J. Dairy Sci. TBC
https://doi.org/10.3168/jds.2023-23958

# Perspective: Can we actually do anything about inbreeding?

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## INTRODUCTION

Artificial insemination (**AI**) companies create elite genetics in the form of frozen semen and embryos for use in dairy cattle genetic improvement programs. The most-marketable bulls are those with the highest genetic merit (Hutchins et al., 2023) and, in addition to hundreds or thousands of milking daughters, elite bulls may have dozens of sons that themselves are used for AI. This intensive within-family selection also produces ever-increasing levels of relationship which results, ultimately, in more inbreeding. As a result, reducing – or even limiting – inbreeding often means the selection of lower-index bulls. As the rate of adoption of advanced reproductive procedures grows (Doublet et al., 2020) and long-term technologies such as in vitro breeding (Kasinathan et al., 2015) continue to develop, selection intensities on dams of bulls and dams of cows may dramatically increase, further exacerbating the problem. The key question that the dairy genetics community is now faced with is, who is willing to slow the rate of genetic gain to better manage inbreeding?

## ARE WE WORRIED ABOUT NOTHING?

The literature provides many examples of the harmful effects of inbreeding (Doekes et al., 2021; Bertorelle et al., 2022; Gutiérrez-Reinoso et al., 2022) – or does it? A close examination of the research suggests that the reality is more complicated than "inbreeding is bad" (Charlesworth and Willis, 2009; Maltecca et al., 2020). It absolutely is true that excessive levels of inbreeding in a population can have harmful effects (e.g., Swett et al., 1949), but what is untrue is that all inbreeding is created equal and that there is a clear dividing line between "safe" and "unsafe." There is likely to be a tipping point, beyond which we do not want to pass, but its location is unknown. However, Lush (1945) suggested that generations of high-intensity selection might lead inevitably to high levels of homozygosity: "When the pure breeds finally reach equilibrium between the production of heterozygosis by mutations and the loss of heterozygosis because the effective number of animals in the breed is small, it is possible that the pure breed may support only a few scores of unfixed loci."

What we can do is compare changes in phenotypic performance under inbreeding (Table 1) with rates of genetic gain (Table 2) to assess the current situation, with the caveat that we're comparing phenotypic with genetic values. Table 1 contains estimates of inbreeding depression for 9 traits included in the Lifetime Net Merit selection index (VanRaden et al., 2021) for both 1% and 0.25% (the current annual rate at which inbreeding is increasing in the US Holstein population; https://webconnect.uscdcb.com/#/summary-stats/inbreeding-information). Annual genetic gains are greater than inbreeding depression in all but one case, daughter pregnancy rate, where there is a net decrease per year of 0.02 PTA units (0.02%). This does not mean that there is nothing to be concerned about, it only means that we are not yet losing ground. As the saying goes, when you're in a hole, stop digging – we need to take action before that.

## CAN WE ACTUALLY DO ANYTHING ABOUT IT?

Brotherstone and Goddard (2005) optimistically suggested that "Maintenance of genetic variation and long-term genetic gains would be aided by rational payment systems, use of crossbreeding where profitable, inclusion of all economically important traits in the breeding objective, recognition of genotype by environment interactions and the use of selection algorithms that balance estimated breeding value against the average relationship among the selected animals." It is true that all these things happened to some degree, but they are not sufficient to maintain heterozygosity in most dairy cattle populations. There is a fundamental conflict in our selection programs: the demand for elite genetics drives the ongoing loss of genetic diversity. Nobody is willing to slow down that chase and "elite" (high-index)

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Received July 12, 2023.
Accepted September 7, 2023.

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**Table 1.** Change in phenotypic performance per 1% (top row) and 0.25% (bottom row) increase in inbreeding.[1,2,3]

| M | F | P | PL | SCS | DPR | HCR | CCR | LIV |
|---|---|---|---|---|---|---|---|---|
| −33.1 | −1.22 | −0.95 | −0.28 | 0.01 | −0.22 | −0.21 | −0.30 | −0.10 |
| −8.3 | −0.30 | −0.24 | −0.07 | 0.0025 | −0.06 | −0.05 | −0.08 | −0.03 |

[1] M = milk (kg); *F* = Fat (kg); *P* = Protein (kg); PL = Productive live (mos.), DPR = daughter pregnancy rate (%), HCR = heifer conception rate (%), CCR = cow conception rate (%), and LIV = cow livability (%).

[2] Council on Dairy Cattle Breeding (https://webconnect.uscdcb.com/#/summary-stats/breed-means-bases-heterosis-inbreeding-regressions).

[3] The annual rate of change in inbreeding in the US Holstein population is ~0.25%.

bulls are no longer sufficient – they also must have favorable (above average) breeding values for milk, components, fertility, and many other traits. It is not possible for most marketed bulls to reach all of these thresholds, but it is commonly expected that they will.

It is easy, but not particularly worthwhile, to identify problems without offering solutions. In that spirit, here are some approaches that might be used to manage rates of inbreeding in dairy cattle populations. Some of these proposals are more feasible to implement than others, but each is offered in good faith.

## *Refine PTA adjustments*

Genetic evaluations in the US are adjusted to account for the expected effects of future inbreeding (VanRaden et al., 2005). Predicted transmitting abilities (**PTA**) for bulls highly related to the population are adjusted down (reduced) to account for inbreeding depression, and PTA for bulls less related to the population than average are adjusted up (increased) to account for favorable heterosis. The challenge with this approach is that the elite AI bulls which drive genetic change in the population are generally such extreme outliers that PTA adjustments based on estimated inbreeding effects are not large enough to cause notable reranking. Genetic evaluation models are tools for ranking animals for selection (Henderson, 1990), and *post hoc* adjustments lack theoretical justification.

## *Use the right metric*

The rates of inbreeding shown in Figure 1 may appear alarming but remember that genomic inbreeding measures both identity-in-state and identity-by-descent, while pedigree inbreeding includes only the latter. This difference is important because the chance of inheriting 2 undesirable alleles from the same ancestor is greater than that of the same mutation occurring independently in separate animals which are then inherited through separate paths. One way to reduce apparent rates of inbreeding is to revert to using pedigree inbreeding in place of genomic inbreeding. A more appealing approach is to move away from coarse measures of inbreeding, however they are calculated, and focus on "better" measures of diversity, such as runs of homozygosity (**ROH**; e.g., Gibson et al., 2006) or direct measures of identity-by-descent (**IBD**; e.g., Meuwissen and Goddard, 2010). The important point here is to take advantage of new technology and improved methods and adopt measurements that measure the quantities of greatest interest. Timing matters, and it is clear that old inbreeding is of less concern than recent inbreeding because older haplotypes have been purged of potential recessives (Kim et al., 2013; Makanjuola et al., 2020). Since ROH can be used to compute measures diversity account for the age of inbreeding, not just the probability of IBD segments irrespective of age, the former might be preferable to the latter.

## *Trim pedigrees*

The particular benefit of pedigree information is that it can be easily and cheaply recorded, but there

**Table 2.** Change in genetic potential per year when selecting on the 2021 version of Lifetime Net Merit (NM$).[1,2]

| M | F | P | PL | SCS | DPR | HCR | CCR | LIV |
|---|---|---|---|---|---|---|---|---|
| +57.5 | +3.5 | +1.9 | +0.49 | −0.02 | +0.03 | +0.15 | +0.15 | +0.25 |

[1] M = milk (kg); *F* = Fat (kg); *P* = Protein (kg); PL = Productive live (mos.), DPR = daughter pregnancy rate (%), HCR = heifer conception rate (%), CCR = cow conception rate (%), and LIV = cow livability (%).

[2] VanRaden et al. (2021; https://www.ars.usda.gov/ARSUserFiles/80420530/Publications/ARR/nmcalc-2021_ARR-NM8.pdf).

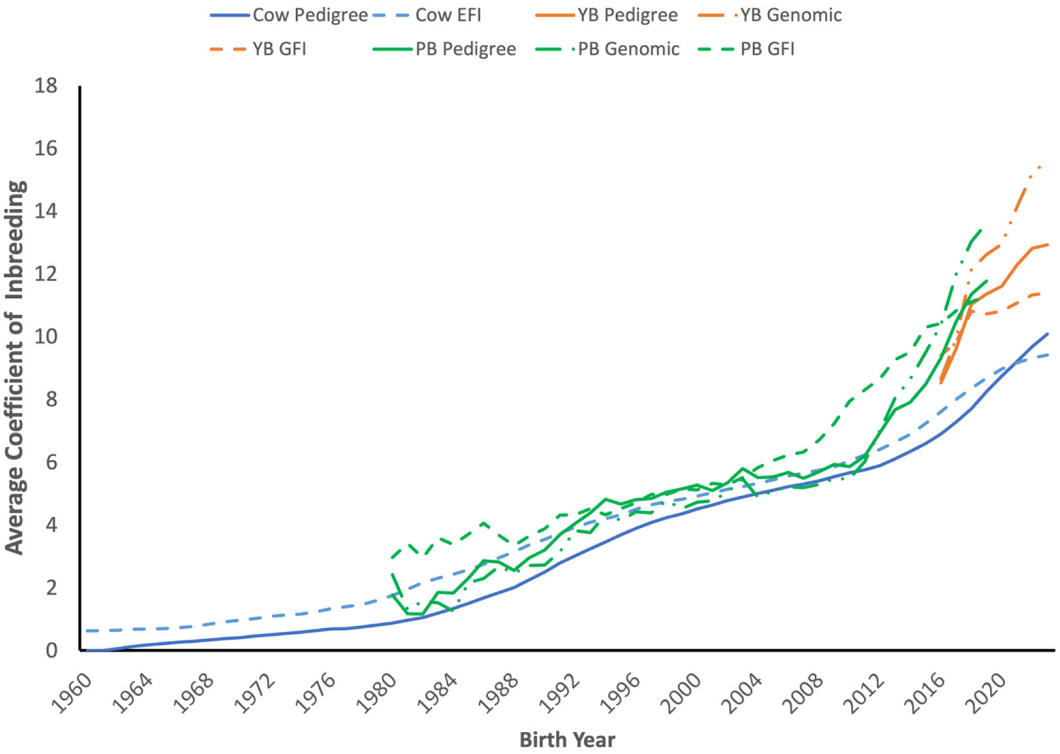

**Figure 1.** Pedigree and genomic inbreeding, expected future inbreeding (EFI), and genomic future inbreeding (GFI) for US Holstein cows and young (YB) and progeny-tested (PB) bulls (Council on Dairy Cattle Breeding, April 2023; https://webconnect.uscdcb.com/#/summary-stats/inbreeding-information).

are also many challenges that arise from these data: they are usually incomplete, true inbreeding is often higher than predicted, and true relationships among individuals are often underestimated. When computing inbreeding from pedigrees, all paths are traced back to some founder population that serves as a fixed reference point, not unlike the fixed and floating bases used in genetic evaluation models (Schaeffer, 2019). One easy way to reduce inbreeding is to trim pedigrees so that they go back only a certain number of generations (3 generations is an often-used default in software, but that feels very shallow). This is not a particularly controversial idea and is currently used by several national genetic evaluation centers (e.g., Italy, Slovakia, United Kingdom). A related option is to use a moving base year for inbreeding instead of a fixed reference year (the US uses 1960 as its base population). The effect of both these changes is to keep focus on recent inbreeding, which is most likely to result in inbreeding depression. Trimming pedigrees does not directly address rates of inbreeding, pedigree or genomic, in the population, but this idea is suggested because it might drive selection decisions away from the families with the highest rates of recent inbreeding, which are the lineages most likely to contain genetic load that has not yet been purged.

### *Stop publishing individual genetic values*

A recurring challenge in the field is that the bulls with the largest PTA are also those in greatest demand, regardless of how small differences among individual bulls actually are. Compounding this problem is an insistence by many farmers that independent culling levels (minimum trait thresholds) must be imposed on top of the selection index, further reducing the pool of “desirable” bulls and violating well-known principles of genetic improvement (e.g., Hazel and Lush, 1942). The net result of this is that the realized selection objective is not what it is believed to be (Simianer et al., 2023). One way to avoid this problem is to stop publishing PTA for individual traits; instead, bulls will be mated at random to the cow population. Alternatively, bulls can be assigned “red,” “yellow,” or “green” badges for each trait to indicate that they have “poor,” “average,” or “good” PTA, but it seems likely that everyone would then demand green badges across the board. If neither of these approaches is palatable, the PTA could be made available only to mate selection software and those values would not be viewable by users. Instead, the software would output ranked bull-cow pairs in order of their desirability. Homomorphic encryption allows calculations to be performed on encrypted data (Fontaine and Galand, 2007), so it is possible to "conceal" the PTA sent to software from the end-users (the PTA would be encrypted and not stored in plaintext that is human-readable). However, this is not a commonly used approach, implementation remains challenging, and it is difficult to find software developers with experience using these tools. Hiding PTA would be a substantial change over current practices and I do not think that most customers or salespeople would find this approach appealing because they are used to having access to genetic evaluations.

## Change the selection indices

Some measures of genetic diversity could be added to selection indices as a trait, resulting in direct selection pressure applied to heterozygosity. Adding this to the overall selection objective would mean that selecting high-index bulls would also include some selection for greater heterozygosity, as well, instead of hoping that inbreeding is considered in the mating process. However, this is just a less-efficient way of implementing optimal contribution selection (e.g., Clark et al., 2013), which has been carefully ignored in the US since it was proposed. It also is worth nothing a point made eloquently by Lush (1945): "Selection, however – in marked contrast to its effectiveness in changing average merit – is a very feeble tool for changing homozygosity, except under the very simplest genetic situations."

Varona et al. (2019) showed that an individual inbreeding load can be calculated for each animal in the population and proposed that a selection index including both breeding values and inbreeding loads could be used as the basis of an "artificial" purging system. This is a more appealing idea than adding an ad hoc measure of diversity to the index, and there is a clear theoretical framework to justify its use. It is not yet clear how economic weights would be assigned to the individual inbreeding loads. A logical starting point would be the cost of inbreeding depression calculated over each of the traits in the selection objective.

The adoption of optimal contribution in some areas, such as the USA, is not particularly controversial, so why has it not happened? It is more complex to program that the (often fairly simple) tools currently used by AI companies, and there is a perception that the benefits do not justify the added complexity. It also is true that many end-users of genetics are not willing to make the tradeoff between genetic trend and maintenance of heterozygosity that is at the heart of optimal contribution selection and, in a very competitive market, will simply purchase their semen and embryos from another company. Consumer expectations also differ, for example, between the EU and USA in ways that make adoption possible in one market and not another.

## Make outcrosses between genetic programs

The breeding programs operated by different AI companies are becoming different sub-populations within breeds because of genetic protection programs that prevent the exchange of germplasm. Lush (1945) noted, "A combination of moderate inbreeding alternating with occasional wide outbreeding is an effective plan for producing many distinct families which are moderately uniform within themselves." Continued divergence between nucleus programs could lead to rotational mating from each stud in turn, but it is not clear that these groups are different enough to produce "wide outbreeding," occasional or otherwise, because AI companies are all using similar breeding objectives. However, recent research by Steyn et al. (2023) suggests that there may be greater differences between families within a breed than previously supposed.

## Use terminal dairy embryos

Instead of selling semen to farmers, genetics companies could pivot to selling only embryos that represent ideal terminal dairy cows. In this case, each company would have its own "cross," which could be a true crossbred animal or some sort of within-breed cross. It would be possible to create embryos that have either no inbreeding (true crossbred animals) or which have very low inbreeding (within-breed crosses). This scheme still requires that someone maintain the purebred lines, and it will require a massive increase in the scale of dairy embryo transfer, but the rise of the embryo-centric world has been discussed for many years (Hansen and Block, 2003). This would result in a system that resembles contemporary swine production more than historical dairy cattle breeding (Kargo et al., 2022). While I do not think this is likely to occur at the scale seen in the swine and poultry sectors, I think it is likely that some genetic companies will start selling embryos into smaller-scale specialty markets, such as customers demanding high-genetic-merit polled genetics.

## Fix everything with gene editing

The tools used for gene editing continue to improve, resulting in greater efficiency of editing and the ability to "stack" multiple edits (Mueller and van Eenennaam, 2022). This could be a way to maintain rates of genetic gain without suffering adverse consequences or needing to depend on natural purging (Gulisija and Crow, 2007; McParland et al., 2009). Johnsson et al. (2019)

suggested that gene editing could be used to reduce or eliminate impacts of genetic load, creating a form of artificial purging. Clearly, there are many challenges to this approach, including our lack of knowledge of editing targets, our inability to routinely edit dozens or hundreds of simultaneous targets, and the ever-shifting regulatory landscape.

### *From the sky the highway's straight as it could be*

If we – meaning a partnership between the AI companies and the scientific community – wish to effectively address the challenges posed by inbreeding then we have to convince farmers of several points: 1) there is an actual problem to be solved, 2) the problem really needs to be solved, 3) our proposed solutions will work, and 4) they are not being asked to harm their livelihood by participating in this process. Items 1 and 2 may appear to be the same thing, but just because a problem exists does not mean that it needs to be solved – the magnitude of the problem matters. That is very relevant to this discussion of inbreeding because many farmers will agree that they are concerned about future impacts of inbreeding, but they do not necessarily agree that aggressive action needs to be taken today. There is also considerable skepticism that the people who "caused" the problem can be trusted to fix it, and there is widespread consensus that things work differently in the real world than they do on paper. Finally, there are concerns about that most of these solutions require that some genetic gain be sacrificed to preserve population diversity, and only one of those things – genetic potential – is widely believed to have an impact on farm profitability. Arguing about marginal costs at levels of inbreeding that are much higher than most producers see is not persuasive. This is a challenging situation because it is easier to propose solutions than it is to see them out into practice.

## DISCUSSION AND CONCLUSIONS

It seems likely that inbreeding will receive more attention in the future because of its impact on social license than its effects on production economics, placing it in that realm of increasingly complex problems with which society is faced. Most laypeople do not understand that there is a critical difference between inbreeding with strict selection on performance, as is practiced in livestock breeding programs, and inbreeding with no selection on performance. The latter scenario can lead to the health and fitness problems that many consumers have experienced first-hand with their pet dogs (Bannasch et al., 2021). Increased genetic load also compromises an animal's ability to adapt to changes, which is a concern as the climate changes, and we seek to increase the resiliency of animal production in more challenging environments.

When there is tight control throughout the production chain (as in typical pork and poultry breeding) genetic diversity can be managed effectively. Dairy cattle breeding is a loosely coupled system where that degree of control is lacking, and outcrossing is a logical approach to deal with genetic diversity challenges. It is clear, however, that neither farmers nor consumers will accept inaction on the topic of inbreeding. Effective population management will not be easy and will require changes on the part of AI companies, who need to find a way to exchange germplasm between breeding programs, and farmers, who will have to accept that there are strong bulls outside of the top 100 lists even if they sometimes have weaknesses as well as strengths.

## ACKNOWLEDGMENTS

The author thanks the Editor for the invitation to present this Perspective. Some of the ideas in this manuscript were presented at the 42nd ADSA Discover Conference, "Managing Genetic Diversity for Future Dairy and Livestock Breeding," and were shaped by discussions with colleagues that began there and, in some cases, have not yet reached a conclusion. Two anonymous reviewers are thanked for their helpful feedback, including an important clarification of a point misunderstood by the author.

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