaptation or mitigation will not be necessarily different from existing breeding programs but success depends on measuring the phenotypes at individual animal level and traits relevant for adaptation or efficiency. Care must be taken to ensure that right balance between breeding objectives for all the traits (heat resilience, fertility, feed conversion efficiency, disease tolerance and longevity in addition to higher productivity etc.) are implemented. It is important to consider genotype by environment interactions to identify animals most adapted to specific conditions and natural stratification of breeds and species by climatic zones. Since India has seven climatic zones, the selection of genomic merit can be tailored to each climatic zone and that could benefit the farmers in different regions of India.

### Concluding remarks

The demand for livestock products is increasing and application of genomic selection in livestock species has been significantly contributing to meet that demand in several developed countries, already for over 7 years. Employing genomic selection to increase livestock production and its efficiency to meet these modern demands for food of animal origin in the developing world will be critical and required. Faster genetic gains for these traits can be achieved with new technologies, including genomic selection and advanced reproductive technologies such as OPU-IVP ([www.gift.ku.dk](http://www.gift.ku.dk)). Adoption of genomic tools, especially genomic prediction will be very necessary to accelerate enough genetic gain for production traits as well as to improve the genetic merit of disease resistance and adaptation ability, in developing world. Certainly, many other facilities and concerted efforts are required to overcome the challenges, including improved policies, and development of human and institutional capacities. For certain, livestock production to contribute significantly to Indian economy, adoption of genomic solutions to livestock production is very critical and important. India and other developing countries will have to focus on the production, but efforts must be made to balance the productivity with conservation of genetic resources or genetic diversity, reducing environmental impact and improve animal welfare. This will facilitate sustainable animal agriculture.

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