Heritability – what is it, and what is it not; implications for improving cattle health

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ABSTRACT
The persistently high prevalence of many cattle diseases necessitates consideration of other mitigation strategies, one of which could be animal breeding. Although low heritability, which is a general characteristic of many cattle health traits, is often cited as a reason why breeding strategies may not be fruitful, this is certainly not a correct deduction. Low heritability does not necessarily imply a lack in genetic variability, nor does it imply that the majority of the observed inter-animal variability is due to management. Annual genetic gain for any trait is a function of 1) the intensity of selection, 2) the accuracy of differentiating genetically divergent animals, 3) the extent of genetic variability present, and 4) the generation interval. Heritability impacts the accuracy of selection, but the impact of low heritability can be negated against by accessing more information; such information was traditionally phenotype-based, but more recently is being complemented with DNA information. Considerable exploitable genetic variability exists in most health-related traits in cattle. The high accuracy of selection achievable for health traits, coupled with the presence of large inter-animal genetic variability, can translate to rapid genetic gain. Therefore, breeding programmes should constitute a component of devised strategies to improve the cattle health.

KEYWORDS: Genetic, phenotypic, breeding, disease, beef, dairy

INTRODUCTION
The contribution of breeding programmes to changes in performance metrics in cattle populations is well acknowledged (Berry and others 2014, Berry and others 2016, García-Ruiz and others 2016); change here implies either favourable or unfavourable change. Clearly rapid favourable genetic gain in milk production and composition in recent decades has occurred in many dairy cow populations (Berry 2018, García-Ruiz and others 2016); the contribution of many dairy cow breeding programmes to an erosion in dairy cow reproductive performance in the latter years of the last century has also been well documented (Lucy 2001). Despite commentary that genetic selection for lowly heritable reproductive traits would not be successful, the global broadening of dairy and beef cow breeding goals has resulted in rapid genetic gain for reproductive performance in both dairy and beef cattle populations (Berry and others 2014); in turn the genetic gain has translated into rapid observable on farm improvements in phenotypic performance in both dairy (Coleman and others 2009) and beef (McHugh and others 2014) cattle. The low heritability of many health traits in cattle (Berry and others 2011a) sometimes leads to a (incorrect) conclusion that breeding for improved health will not be fruitful. The heritability statistic is, however, arguably one of the most misinterpreted in animal breeding. The objective of this review is to define what is meant by heritability and, in doing so, also clarify what it is not. The components contributing to genetic change in population performance are described using health traits in cattle for illustrative purposes.

HERITABILITY DEFINITION
Heritability may be defined as:

- The proportion of inter-animal phenotypic variance attributable to inter-animal genetic differences.
- The strength of the relationship between the true genetic merit of an individual for a trait and its observed performance (after adjustment for systematic environmental effects such as herd, animal age).

Heritability does not, however, depict the fraction of a phenotype which is caused by genetics. Two types of heritability exist, the narrow sense heritability (h^2) and the broad sense heritability (H^2). Generally, unless otherwise stated, it is the narrow sense heritability that is cited in animal genetic studies because this considers only the proportion of phenotypic variation which is directly transmitted from one generation to the next without cognisance of the mate of the animal.

Based on the first definition above, the heritability is the proportion of the phenotypic variability (*i.e.* the variation observed on-farm) attributed to genetic differences, and therefore heritability is a ratio trait which be expressed as a proportion or percentage ranging from zero to one:

$$\text{Heritability } (h^2) = \frac{\text{Genetic variance}}{\text{Phenotypic variance}} = \frac{\text{Genetic variance}}{\text{Genetic variance + residual variance}}$$

Heritability estimates not only vary by trait, but they also vary by population. The degree of genetic variance in a population (*i.e.* the numerator term of the heritability), is dependent on factors (Berry and others 2017) such as the frequency of the alternative DNA variants at a given location that affect the trait, the extent of segregation of the DNA variants, and the mode of gene action (*e.g.* do the variants act independently or is their effect a function of the variants in other genes). Some of these factors can be influenced by evolutionary forces such as migration, selection, inbreeding, assortative mating and genetic drift (Berry 2018).

Heritability myths

1. Low heritability implies little genetic variance. Because heritability is, by definition, a ratio trait, no inference to the extent of genetic variance can be made from a heritability estimate. Using a heritability of 0.05 as an example, it can be clearly seen that the same heritability is achievable irrespective of the estimate of genetic variance:

$$\text{Heritability} = 0.05 = \frac{0.05 \text{ units}^2}{0.05 \text{ units}^2 + 0.95 \text{ units}^2} = \frac{5 \text{ units}^2}{5 \text{ units}^2 + 95 \text{ units}^2} = \frac{500 \text{ units}^2}{500 \text{ units}^2 + 9500 \text{ units}^2}$$

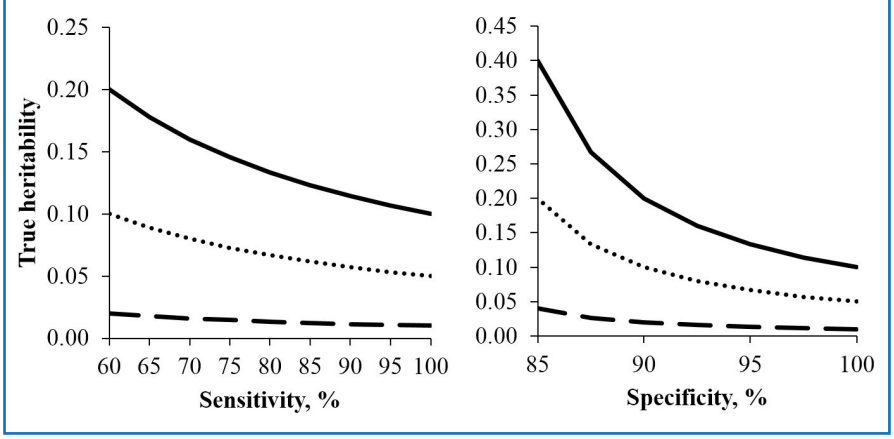
2. Low heritability means most of the variation is due to management – for example a heritability of 0.05 is sometimes construed to imply that 5% of the variability is genetic and 95% of the variability is due to management effects. Phenotypic variance (*i.e.* variance observed on farm), which constitutes the denominator of the heritability equation, is the sum of the genetic variance and the residual variance. The residual variance, as the name suggests, is comprised of noise; this noise can include errors in the data, including pedigree data, and/or variability unexplained by the fitted statistical model.

Based on heritability estimates derived using paternal sib correlations, Van Vleck (1970) documented that estimated heritability statistics were biased downwards by a fraction of p^2 where p is the proportion of animals with correctly identified sires. Given that parentage errors in Irish cattle range from 10% to 13% (Purfield and others 2016), the true heritability of a trait is expected to be 23% to 32% greater than that estimated with the errors; for example, for a documented heritability estimate of 0.05 that has parentage errors of 13%, the true heritability estimate is likely 0.07.

Of particular relevance to animal health, and of concern to animal breeders, is the impact of misclassification of animals for health traits because of 'noise' in field data; such noise includes incomplete exposure, imperfect sensitivity and specificity of diagnostic tests, as well as heterogeneity of phenotype recording. Bishop and Woolliams (2010) documented that false-positive and false-negative results will suppress the estimate of the true heritability (Figure 1). As an example, Twomey and others (2016) reported an observed heritability of 0.013 and prevalence of 20% for liver damage caused by *Fasciola hepatica* in Irish cattle. The sensitivity and specificity of *F. hepatica*-damaged liver diagnosis in that study was assumed to be 68% and 88%, respectively; however, if the sensitivity and specificity were both perfect, then the observed heritability and prevalence would be 0.055 and 14%, respectively. In addition, Ring and others (2018a) discussed the consequences of inconsistency in phenotype recording on the heritability estimates of hoof health traits. By way of example, Ring and others (2018a) randomly re-dichotomised the binary trait of overgrown sole to reflect recording discrepancies likely to occur in field data, perhaps collected by producers; the result was a reduction in the heritability estimate for sole ulcers from 0.09 to 0.03 due to an increase in residual variance.

3. Low heritability translates to slow genetic gain. Theoretical genetic gain in any given trait or index

Figure 1. The true heritability when sensitivity or specificity is imperfect for disease traits with an observed heritability of 0.01 (solid line), 0.05 (dotted line) and 0.10 (dashed line; Bishop and Woolliams 2010).

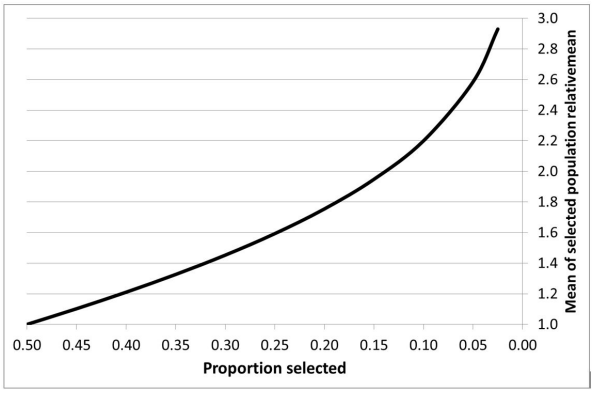


of traits can be calculated using the "breeder's equation" first described by Rendel and Robertson (1950) as:

$$\text{Genetic gain per year} = \frac{\text{Selection intensity x accuracy of selection x genetic standard deviation}}{\text{generation interval}}$$

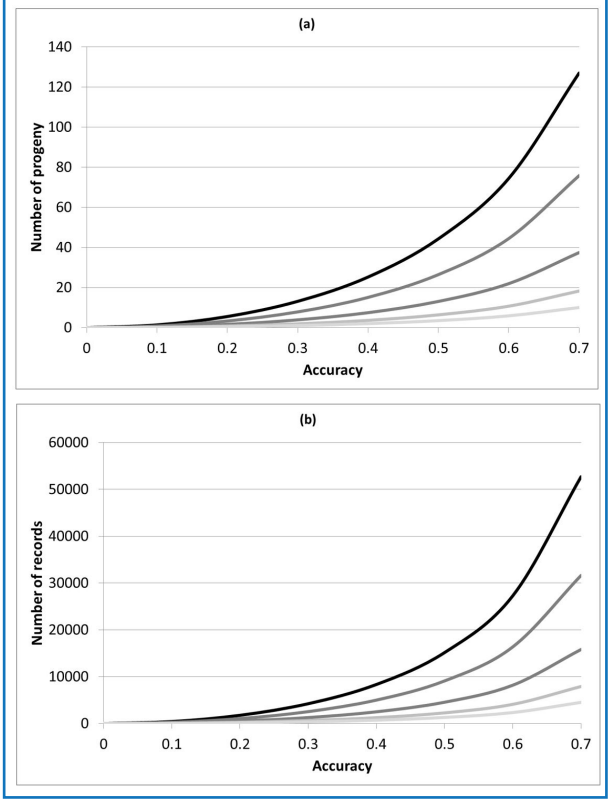
Selection intensity represents the mean, in standard deviation units, of the selected parents of the next generation relative to the current generation. Figure 2 illustrates, using a different proportion of a population selected as parents of the next generation, how the expected mean of a selected population differs relative to the mean if half the population were selected. Clearly, the greater the selection intensity (*i.e.* the fewer elite animals selected to be parents), the greater the expected mean of the selected population (all else being equal) and thus the greater the expected genetic gain; moreover, the trajectory of the expected mean of the selected population increases at an increasing rate as the selection becomes more intense.

Figure 2. The expected mean of a population of selected animals (in standard deviation units) as the proportion of animals selected changes, relative to the mean of a population with half (*i.e.* 50%) of animals selected.



Accuracy of selection depicts how closely the measure used to select the parents of the next generation reflects their true genetic merit. If selection is based on the observed phenotype of the animal alone, then the accuracy of selection is simply the square root of the heritability of the trait; therefore phenotypic selection can be very effective when heritability is high. Most selection schemes, however, exploit estimated breeding values of the candidate parents. The accuracy of these estimates of the breeding values is a function of the information available on relatives (including the animal itself) and the heritability of the trait; in the last decade, performance information in cattle from relatives has been complemented with genomic information using a process termed genomic selection (Meuwissen and others 2001). The number of animals required to achieve a given accuracy of breeding values based on traditional genetic evaluations, using just phenotypic information from progeny, for a selection of heritability estimates is in Figure 3. Assuming a heritability of 0.03, phenotypes on 127 progeny per parent would be required to achieve an accuracy of 0.70; the number of progeny per parent required to achieve the same accuracy would be 37 and 10 if the heritability was 0.10 or 0.35, respectively. Hence, the lower the heritability, the greater the number of progeny records required to achieve a given accuracy of selection. Figure 3 also illustrates the expected accuracy of genome-based estimated breeding values for traits differing in heritability when based on genomic information (Daetwyler and others 2008). Genome-based estimated breeding values, also known as genomic selection,

Figure 3. For trait heritability values of 0.35, 0.20, 0.10, 0.05 and 0.03 (in order of descending darkness of lines), the a) number of progeny required to achieve a given accuracy of selection using traditional pedigree-based genetic evaluations and b) number of records of phenotyped and genotyped animals to achieve a given accuracy of genomic evaluations; the latter is based on 1000 effective chromosomal segments and 80% of the genetic variance accounted for by the genotyped markers.



are now routinely used in most cattle genetic evaluations. Again, the lower the heritability, the greater the number of phenotyped and genotyped animals (*i.e.* animals with DNA information) required to achieve a given level of accuracy. Phenotypes and genotypes on 8,333 animals would be required to achieve an accuracy of genomic predictions of 0.4 for a trait heritability of 0.03; this number reduces to 2,500 animals if the heritability is 0.10 and further to 714 if the heritability is 0.35. Nonetheless, high accuracy of selection, even for low heritability traits, irrespective of whether based on progeny phenotypic information or animal genomic information, is still certainly achievable and thus low heritability should not always be a constraint on genetic gain. Hence, to achieve genetic gain in health traits needs to a) be a belief that breeding programmes can deliver on improving animal health, and b) a willingness to make this happen which itself entails data recorded into a repository (linked with other information) and the sharing of these repositories (ideally into a centralised database).

Arguably the most important factor affecting genetic gain is the extent of genetic variability present. All else being equal, the greater the genetic variation, the greater theoretical rate of genetic gain. (Genetic) variation is often represented as the genetic standard deviation. Assuming a normally distributed trait, 16% of individuals are expected to be one standard deviation superior to the population mean.

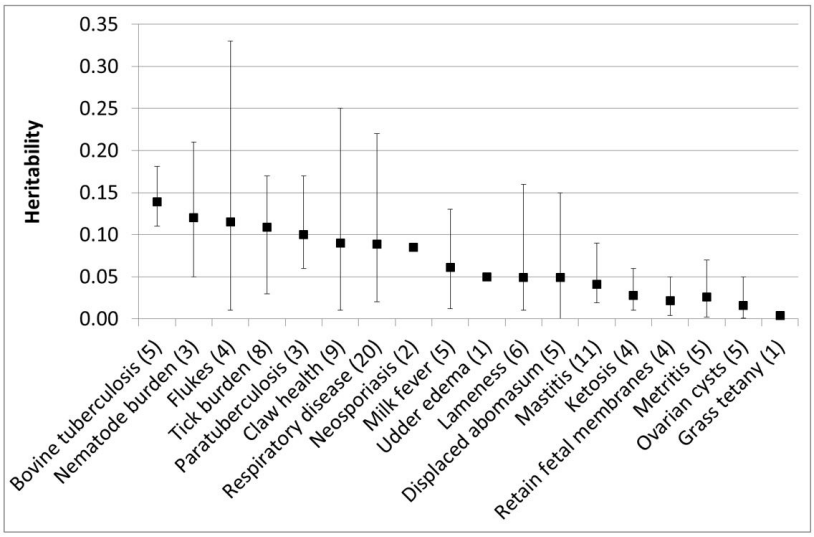
The generation interval is the average age of the parents at the birth of their progeny who in turn become parents of the next generation. Prior to the introduction of genomic selection, the mean generation interval in dairy and beef cattle was 6.03 to 6.71 years (McParland and others 2007). Cattle breeding schemes are rapidly evolving to maximise the exploitation of genomic selection and hence the generation interval in cattle is constantly reducing (Garcia-Ruiz and others 2016).

All in all, because selection intensity is largely at the discretion of the breeder, and a high accuracy of selection is usually achievable even for low heritability traits (assuming sufficient phenotypes exists), when coupled with the fact that genomic information on individual animals is available at a young age (thereby reducing the generation interval), it is the extent of genetic variability in health traits that is the main determinant affecting the rate of genetic gain in health. This conclusion, however, does not negate the importance of collating large datasets on health phenotypes from which to generate accurate estimates of genetic merit.

GENETIC PARAMETERS FOR HEALTH TRAITS IN CATTLE AND EXPECTED GENETIC GAIN

Heritability estimates for a whole range of health traits in cattle are summarised in Figure 4. Mean

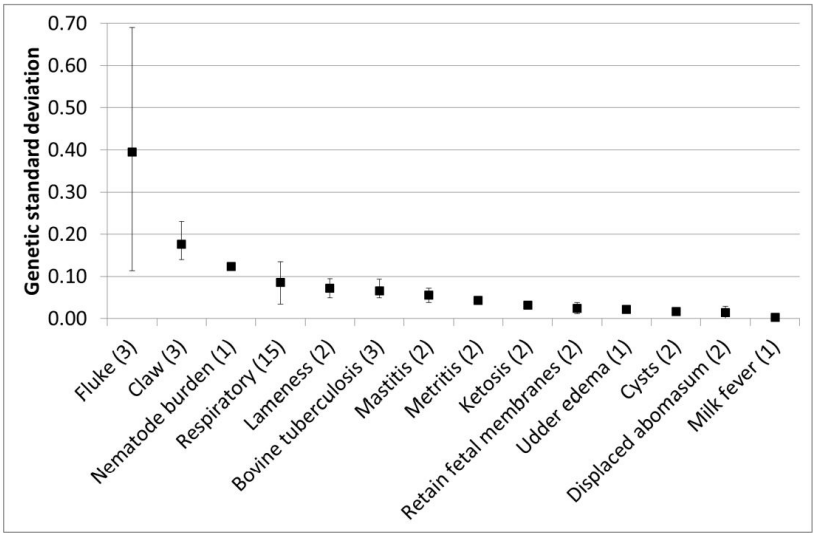
Figure 4. Mean heritability estimates (marker) on the observed scale with minimum and maximum heritability estimates per study (represented by standard error bars) for a series of health traits in cattle; the number of studies/populations contributing to each estimate are in parenthesis after the trait name.



References: Thompson 1984, Muggli-Cockett and others 1992, Poso and Mantysaari 1996, Pryce and others 1998, Van Dorp and others 1998, Kadarmideen and others 2000, Hansen and others 2002, Carlén and others 2004, Pan and others 2004, Zwald and others 2004 Abdel-Azim and others 2005, Snowder and others 2005, van der Waaij and others 2005, Snowder and others 2006, Heringstad and others 2008, Holtsmark and others 2008, Budeli and others 2009, Coppieters and others 2009, Laursen and others 2009, Attalla and others 2010, Berry and others 2010, Brotherstone and others 2010, Heringstad 2010, Koets and others 2010, Schneider and others 2010, Berry and others 2013, Pritchard and others 2013, Koeck and others 2014, Richardson and others 2014, Carthy and others 2015, Jamrozik and others 2016, Twomey and others 2016, Biegelmeyer and others 2017, May and others 2017, Ring and others 2018a, Ring and others 2018b, Twomey and others 2018.

heritability estimates per trait varied from 0.004 for grass tetany to 0.14 for tuberculosis; half the traits had a mean heritability of ≤0.05. Considerable variability in heritability estimates for a given trait amongst populations was nonetheless evident. Based on a meta-analysis of up to 20 different Holstein-Friesian dairy cow populations, Berry and others (2014) reported a mean heritability estimate for traditional fertility traits of between 0.021 (number of services) to 0.174 (the interval from calving to first heat) with 8 of the 12 traits evaluated having a heritability of <0.04; a similar conclusion existed for traditional fertility traits in other dairy breeds (Berry and others 2014). Nonetheless, despite the low heritability for these fertility traits, rapid genetic gain (following rapid deterioration) in reproductive performance in the Holstein-Friesian breed has been achieved (Berry and others 2014, Berry 2018). The rapid genetic gain in reproductive performance in most dairy cow populations has been attributable to the known large inter-animal genetic variability in reproductive performance (Berry and others 2014) coupled with a "can-do" attitude among stakeholders ensuring reproductive performance measures were recorded to overcome the low heritability and achieve high accuracy of selection and thus rapid genetic gain. The mean standard deviation for a range of health traits in cattle are presented in Figure 5 for studies that analysed the trait as a binary trait using linear models. Berry and others (2003) documented a genetic standard deviation for the binary fertility trait of pregnancy rate to first service of 0.051 in dairy cows; half of the health traits in Figure 5 had an average genetic standard deviation greater than 0.051. Given the well-acknowledged improvement observed in reproductive performance from breeding programmes in dairy cattle (Berry and others 2014, Berry 2018), sufficient genetic variability clearly exists for most of the health traits implying that indeed rapid genetic gain is possible if high accuracy of selection (and intense selection) is achieved.

Figure 5. Mean additive genetic standard deviation (marker) with minimum and maximum standard deviation estimate per study (represented by standard error bars) for a series of binary health traits in cattle; the number of studies/populations contributing to each estimate are in parenthesis after the trait name.



References: Van Dorp and others 1998, Snowder and others 2005, Bermingham and others 2009, Pritchard and others 2013, Richardson and others 2014, Carthy and others 2015, Jamrozik and others 2016, Twomey and others 2016, Ring and others 2018a, Twomey and others 2018.

Challenges impacting successful genetic selection for improve health status

Accurate genetic evaluations are predicated on vast quantities of individual animal phenotypic data (Figure 3) and the necessity for data is particularly important for most health traits which tend to be, on average, lowly heritable (Figure 4). Genetic evaluations for health traits in dairy cattle have been underway for many decades in Scandinavia (Philipsson and Lindhé 2003) but this is owing to the imposed legislation requiring veterinarians to administer all animal treatments. These data are subsequently collated for use in genetic evaluations which, when coupled with the traditionally large progeny testing programme in Scandinavia, facilitate the achievement of high accuracy of selection; the outcome is the well-documented superior health performance of cows originating from Scandinavian breeding programmes (Heringstad and others 2003). Veterinary practitioners still diagnose most diseases in most countries and capturing at least these data would provide useful information from which to generate accurate genetic evaluations. Moreover, the expected greater accuracy of diagnoses logged from veterinarians should contribute to lesser residual noise and thus higher trait heritability; the impact of the higher heritability is the requirement for fewer phenotypic records to achieve a high accuracy of selection (Figure 3).

Unless an animal is exposed to a disease, then it will be unable to express its genetic potential via its phenotype. Moreover, the virulence (and duration) of the pathogenic load could impact the expression of the inter-animal genetic variability in resistance to the disease under investigation. Hence, certainty on the exposure conditions of each animal

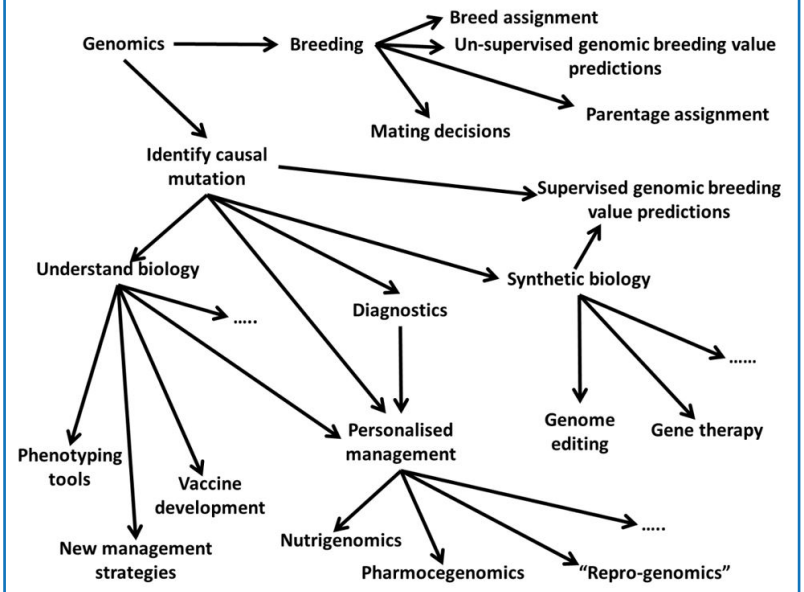
is critical to the precision of genetic evaluations; precision is somewhat different to accuracy with the latter simply being a function of the number of records in the evaluations and although improper deductions on the exposure conditions should cause a deflation in the heritability of the trait for the population as a whole, it will not impact the accuracy of genetic evaluations for an individual animal. Geneticists use careful data editing procedures prior to analyses as a strategy to maximise the probability that all animals eventually included in the genetic analyses have been exposed to the disease. Twomey and others (2016), for example, in their genetic analysis of liver damage caused by liver-fluke, undertook several different data editing approaches in an attempt to, as far as possible, only consider exposed individuals in their genetic analyses; this was based on the fact that the only animals considered were herd contemporaries of animals with observed liver damage.

Given the difficulty in collating vast quantities of health data in many countries, improving the trait heritability warrants some effort. Increasing the heritability through a reduction in random noise can be achieved through more precise definition of animal-level exposure, as alluded to previously, but also through improved consistency in phenotype definition and diagnosis; improved diagnostics here also includes improved sensitivity and sensitivity of laboratory tests as well as awareness and extension campaigns for producers on the (sub)clinical signs and differentiation of alternative aliments. The large-scale uptake of genotyping should help reduce the impact of parentage errors on deflating heritability estimates.

GENOMICS OF ANIMAL HEALTH AND HERITABILITY

Genomics is the study of the structure, function and intragenomic interactions within the genome (Berry and others 2011b). Many genome-based studies attempt to relate regions of the bovine genome with performance, including animal health (Meredith and others 2013, Richardson and others 2016). The justifications proposed for such studies often revolve around the use of discovered regions in breeding programmes under the guise of genomic selection (Meuwissen and others 2001). Dissecting the underlying genomic architecture affecting animal health, however, has far reaching

Figure 6. Adaptation of the uses from known the causal DNA variants in animal health (breeding) programmes.



uses over and above those for breeding purposes (Figure 6; Berry 2015). While many genome-based studies are based on a description of the dataset under investigation, it is the predictive ability of future performance, and more importantly the necessary data informing more accurate prescriptive ability which will undoubtedly be one of the main outcomes of genomic studies in animal health (Figure 7). Therefore, helping predict predisposition to a given disease but also provide a better understanding of the underlying biology should form a major outcome of such genomic studies.

Figure 7. Proposed development of descriptive models, to those that are predictive and eventually prescriptive models.

Prediction of predisposition to disease: The application of predicting (genetic) predisposition to disease is a rapidly growing discipline in human medicine (Vogenberg and others 2010). One of the best known examples is the role of mutations in the BRCA1 and BRCA2 genes in the likelihood of cancer development in humans (Narod 2002). Knowledge of genetic risk can trigger one or all of

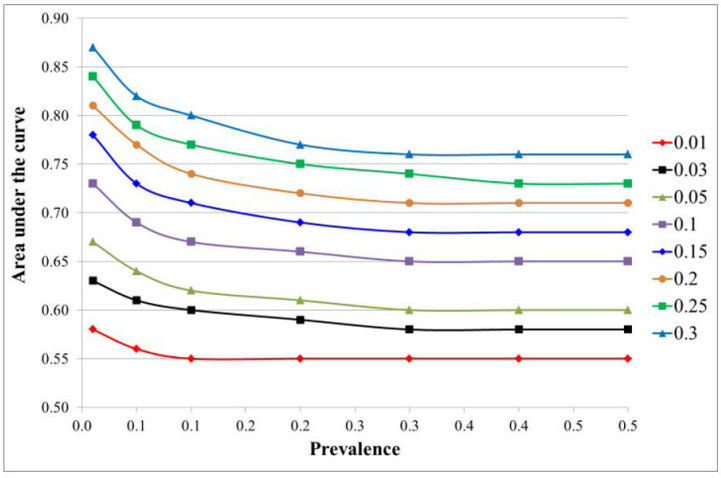
1. Enhanced screening,
2. Prophylactic treatments, or
3. Management or chemoprevention

The endless possibilities of predictive diagnostics are also true for animal health. Using mastitis as an example, cows with a known greater genetic

predisposition to udder infection could be subjected to enhanced screening by always drawing milk prior to milking with closer examination of the milk, possibly even through using a California milk test; in large herds, these cows could be managed as a separate group and milked last. As a means of prophylactic treatment, these animals could receive dry cow therapy, or at the very least, their estimate of genetic predisposition could be included as a factor in any model or system allocating cows to dry cow therapy. For managing the risk, the udders of the at-risk cows could, for example, be more thoroughly cleaned prior to milking. Furthermore, these at-risk cows could receive supplementary doses of, for example, Vitamin E or Selenium (Smith and others 1997). A more drastic strategy would be to cull from the herd the at-risk animals as heifers.

Nonetheless, the heritability for a given trait limits the maximum accuracy of phenotypic prediction achievable for any genomic test. One cannot simply explain more genetic variability than actually exists; in fact, properly executed genomic studies generally explain only a small proportion of the heritability of traits leading to the debate on the reasons for the "missing heritability" (Manolio and others 2009, Eichler and others 2010). Wray and others (2010) deterministically calculated the maximum accuracy of predicting a binary outcome (*i.e.* observed with or without mastitis) for traits differing in heritability and prevalence. The accuracy of prediction increases with heritability (Figure 8); the accuracy of prediction also improves as the prevalence deviates from 50% with the trend being stronger for higher heritability traits. Assuming a heritability of 0.03 for mastitis (Berry and others 2013), the accuracy of differentiating animals with a high or low risk of mastitis assuming a prevalence of 20% would be expected to be 0.59 when all the genetic variance can be explained. Thus, even with genomic tools that explain all the available additive genetic variation, the accuracy of prediction of mastitis is relatively low; a value of 0.50 is equivalent to simply flipping a coin. If however, a trait like bovine tuberculosis was considered with a heritability of 0.14 (Figure 4; Bermingham and others 2009, Brotherstone and others 2010) and an animal level prevalence of 10% (Bermingham and others 2009), then the accuracy is 0.70 if all the genetic variance could be explained or 0.65 if half the genetic variance could be explained. Hence, the usefulness of genetics as an aid in individual animal management is trait dependent.

Figure 8. Area under the cure for binary (health) traits differing in heritability and prevalence.



Better understanding of the underlying biology

The general foundation to addressing any disease, irrespective of species, is a thorough understanding of the disease itself and the mechanisms by which the host and pathogen interact. Animal defences against disease can be broadly classified into innate immunity and adaptive immunity. Likewise, genetic mutations governing the animal's response to a pathogen may be stratified into: a) controlling susceptibility or resistance to acquiring the infection (*i.e.* the innate immunity), b) dictating the specificity of the adaptive immune response, or c) the extent of the specific immune response (*i.e.* cell mediated resulting in inflammation or the generation of humoral antibodies).

Knowing the mechanisms governing resistance or resilience to disease is invaluable for the development of phenotyping strategies, the advancement of vaccines/treatments, as well as informing herd-management decisions. For example, if genes associated within the innate immune system were associated with inter-animal variability in infection rate to a pathogen, then it is likely that barriers to penetration such as the skin, hair, and mucus are important. This could provide knowledge on the infection mechanism of the pathogen possibly leading to strategies to augment the innate immune system for this particular pathogen. Moreover, up-regulation of such genes and the production of factors like acute-phase proteins or cytokines could lead to the development of tests that can be routinely undertaken (*e.g.* through milk samples in lactating dairy cows) that alert the producer to an imminent attack and trigger remedial action, especially for susceptible animals; the same is true for the products of adaptive immune responses. Furthermore, understanding the biological mechanisms underpinning animal health status could

facilitate more appropriate statistical modelling of the phenotype or editing of the dataset, thereby helping reduce the residual variation or indeed identify novel phenotypes for genetic selection where data capture may be easier. Detection of gene expression at an individual animal level, either through the detection of the RNA or the translated protein, could also identify infection in progress, possibly still at the subclinical stage; this in turn could trigger the appropriate remedial action which may not necessarily always be an antibiotic for bacterial infection but could include treatments like non-steroidal anti-inflammatory or multi-vitamins.

Deep phenotyping of animals genetically divergent for resistance to certain diseases can also help inform experimental study design to elucidate the underlying mechanisms governing inter-animal differences in infection rates. More accurate genetic differentiation could be possible with the use of animal-level genomic data trained to detect differences in animal-level resistance. Such a strategy of thorough examination of animals genetically divergent for a given trait as a tool to understand the underlying biology has been successfully implemented for understanding the biological mechanisms conferring advantages in reproductive performance in dairy cows (Moore and others 2014). The same can be undertaken for health traits where the biological mechanisms governing animal response to infection is not fully understood.

Augmenting the accuracy of identifying genetically elite animals

Traditional progeny testing schemes were based on evaluating the genetic merit (*i.e.* DNA-merit) of candidate sires of the next generation via the measurement of progeny performance. This was undertaken using sophisticated statistical methodology (Henderson 1950) exploiting the knowledge that each progeny receives half its DNA from its sire. Given the long generation in cattle (McParland and others 2007), annual genetic gain was not excessively rapid and receiving an accurate genetic evaluation for a bull was both costly and time consuming. Such a demand on resources also therefore limited the number of candidate sires that could be tested annually. Pioneering work by Meuwissen and others (2001) proposed genome-wide enabled selection (abbreviated to genomic selection) as a tool to improve the accuracy of selection. Genomic selection is based on the principle that the effects of many thousands of pieces of DNA could be estimated simultaneously, irrespective of the traditional statistical significance of these associations. Once estimated, the DNA effects could be transferred onto the genotypes of candidate bulls and an accurate estimate of genetic merit generated. The theory of genomic selection was made possible with the commercial availability of low cost platforms that could generate thousands of genotypes per animal.

Despite the potential usefulness of detected causal DNA variants, genome wide association studies in cattle have remained largely unsuccessful and certainly not in line with the initial promises. There are multiple possible reasons for these failures, not least the quantity of data available for use in these studies; quantity of data here implies the number of DNA variants evaluated but also the number of experimental units (*e.g.* animals). Undertaking successful genome wide association studies are particularly difficult for health traits in cattle given the impact of heritability on the associated statistical power (Shin and Llee 2015) with a low heritability requiring more phenotypes to achieve the same statistical power as a higher heritability trait with fewer phenotypes. The ability to collate phenotypic data is difficult for health traits but the dilemma is exacerbated for genome wide association studies by their generally lower heritability (Figure 4).

With the exception of some monogenic phenotypes (*i.e.* controlled by a single gene) such as complex vertebral malformation (CVM; Thomsen and others 2006), bovine leukocyte adhesion deficiency (BLAD; Shuster and others 1992) and deficiency of uridine monophosphate synthase (DUMPS; Robinson and others 1984) in cattle, most traits are likely to be polygenic in nature. Animal breeders conform to the infinitesimal model which suggests that there are a very large (*i.e.* infinite) number of DNA variants each having a very small (*i.e.* infinite) effect on the phenotype. Assuming the infinitesimal model is true, then it would be extremely difficult to identify DNA variants causing effects, and even if they were found, their impact individually on the accuracy of (genomic) predictions is expected to be negligible. While the hypothesis of an infinitesimal model is the foundation to quantitative genetics, the impression that all underlying DNA variants each have an infinitely small effect is certainly not true. A clear example is the effect of the K232A polymorphism in DGAT1 gene (Grisart and others 2002) on milk yield and composition; using a population of 848 Holstein-Friesian bulls with milk production phenotypes based on daughter performance in Irish dairy herds, Berry and others (2010) reported

an effect of 77kg milk yield, 4.22kg fat yield and 0.99kg protein yield for just one copy of the K232A variant. Hence, some genes do harbour mutations with a large effect although such large effects are likely to be the exception than the norm.

CONCLUSIONS

The low heritability of many health traits in cattle should not be a reason for slow genetic gain but instead used to promote more widespread recording of such phenotypes in the pursuit of high accuracy of selection. The existence of ample, exploitable genetic variability in health traits indicates that once a high accuracy of selection is achieved, then rapid genetic gain, and thus phenotypic gain, is indeed possible. Hence, breeding programmes must constitute a major component of a health plan either nationally or within herd as a complementary strategy to on-going disease prevention programmes. Part of such a programme must include due recognition of the necessity to collate health-related phenotypes into a central repository for use in genetic analyses; many of these data are already routinely recorded somewhere. The potential of cattle breeding programmes to improve dairy cow reproductive performance is well established; the time has now come to turn the attention of breeding programmes and the generated critical mass and expertise to improve animal health status.

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