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Advances in breeding of dairy cattle

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E-CHAPTER FROM THIS BOOK

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Advances in dairy cattle breeding to improve resistance to mastitis

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1 Introduction

Mastitis, an inflammation of the mammary gland associated with bacterial infections, is generally regarded as the most costly disease of dairy cattle because of its high incidence and effects on milk production and composition (Seegers et al., 2003). Genetic selection for highly productive dairy cows has been very successful; however, udder health has declined in many dairy breeds because of its unfavourable correlations with milk production. Poor udder health results in higher veterinary and farm labour costs, increased rates of involuntary culling, decreased farm revenue and adverse impacts on animal welfare. However, genetic selection can be used to improve udder health just as it has been used to increase production (e.g. Schutz, 1994; Heringstad et al., 2003). Selection may be based on direct (e.g. cases of clinical infection) or indirect (e.g. somatic cell counts) indicators of mastitis. Genetic improvement programmes for resistance to clinical mastitis have often been limited to selection for improved somatic cell count (SCC) (or functions thereof), rather than records of clinical cases of disease, due to the cost of data collection. The now-routine use of on-farm computer for record-keeping and data transmission

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Table 1 Potential udder health phenotypes

Type	Measure	Illustrative reference	Type	Measure	Illustrative reference
Direct	Clinical mastitis	Bramley et al. (1996)	Indirect	Changes in SCC patterns	de Haas et al. (2008)
	Subclinical mastitis	Bramley et al. (1996)		Differential SCC	Schwarz et al. (2011)
	Pathogen-specific mastitis	de Haas et al. (2004)		Electrical conductivity	Norberg et al. (2004)
Indirect	SCC	Schukken et al. (2003)		Lactoferrin content	Soyeurt et al. (2012)
	Milking speed/ milkability	Sewalem et al. (2011)		Pathogen-specific mastitis	Schukken et al. (1997)
	Udder conformation	Nash et al. (2002)		Immune response	Thompson-Crispi et al. (2012)
	Thermal imaging	Hovinen et al. (2008)			

References provided are for illustrative purposes as the literature on some traits is quite extensive.

has increased the ease of data collection in many countries that previously did not record those data in a central database (e.g. Zottl, 2016).

Several new phenotypes that can be used to select healthier udders have recently been described, including electrical conductivity of milk, lactoferrin levels, cytokine concentrations and mid-infrared spectra of milk samples (Table 1). These phenotypes fall into two classes: direct observations of clinical or subclinical mastitis, and indirect observations of animal performance or milk composition. Indirect measurements are often more affordable and have the potential to generate lots of phenotypes in an automated fashion, but there is some imprecision because they can be affected by factors other than mastitis. These new data, in combination with existing recorded phenotypes, can be used to improve the genetic merit of milking cows, regardless of breed, for resistance to clinical mastitis. Such improvement will benefit cows, farmers and consumers.

2 Conventional phenotypes for improving resistance to clinical mastitis

Udder health improvement schemes require recording of direct or indirect indicators of mastitis. Directly recorded mastitis is, for example, the number of cases of clinical mastitis per cow per lactation. Subclinical mastitis is typically recorded using SCC as a proxy. Other traits for indirectly recording mastitis include milkability (milking speed) and udder conformation traits (e.g. udder depth, fore udder attachment teat length).

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Selection for improved (decreased) somatic cell score (SCS) has been effective for the US Holstein population (Fig. 1), with both cows and bulls showing improvement in average breeding value. Similar trends have been observed in other populations, such as Norwegian Red cattle (Heringstad et al., 2007). Results from the International Bull Evaluation Service (Uppsala, Sweden) evaluations for Holstein cattle confirm earlier results showing that lower breeding values for SCC are accompanied by lower rates of clinical mastitis (Mark et al., 2002).

In many countries, reliable recording of clinical mastitis incidents is hard to achieve, so udder health improvement must begin with a focus on indirect measures. SCC is genetically correlated with clinical mastitis (r_g = 0.60–0.70). This means that when analysing field data, an observed high level of SCC is generally accompanied by a clinical or subclinical mastitis event. While milk of healthy cows commonly shows day-to-day variation in SCC, but most of the variation in SCC is associated by clinical or subclinical mastitis.

There also is some evidence that udder health decreases when herds move from conventional to automated milking (Hovinen and Pyörälä, 2011). Some of these changes may be attributable to limitations in the technology available, but others are due to trade-offs related to more frequent milking, such as reduced time for teat canal closure and attendant risk of bacterial infiltration between milkings. As herd sizes continue to increase in many countries, cows also may receive less individual treatment, which may result in less-frequent treatment for mastitis.

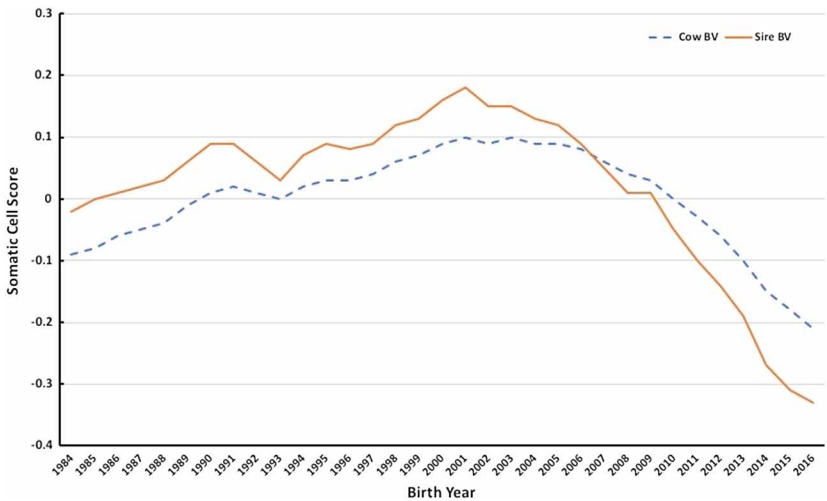

Figure 1 Genetic trend for somatic cell score [$\log_2$(somatic cell count)] in US Holsteins. Data source: Council on Dairy Cattle Breeding, Bowie, Maryland, USA; https://queries.uscdcb.com/eval/summary/trend.cfm?R_Menu=HO.s#StartBody.

2.1 Clinical mastitis

Clinical mastitis is an outer visual or perceptible sign of an inflammatory response of the udder: painful, red, swollen udder. The inflammatory response can also be recognized by abnormal milk, or a general illness of the cow, with fever. Subclinical mastitis is also an inflammatory response but without outer visual or perceptible signs of the udder. An incident of subclinical mastitis is detectable with indicators such as the electrical conductivity of the milk, *N*-acetyl-β-D-glucosaminidase and cytokine concentrations and SCCs in the milk. Recording of clinical mastitis cases may be used in many ways, including veterinary support of farm management (i.e. identification of diseased animals and establishment of consistent treatment procedures), national veterinary policy-making (i.e. drug regulations and preventive epidemiological measures), addressing citizens' and consumers' concerns about animal health and welfare and product quality and safety (i.e. food chain management and product labelling) and genetic improvement (i.e. monitoring the genetic level of the population and selection and mating strategies).

Clinical mastitis ideally should be evaluated as a binary trait using a threshold model (e.g. Zwald et al., 2004; Koeck et al., 2010; Gaddis et al., 2014; Vukasinovic et al., 2017), although some genetic evaluation centres currently use linear models for health disorders (Council on Dairy Cattle Breeding, 2018). A binary trait is coded using only two categories, which would represent presence or absence of infection in the case of clinical mastitis. These traits differ from 'classical' traits, such as milk yield, because there are only two distinct values represented in the population rather than a wide range of values that commonly follows a normal distribution. From a theoretical point of view, the two types of coding should be modelled using different statistical approaches, but for purposes of ranking animals, the models are reasonably robust when assumptions are violated. Literature estimates of heritabilities for clinical mastitis range from 0.06 to 0.10 on the underlying scale (Zwald et al., 2004; Gaddis et al., 2014) and from 0.01 to 0.14 on the observed scale (e.g. Rupp and Boichard, 1999; Nash et al., 2000; Heringstad et al., 2001). Larger values, ranging from 0.21 to 0.42, have been reported from linear models (Pryce et al., 1997; Nash et al., 2000) but may be attributable in part to small datasets. When feasible, animal models are preferred to sire or sire–maternal grandsire models because they provide estimates of cow breeding values, as well as those of bulls.

2.2 Milk somatic cell count

Somatic cells in milk are primarily leukocytes or white blood cells but also include sloughed epithelial (milk-secreting) cells. Epithelial cells are always

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present in milk at low levels as a result of the replacement of old with new cells, with normal milk SCC levels being lower than 50 000. White blood cells are present in milk in response to tissue damage and/or clinical and subclinical infections. As the degree of damage or the severity of infection increases, so does the level of white blood cells. Reduced SCC is associated with lower incidence and fewer clinical episodes of clinical mastitis; greater quality and shelf life of dairy products; increased cheese yield; and higher premium payments for milk quality. Hadrich et al. (2018) found that persistent SCC above 100 000 cells/mL results in lost milk yield ranging in value from US$1.20/cow/day in the first month of lactation to US$2.06/cow/day in the tenth month of lactation.

The International Dairy Federation (IDF, 2013) provides a comprehensive set of guidelines for the measurement and interpretation of milk SCC. Thresholds for declaring that a cow is likely to have mastitis based on quarter- or cow-level SCC based on those guidelines are presented in Table 2. A bulk tank SCC threshold also is provided, and herds exceeding that limit could lose their ability to market their milk. However, it is important to note that these thresholds are not absolute indicators of infection, and animals exceeding these limits should be interpreted as having a higher risk of mastitis.

Can SCC be reduced to the point that cows are at increased risk of infection? This question was hotly debated when genetic evaluations for SCC were proposed because SCC is associated with innate immune responses to infection (Wellnitz and Bruckmaier, 2012), and it does appear that some herds with very low average SCC may have reduced ability to respond to clinical infections (e.g. Suriyasathaporn et al., 2000; Beaudeau et al., 2002), although the precise meaning of 'very low' varies from study to study. An average below 50 000 cells/mL is often considered undesirable by mastitis experts. This can be managed in a genetic programme by using selection index theory in a couple of different ways. First, if the average SCC in a population has reached a desirable level, then restricted selection index (Kempthorne and Nordskog, 1959) can be

Table 2 Recommended thresholds for quarter, cow and bulk tank somatic cell counts likely to indicate the presence of clinical mastitis

Level of measurement	Threshold (cells/mL)	Interpretation	Source
Quarter (teat) level	100 000	Above this level, a quarter is likely to be infected	IDF (2013)
Cow level	200 000	Above this level, a cow is likely to have an infected mammary gland	IDF (2013)
Bulk tank level	400 000	A 3-month geometric mean bulk tank SCC above this level should be placed on a watch list and monitored	Hillerton and Berry (2004)

used to maintain that genetic level. Another alternative is to use a non-linear selection index to assign higher weight to animals with breeding values near the optimum (Thompson, 1980), which is intermediate between very high and very low SCC. It is important to emphasize that the heritability of SCS, a $\log_2$ transformation of SCC used in the United States for genetic evaluation, has a heritability of only 12%, so most variation from animal to animal is due to management and other non-genetic factors.

2.3 Milking speed (milkability)

Strictly speaking, milking speed is not a measure of udder health. Rather, it measures a physical property of the udder – how fast the milk flows from each quarter into the milking unit – that may be associated with udder health. It is of interest to this discussion because milking speed data are routinely collected by many milking systems and stored in on-farm computer systems. Genetic correlations of SCS with milking speed generally are moderate and antagonistic (e.g. Zhang et al., 1994; Boettcher et al., 1998; Rupp and Boichard, 1999), which suggests that the optimal milking speed may have an intermediate optimum. Cows that milk too quickly may have elevated risk of intramammary infections, while cows that milk very slowly disrupt milk procedures. The latter case is of growing concern as more farms switch to robotic milking, where there is a need to minimize the number of milking unit purchases while ensuring that robots are available when cows want to be milked.

Milking speed has appeal as a correlated trait because, on many farms, the cost of data collection is minimal. However, there is no consistent scale used for milking speed across models within a manufacturer, or across manufacturers. Even systems which record actual (wall clock) milking times may produce records that are not generally comparable because of differences in when during the milking process recording begins and ends. Some national genetic evaluations for milkability are based on qualitative (Wiggans et al., 2007), rather than quantitative, scales. Such scales generally express milking speed in discrete categories ranging from 'much slower than average' to 'much faster than average'.

2.4 Udder conformation

Linear scoring of udder conformation is recommended by the World Holstein Friesian Federation (WHFF[1]) and International Committee for Animal Recording (ICAR[2]). A full description of conformation traits is given in Section 05 of the

1 http://www.whff.info/documentation/typeharmonisation.php#go1
2 http://www.icar.org/Guidelines/05-Conformation-Recording.pdf

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ICAR Guidelines, as well as in the WHFF report 'Progress of type harmonisation, May 2016',[3] and traits should be scored according to those recommendations.

Genetic correlations of udder depth and fore udder attachment with SCS and clinical mastitis suggest that these traits should be included in selection indices to help improve udder health. Some teat conformation traits (e.g. Seykora and McDaniel, 1985), which are not routinely scored, have also been associated with the ability of the mammary gland to resist infection by preventing the infiltration of microorganisms through the teat canal. It is possible that some of these traits may be routinely recorded in the future because teat conformation is important in the context of automated (robotic) milking systems (Jacobs and Siegford, 2012).

3 New phenotypes for improving resistance to clinical mastitis

Several of the phenotypes described in this section are not 'new' in the sense of being recently discovered, but advances in technology now make their direct or indirect measurement on a large scale feasible, when it previously was not. Ideally, new traits will have low genetic and phenotypic correlations with existing traits (there is a lot of additional information in the new observations), or the cost of recording will be very low so that many new phenotypes can be collected rapidly to provide high-reliability predicted transmitting ability (PTA).

3.1 Electrical conductivity of milk

Electrical conductivity is measured by most modern milking systems, and milk produced by cows with mastitis has higher conductivity than milk from healthy animals because of increased Na^+ and Cl^- levels (Norberg et al., 2004). Conductivity measurements at milking can also be compared with previous measurements to identify changes consistent with subclinical mastitis. However, studies show substantial variation in both sensitivity (true positive rate) and specificity (true negative rate), although modern milking systems that take measurements at the quarter level produce better results than systems that pooled milk samples. Norberg et al. (2004) showed that simple thresholds can be used to differentiate between healthy, subclinical and clinical cows with reasonable sensitivity and specificity. For example, a threshold of 1.15 applied to the inter-quarter ratio between the maximum and minimum averages of the 20 highest valid electrical conductivity measures taken during a milking correctly classified 80.6% of clinically and 45.0% of subclinically infected cows, as well as 74.8% of the healthy cows. More sophisticated models may provide

3 http://www.whff.info/documentation/documents/progressoftypeharmonisationversionafterBuenosAiresv2.pdf

higher sensitivity and specificity at the cost of greater complexity (Norberg, 2005).

3.2 Lactoferrin

Lactoferrin is an iron-binding glycoprotein naturally present in milk that is a major component of the mammalian innate immune system (González-Chávez et al., 2009), and it also is released by neutrophils during inflammation. Elevated lactoferrin levels are, therefore, indicative of a physiological response to infection and may be used to diagnose clinical mastitis (Shimazaki and Kawai, 2017). Soyeurt et al. (2012) showed that MIR spectroscopy can be used to cheaply and rapidly predict milk lactoferrin content, which may be useful as an indirect indicator of mastitis. Lactoferrin is significantly higher in cows with clinical mastitis than those without, and there also appear to be differences between animals with environmental and infectious mastitis (Kawai et al., 1999). Healthy cows averaged 169 μg/mL of lactoferrin, cows with subclinical mastitis averaged 495 μg/mL, and animals with clinical mastitis averaged 895 μg/mL. Differences in lactoferrin concentration were significant for each of these groups. Soyeurt et al. (2012) proposed a threshold of 200 μg/mL of lactoferrin to differentiate between healthy and sick animals.

3.3 N*-acetyl-β-*D*-glucosaminidase*

N-acetyl-β-D-glucosaminidase (NAGase) is a lysosomal enzyme that is released into milk from neutrophils during phagocytosis and cell lysis, as well as from damaged epithelial cells (Pyörälä, 2003). Hovinen et al. (2016) reported that NAGase activity can be used to detect both subclinical and clinical mastitis with high levels of accuracy, although Nyman et al. (2016) reported that SCC was the best overall predictor of intra-mammary infection. If the cost of recording NAGase levels is competitive with that of SCC and can easily fit into a milk-testing laboratory's workflow, then there may be value in routinely recording the phenotype.

3.4 Pathogen-specific mastitis

Pathogens associated with contagious mastitis (e.g. *Staphylococcus aureus*) produce different patterns of SCC than do pathogens associated with environmental mastitis (e.g. *Escherichia coli*, *Streptococcus uberis*). This is because different pathogens stimulate responses by different parts of the immune system (innate versus adaptive responses; e.g. Schukken et al., 1997). Bacteriological cultures are not routinely used to identify the causative organism for cases of clinical mastitis, and the cost of doing so is likely to prevent such

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data from being available for routine genetic evaluation. Patterns of infection differ among pathogens, with some species (e.g. *E. coli*) being primarily responsible for clinical infections, while others (e.g. *S. aureus*) are primarily responsible for subclinical infections (Schukken et al., 1997). Knowledge of the causative pathogen could provide useful information for modelling clinical and subclinical mastitis with greater precision. Pathogen information from the mastitis laboratories are recorded routinely in Norway (Haugaard et al., 2012), Denmark (Sørensen et al., 2009), Sweden (Holmberg et al., 2012) and Finland (Koivula et al., 2007). This information can be combined with other relevant information, such as CM or SCC, to define pathogen-specific mastitis for individual cows.

3.5 Patterns of somatic cells in milk

De Haas et al. (2008) compared several traits computed from test-day SCC and patterns of peaks in SCC against lactation-average SCC for their ability to detect clinical mastitis. The heritabilities of the new traits ranged from 0.01 to 0.11, and genetic correlations with clinical and subclinical mastitis ranged from 0.60 to 0.93 and 0.55 to 0.98, respectively. Different patterns of SCC are associated with different pathogens, and adding that information to models could improve prediction accuracy. However, monthly intervals are too long to capture changes in SCC due to organisms such as *E. coli* that cause rapid, acute infections. An important point noted by de Haas et al. (2008) and others (e.g. Schepers et al., 1997) is that log transformation of SCC to produce an SCS tends to reduce high test-day SCC. More recently, Bobbo et al. (2018) found that novel traits derived from SCC had heritabilities at least as large as SCS but were sensitive to environmental effects. New traits may be useful for improving current over previous lactation udder health, but care is needed to ensure that models properly account for environmental factors. Test-day SCC records should be stored in addition to SCS records so that patterns in SCC can be analysed, as well as lactation average SCC.

3.6 Differential somatic cell count

The distribution of leukocytes (white blood cells) is different in milk from healthy and infected mammary glands (Nickerson, 1989). Differential somatic cell counts (DSCCs) are used to quantify the proportions of different types of cells in the mammary gland and may be used to identify cases of subclinical mastitis that cannot be detected by SCC alone (Pilla et al., 2013). Patterns of DSCC also may be used to distinguish between acute and chronic mastitis (Leitner et al., 2000). Piepers et al. (2009) described a method for the flow cytometric quantification of the proportion of viable, apoptotic and necrotic polymorphonuclear neutrophilic leukocytes in cow's milk that can serve as the basis of automated,

routine phenotype collection. Subsequent research has also shown that DSCC can be used to identify inflammatory responses in quarters that are classified as healthy based on overall SCC (Schwarz et al., 2011). Damm et al. (2017) recently demonstrated that DSCC and SCC can be reliably and repeatably estimated simultaneously, at low cost, in commercial milk-testing laboratories using a method developed by Foss Analytical A/S (Hilleroed, Denmark; Holm, 2013). The principal obstacle to the adoption of routine DSCC now appears to be the availability of suitable equipment in testing laboratories. The Fossomatic 7 DC and CombiFoss 7 DC instruments now support routine collection of DSCC, and it is anticipated that other manufacturers will develop their own products that will provide similar analyses.

Schwarz (2017) suggested that a DSCC threshold of 75% could be used to distinguish between active and inactive inflammatory responses but noted that a two-factor classification system involving both SCC and DSCC is more useful for categorizing test-day milk samples. Such a scheme is described in Table 3 and allows users to differentiate among clinical and chronic infections, as well as subclinical cases of mastitis.

3.7 Thermal imagery

Berry et al. (2003) showed that infrared thermography (IRT) could be used to predict actual udder surface temperatures and proposed that thermal imagery could be used as a predictor of inflammation associated with mastitis. This is appealing because the cost of thermal imagers has decreased steadily over the last several years, which enables their use in precision dairy settings. Colak et al. (2008) reported that IRT can be used to differentiate between udder surface temperatures that are associated with varying degrees of infection, and subsequent studies (e.g. Hovinen et al., 2008; Bortolami et al., 2015) supported these findings but found that IRT data are not useful for identifying causal organisms of infection. If the cost of installing thermal cameras is sufficiently low, changes in udder skin surface temperature identified using IRT may be a useful mastitis indicator, particularly when combined with other data on animal behaviour and milk composition.

Table 3 Decision support grid for classifying mastitis status based on somatic cell count (SCC) and differential somatic cell count (DSCC) measurements

	Low DSCC (≤75%)	High DSCC (>75%)
Low SCC (≤100 000 cells/mL)	Normal/healthy mammary gland	Onset/early stage of clinical mastitis (SCC <100 000 cells/mL and elevated proportions of PMN)
High SCC (>100 000 cells/mL)	Chronically infected cows	The cow's immune system is actively fighting mastitis pathogens

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3.8 Collection of new phenotypes

The expected benefit of developing large reference populations for new phenotypes is unclear and will be closely associated with the cost of data collection. The most promising phenotypes may be indirect predictors developed from mid-infrared spectral data because many milk-testing laboratories are now equipped with instruments for that analysis. However, there is still infrastructure needed for calibration, data collection and data transfer before that information can routinely feed into genetic improvement programmes. If the cost of on-farm sensors continues to decrease rapidly, we may see a substantial increase in per-milking SCC data collected before spectral data gain ground. Regardless of the technology, there has to be a clear benefit to farmers from new data if they are being asked to pay for it. The best way to collect phenotypes for new traits may be to pay for extensive phenotyping in a small group of herds with high-quality data (e.g. Chesnais et al., 2016; Schöpke and Swalve, 2016), but the discussion remains largely theoretical at this time.

4 National and international genetic improvement programmes for resistance to clinical mastitis

4.1 International evaluations

The International Bull Evaluation Service (Interbull, Uppsala, Sweden) distributes genetic evaluations for SCC and clinical mastitis for Holsteins in member countries. Twenty-seven countries (Australia, Belgium, Canada, Croatia, Czech Republic, Denmark & Sweden & Finland, Estonia, France, Germany & Austria & Luxembourg, Great Britain, Hungary, Ireland, Israel, Italy, Japan, Latvia, Lithuania, the Netherlands (including the Belgium Flemish region), New Zealand, Poland, Portugal, Republic of Korea, Republic of South Africa, Slovenia, Slovak Republic, Spain and Switzerland) currently participate in the Interbull SCC evaluations, and five (Canada, Denmark & Sweden & Finland, France, Great Britain, the Netherlands (including the Belgium Flemish region)) in the clinical mastitis evaluations. The United States has submitted data for the August 2018 test run but is not yet an official participant in the clinical mastitis evaluations. International evaluations are not available for other breeds due to the limited number of daughter records available for health traits in non-Holstein populations.

4.2 Total merit indices

Many countries use total merit indices (TMI) as their national selection objective. Selection indices (e.g. Cole and VanRaden, 2018) combine information about

many traits into a single criterion that can be used for ranking and selecting animals. Indices differ from one country to another because economic conditions, farm policies and markets differ. Figure 2 shows the weights assigned to different traits and trait groups in the TMI of 21 different countries. While there are similarities between indices, there are also substantial differences. For example, the US lifetime net merit index (NM$; Cole and VanRaden, 2018) has almost no weight on mild yield, but the US fluid merit index includes substantial weight on milk. These differences reflect differential payment for milk components in different parts of the US. Every index shown includes selection for improved udder health, either indirectly through SCS or directly for udder health traits.

Changes in rates of genetic change after adding new traits to a selection index may be more limited than initially assumed because of correlations among traits. Table 4 shows correlations of PTA for six health traits in US Holsteins with several production, fertility and fitness traits. Absolute correlations with traits already evaluated range from lows near 0.15 to a high near 0.70. Notably, correlations with longevity (productive life) and fertility (daughter pregnancy rate) are fairly high, which means that there has been selection for improved disease resistance in the US Holstein population for many years despite the lack of direct measures of health for most of that time. Clinical mastitis also has a significant correlation with SCS, which has been in the NM$ index since 1994, and the genetic trend for clinical mastitis shows a favourable trend (Fig. 3) that is due, in part, to correlated response to selection for reduced SCS. The 2017 version of NM$, which did not include the six direct health traits, had a correlation of 0.47 with the PTA for HTH$, which is the lifetime value of all health costs for an individual (VanRaden, Cole and Parker Gaddis, 2018). This is virtually identical to the correlation of the 2018 revision, which does include the health trait, with an HTH$ of 0.46.

4.3 Effects of indicator traits in selection indices

The accuracy of a selection index is based on the genetic parameters of the individual traits in the index, as well as the phenotypic and genetic correlations of the individual traits with one another. When heritabilities and/or correlations of new with existing traits are low, then the reliabilities may be reduced, even if the new traits are more related biologically to the true phenotype of interest. Less-precise traits with large numbers of existing observations may also produce higher reliabilities than more-precise traits with few observations. These issues have been explored in detail by Gonzalez-Recio et al. (2014).

For example, the United States recently introduced genomic evaluations for health traits to complement existing evaluations of health, fertility and longevity (VanRaden et al., 2018). The heritability of SCS is 12%, but the

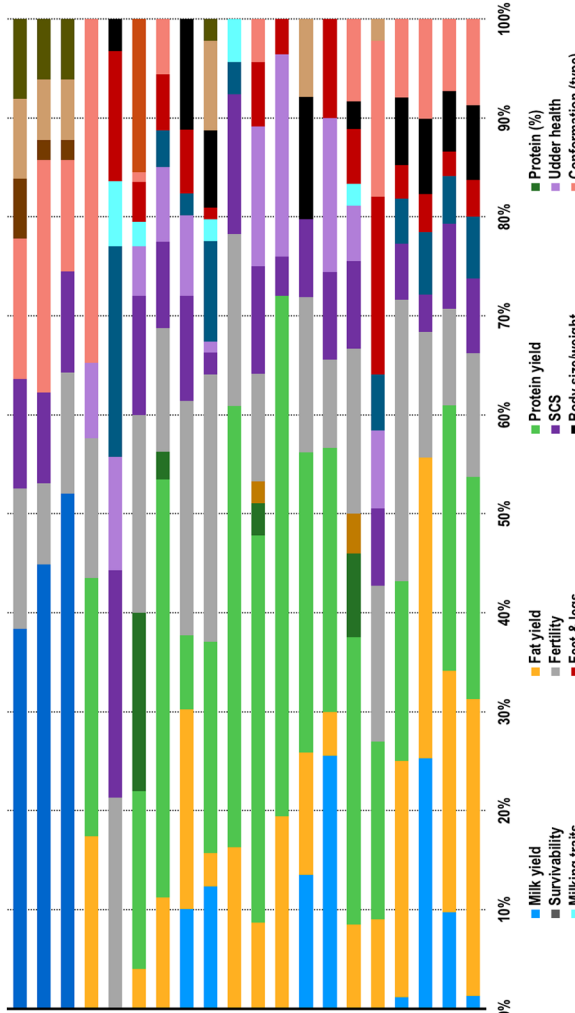

Figure 2 Traits included in 21 total merit indices of the United States and 16 other countries. Data were collected from genetic evaluation centres and purebred cattle associations for Australia (ADHIS, 2014); Canada (CDN, 2017); Denmark, Finland and Sweden (NAV, 2017); France (Genes Diffusion, 2014); Germany (VIT, 2017); Great Britain (AHDB Dairy, 2017); Ireland (ICBF, 2017); Israel (SIÓN, 2015); Italy (ANAFI, 2016); Japan (Holstein Cattle Association of Japan, 2010); New Zealand (DairyNZ, 2017); Spain (CONAFE, 2016); Switzerland (Holstein Association of Switzerland, 2013); the Netherlands (CRV, 2017); and the United States (Holstein Association USA Inc., 2017; VanRaden, 2017). Index abbreviations are HWI = health weighted index; TWI = type weighted index; BPI = balanced performance index; LPI = lifetime profit index; NTM = Nordic total merit; GDM = genes diffusion merit; RZG = Relativ Zuchtwert Gesamt (total merit index); £PLI = profitable lifetime index; EBI = economic breeding index; PD11 = Israeli 2011 breeding index; PFT = production, functionality and type index; NTP = Nippon total profit; BW = breeding worth; ICO = Índice de Mérito Genético Total (total genetic merit index); ISEL = Index de Sélection Totale (total selection index); NVI = Netherlands cattle improvement index; TPI = total performance index; GM$ = grazing merit; FM$ = fluid merit; CM$ = cheese merit; NM$ = net merit. Source: after Fig. 4 in Cole and VanRaden (2018).

Table 4 Correlations of six producer-recorded health traits in US Holsteins with protein yield (PRO), productive life (PL), cow livability (LIV), somatic cell score (SCS), daughter pregnancy rate (DPR), cow conception rate (CCR) and heifer conception rate (HCR)

Health trait	PRO	PL	LIV	SCS	DPR	CCR	HCR
Hypocalcaemia	0.18	0.15	0.19	*–0.29*	0.003	0.01	0.02
Displaced abomasum	0.23	*0.35*	*0.47*	–0.13	*0.32*	*0.28*	0.24
Ketosis	0.03	0.33	0.27	–0.19	*0.59*	*0.49*	0.07
Mastitis	0.06	*0.39*	*0.22*	*–0.68*	*0.20*	*0.21*	0.06
Metritis	0.05	*0.32*	*0.26*	–0.09	*0.46*	*0.41*	*0.23*
Retained placenta	–0.03	*0.17*	*0.13*	–0.10	*0.14*	*0.13*	*0.12*

Correlations for hypocalcaemia and retained placenta were calculated using PTA bulls born since 1990 with reliability of 75%. All other correlations were calculated using PTA for bulls born since 1990 with reliability ≥90%. Italicized correlations are different from 0.
Source: Council on Dairy Cattle Breeding, Bowie, Maryland, USA.

heritability of the health sub-index (which includes CM) is only 1%. Phenotypic correlations with existing traits range from 1% to 28%, and genetic correlations with existing traits range from 1% to 56%. However, there are approximately 2 million CM records on 1.1 million Holstein cows, and there are more than 56 million SCS records from 23 million Holstein cows. If the less-precise trait

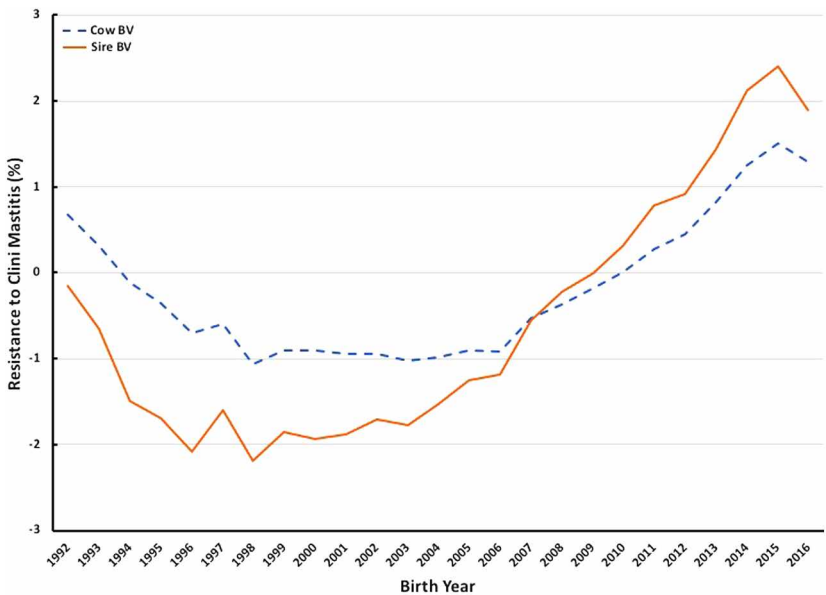

Figure 3 Genetic trend for resistance to clinical mastitis in US Holsteins. Data source: Council on Dairy Cattle Breeding, Bowie, Maryland, USA.

(SCS) was replaced with the more-precise trait, the reliability of the resulting index values would be lower and genetic progress would be reduced relative to an index that includes both.

5 Increasing rates of genetic gain through genomic selection

The rapid adoption of genomic selection by all of the major dairy-producing countries (e.g. Wiggans et al., 2017) has resulted in dramatic decreases in selection intervals and increases in rates of genetic gain (García-Ruiz et al., 2016), and has also supported the development of national evaluations for low-heritability traits with a limited number of phenotypes available (e.g. Pryce and Daetwyler, 2012; Gaddis et al., 2014; Chesnais et al., 2016). The success of this approach is demonstrated in Fig. 4, which shows selection differentials of SCS in US Holsteins for the four paths of selection (lower SCS is desirable, so negative selection differentials are favourable). There is a substantial increase in the rate of change of selection differentials following the launch of genomic evaluations in 2009. As a result of this new selection tool, genetic merit for resistance to mastitis and SCS of sires of bulls and cows and dams of bulls rapidly increased in the US (Figs. 1 and 3).

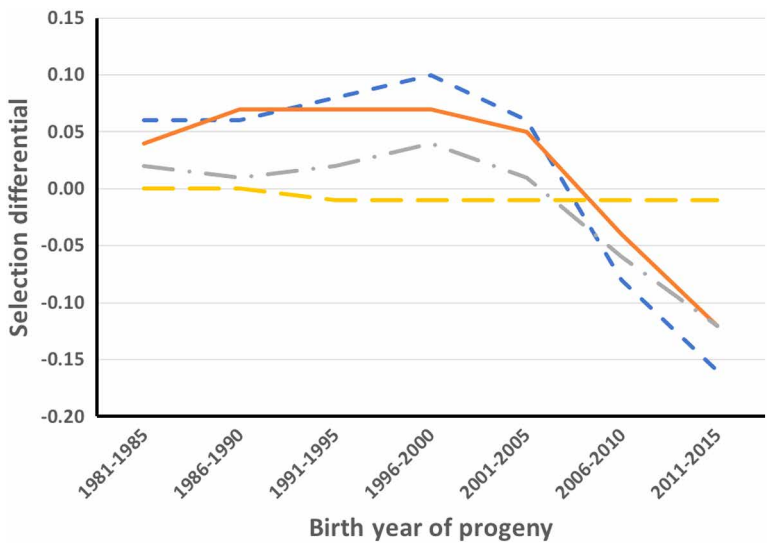

Figure 4 Selection differentials for somatic cell score of the sires of bulls (broken blue line), sires of cows (solid orange line), dams of bulls (dotted-and-dashed grey line) and dams of cows (long dashed yellow line) paths in US Holsteins for 5-year windows between 1981 and 2015. Source: figure created by author from values in Table S2 of García-Ruiz et al. (2016).

Table 5 Mean reliability (%) of traditional and genomic evaluations of young and progeny-tested bulls for six producer-recorded health traits of US Holsteins

	Progeny-tested bulls[a]			Young bulls[b]		
Health trait	Traditional	Genomic	Gain	Traditional	Genomic	Gain
Hypocalcemia	20.0	44.2	24.2	10.9	40.0	29.1
Displaced abomasum	25.7	47.1	21.4	14.6	41.8	27.2
Ketosis	24.0	46.2	22.2	13.4	41.2	27.8
Mastitis	33.3	56.3	23.0	18.3	49.4	31.1
Metritis	27.6	48.1	20.5	15.4	42.2	26.8
Retained placenta	25.6	46.7	21.1	14.2	41.6	27.4

[a] Progeny-tested bulls proofs include daughter information.
[b] Young bull proofs include only parent average and genomic information.
Source: Council on Dairy Cattle Breeding, Bowie, Maryland, USA.

Some countries, such as Norway, have been collecting health data for decades (e.g. Heringstad and Østerås, 2013) and can compute breeding values with reasonable reliabilities for proven bulls. In other countries, data have been available for a much shorter amount of time and, without genomics, reliabilities for most bulls are too low for publication. Table 5 shows the reliability gains for six health traits for US Holstein cattle. The average reliability of clinical mastitis, which has a heritability of 0.03 in that population, increased by 23.0 in proven bulls and 31.1 in young bulls, resulting in average genomic reliabilities of 56.3 and 49.4. These values are similar to those of longevity and fertility traits that are routinely evaluated in the US (VanRaden et al., 2009). This provides an opportunity for countries with shorter histories of data collection to compute useable evaluations for health and fitness traits, such as resistance to clinical mastitis.

5.1 Opportunities for marker-assisted selection

If causal DNA variants with large effects on individual traits can be identified, then marker-assisted selection can be used to increase the frequency of these desirable alleles (e.g. Dentine, 1992). Quantitative trait loci (QTL) associated with udder health have been mapped to many regions of the genome, including chromosomes 6, 11, 13, 14, 18, 20, 24 and 29 in various Holstein populations (e.g. Ashwell et al., 1996; Schrooten et al., 2000; Klungland et al., 2001; Kuhn et al., 2003; Sahana et al., 2013; Tiezzi et al., 2015).

The Animal QTL Database (AnimalQTLdb[4]) provides an exhaustive list of putative QTL associated with CM, SCC and SCS collected from the literature.

4 https://www.animalgenome.org/cgi-bin/QTLdb/index

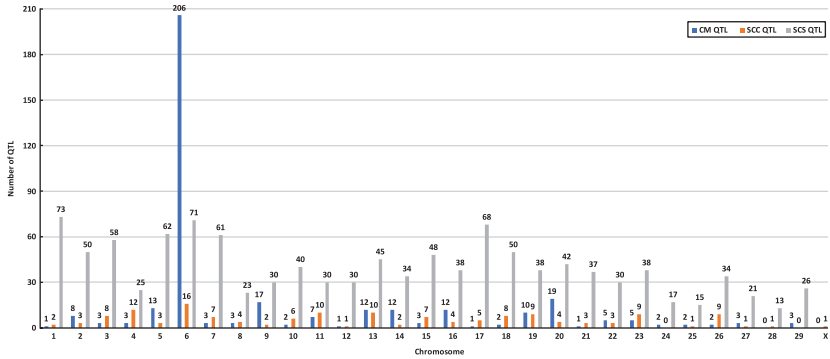

Figure 5 The number of quantitative trait loci (QTL) in the Animal QTL Database on each bovine chromosome for clinical mastitis (CM), somatic cell count (SCC) and somatic cell score (SCS). Note that these results include all breeds represented in the database, and QTL may overlap across studies. Source: figure created by author using data retrieved from AnimalQTLdb: https://www.animalgenome.org/tmp/map554722875.txt.gz, https://www.animalgenome.org/tmp/map121076229.txt.gz and https://www.animalgenome.org/tmp/map185863377.txt.gz.

The large number of QTL identified precludes an exhaustive discussion of them all, but Fig. 5 shows the number of entries in AnimalQTLdb for three udder health traits. While it appears that there are, in general, many more QTL associated with SCS than CM or SCC, that is because there are so many studies on SCS. Each QTL region identified is reported in AnimalQTLdb, which inflates the counts.

6 Conclusion

The major gap to be bridged in order to produce cows that are more genetically resistant to clinical mastitis is that between research and production. The phenotypes most commonly used in genetic improvement programmes are those that are the easiest to measure in many cows, such as SCC. However, those traits will not result in the highest rates of genetic gain because they share only some of the same biological mechanisms in common. While researchers continue to identify more precise measurements of individual infection status, the cost of phenotyping often is high, and many require the purchase of specialized equipment.

The focus of this chapter has been on genetic improvement, but the role of herd management should not be overlooked. As the low heritabilities of different measures of clinical mastitis attest, most of the variation among individuals and between farms is attributable to environmental differences. Management practices that minimize the ability of pathogens to survive on the

farm, and which limit transmission from animal to animal, should be identified and promoted in conjunction with genetic improvement programmes.

7 Future trends in research

International efforts such as the Functional Annotation of Animal Genomes project (Andersson et al., 2015) are working to identify true variants that can be used as targets for genomic selection and gene editing. The identification of key regulatory elements also may provide new therapeutic targets that can be used to improve mastitis resistance. As briefly discussed above, research also continues on new technologies that can be used to rapidly phenotype many individuals. Those phenotypes will support both improved on-farm decision-making as well as genetic improvement programmes.

There is tremendous interest in the use of new molecular biology tools, such as clustered regularly interspaced short palindromic repeats (i.e. CRISPR-Cas9), to make precise, highly targeted changes to animals' genomes. Such approaches may be more acceptable to consumers and regulatory agencies than previous transgenic approaches (e.g. Wall et al., 2005). Some gene-edited products have recently reached the US marketplace (Ledford, 2015; Waltz, 2016), but considerable uncertainty remains about the manner in which gene-edited plant and animal products will be regulated (Maxmen, 2017).

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9 Where to look for further information

9.1 Introductory works

'Current Concepts of Bovine Mastitis', published by the National Mastitis Council,[5] provides an excellent overview of the topic of mastitis. This is a seminal work on the subject that is recommended to anyone interested in udder health.

5 https://www.nmconline.org/publications/

9.2 Key societies

Important international organizations include the American Dairy Science Association,[6] International Committee for Animal Recording,[7] International Dairy Federation[8] and National Mastitis Council.[9] The International Bull Evaluation Service[10] focusses strictly on genetic evaluation practices, which are critical for long-term improvements to mastitis resistance. These organizations publish scientific journals, organize meetings and promote international standards to improve animal health and milk quality.

9.3 Key journals and conferences

The *Journal of Dairy Science*[11] is the most prominent scientific publication in the field, and there are frequently multiple sessions on mastitis at the American Dairy Science Association Annual Meeting. The National Mastitis Council holds an annual meeting specifically on mastitis and related topics, and the *National Mastitis Council Annual Proceedings*[12] commonly publishes reports on cutting-edge research before its publication in peer-reviewed journals. Interbull publishes the *Interbull Bulletin*[13] and hosts annual meetings and workshops, which often include technical reports on genetic evaluation methodology for traits related to mastitis resistance.

9.4 Other resources

The Animal QTL Database (AnimalQTLdb[14]) provides extensive information on putative QTL related to clinical mastitis, SCC and SCS assembled from more than 800 scientific publications. This is an excellent resource to identify genomic regions that have large effects on udder health traits, and it is frequently updated.

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8 https://www.fil-idf.org/
9 https://www.nmconline.org/
10 http://www.interbull.org/index
11 http://journalofdairyscience.org/
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