Identification of functionally active genomic features relevant to phenotypic diversity and plasticity in cattle

Deliverable 8.1

THE SOCIETAL CONTEXT OF INNOVATIONS IN CATTLE GENOMICS

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This deliverable was completed and delivered late. The content of the deliverable conforms to the description of action in the BovReg project plan.

Dissemination and uptake

This deliverable concerns societal aspects of innovations in cattle genomics and should be available in the public domain. It will therefore be made available for consultation at the BovReg website.

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1. Summary of results

The BovReg project is an international research project, funded by an EU Horizon 2020 grant, that investigates the biological basis of traits of interest in cattle breeding. More specifically, it aims to map regions in the cattle genome as well as epigenetic factors that regulate how genes are expressed phenotypically. This should improve the scientific understanding of complex dairy and beef cattle traits, including traits relating to biological efficiency (the type and amount of feed required in the production of milk or meat and the amount of greenhouse gasses emitted), disease susceptibility (mastitis resistance), and robustness (fertility). BovReg also aims to develop tools by which this new knowledge can be integrated into breeding practices. By widening the set of biological indicators that can be used to predict the results of breeding decisions ('biology-driven genomic selection'), BovReg should enable breeding for these traits more effectively. In addition, BovReg should enable developing 'precision' breeding approaches, where breeding decisions are tailored to the biological features of individual cows, and making more accurate predictions when breeding with minority breeds.

The BovReg project includes a work package (WP 8) on societal and ethical issues associated with (biology-driven) genomic selection in cattle breeding. WP8 aims to promote a responsible innovation approach to livestock genomics that demonstrates an awareness and responsiveness to the societal challenges involved, and is an example of science for and with society. The current report, which is the first deliverable from that work package, situates the BovReg project in its wider societal context. It identifies potential opportunities for cattle breeding and considers why these opportunities are of interest according to scientists and breeders, evaluates (biology-driven) genomic selection from an EU law and policy perspective, and considers how genomic selection relates to societal concerns about (bio)technologies. This analysis also provides input for an analysis of the ethical aspects of (biology-driven) genomic selection in cattle breeding, to be delivered in a subsequent report (deliverable 8.2).

The report is based on desk study and a limited number of interviews, including 7 interviews with BovReg scientists, 3 with breeding association representatives, and 3

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with representatives from internationally operating animal advocacy NGOs. Although it presents a broad overview of BovReg's societal context, the current report mainly aims to provide a background to enable more in-depth discussion and ethical reflection on the use of (biology-driven) genomic selection in cattle breeding. The interviews were therefore not meant to deliver a comprehensive overview of the issues involved in cattle breeding and genomic selection. Rather, they served to inform the authors of the current state of scientific developments and their practical applications in cattle breeding and provided some preliminary societal perspectives. An initial round of interviews (with 7 BovReg scientists, 1 breeding association representative and 1 NGO representative) supported the desk study by suggesting relevant directions of inquiry, while a second round of interviews (with 2 breeding association representatives and 2 NGO representatives) complemented the desk study's findings by offering additional perspectives on the societal relevance of applications of (biology-driven) genomic selection in cattle breeding.

The current report is structured as follows. Section A sketches the current state of scientific knowledge underpinning genomic selection in cattle breeding and considers what is novel about the knowledge that BovReg aims to generate. Section B then presents scientists' and breeders' views on the opportunities that BovReg and similar projects create for cattle breeding. After discussing to what extent innovation in cattle breeding is constrained by (EU) legislation in section C, section D discusses the EU's common agricultural policy (CAP) and the values underpinning it. Drawing on this discussion, section E considers to what extent different applications of genomic selection in cattle breeding are supported by CAP. Finally, section F reviews previous public debates on (bio)technologies and discusses what these debates mean for the public acceptability of applying (biology-driven) genomic selection in cattle breeding.

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2. Introduction

Developments in the omics sciences are expected to improve genomic selection in livestock breeding and enable selection which draws upon a wider range of biological parameters ('biology-driven' genomic selection). This could enable a range of opportunities for cattle breeding. These include improvements in efficiency and animal health, breeding approaches for improving minority breeds, and the incorporation of new breeding goals (for example reduced emissions of methane). This deliverable addresses the societal context of potential innovations in cattle genomics: it considers relevant legislative and policy perspectives and anticipates possible public responses by drawing lessons from earlier debates on technologies.

EU legislation permits applications of genomic selection (including biology-driven genomic selection), unless these cause more than minimal or temporary pain or injury to the animals involved. The EU's Common Agricultural Policy (CAP) supports cattle breeding innovations that contribute to the EU's economic, environmental, societal, and ethical objectives. CAP does leave room however for discussion on the desirability of particular innovations in cattle breeding.

Genomic selection has not been a subject of high profile public debate, and in previous debates on genetically modified food, selective breeding was often presented as the more natural and acceptable way of improving the genetics of the organisms we rely on for food. But it cannot be inferred that genomic selection raises no public concerns at all. Its real or perceived connections to other technologies, including genome editing and reproductive techniques, are potentially relevant for public views on genomic selection. Although lay people generally see potential benefit in research and innovation, they may become more critical when innovations are in their view (i) not necessary or not beneficial for society, (ii) driven by inappropriate motives and interests, (iii) progressing too hastily, (iv) not sufficiently accountable to wider society, and/or (v) raises serious ethical concerns. Insofar as lay publics will have attention for genomic selection, their perceptions will presumably depend on both the purposes and the processes of innovation in genomic selection. Outside of deliberate public

engagement efforts, public attention for genomic selection will depend on the profile the issues are given among key NGOs and in the media. The analyses offered in the current report, although partly speculative, offer a broad background for public engagement and ethical reflection on (biology-driven) genomic selection in cattle breeding.

3. Core report

A. BovReg and its scientific context

Prior to the 'quantum leap' that was made by incorporating genomic selection (Seidel et al. 2020), animal breeding depended on selecting candidate breeding animals, making those candidates have a number of descendants, testing the performance of those descendants on traits of interest, and then continuing the breeding program with candidates whose descendants had overall the most desirable traits (Boichard & Brochard 2012). In dairy cattle breeding, for instance, the semen of candidate bulls would be collected and used to generate a hundred daughters. If these daughters were subsequently found to have desirable characteristics, such 'candidate' or 'waiting' bulls would qualify as 'proven bulls', which meant that they would be admitted into the breeding program to sire the next generation of cows in commercial farms and bulls in breeding programs. This way of selecting bulls did lead to 'genetic gain'; the performance of dairy cows on traits of interest (e.g. milk yield) did increase over generations. However, a significant time lag (6-6.5 years according to Pryce & Daetwyler 2012) was required to produce a hundred daughters, waiting for those daughters to reach an age at which the relevant traits would manifest, and testing their performance on those traits, which meant that there had to be a relatively long interval between one generation of breeding bulls and the next.

The introduction of genomics in breeding meant that the qualities of an animal's descendants could be estimated much earlier with higher accuracy and that the generation interval could be reduced (Lillehammer et al. 2011, Pryce & Daetwyler 2012). A prediction of the phenotypic qualities of an animal's descendants could now be obtained by statistically comparing (some of) the animal's genetic features to a reference population, that is, to a database correlating the genotypic and phenotypic traits of a large group of animals. Although such genomic predictions were initially less accurate than predictions based on progeny testing, they could be made at a very young age, or even before birth by genotyping embryos. This meant that breeding animals could be used to spawn the next generation as soon as they reached maturity or even earlier if advanced reproductive techniques were to be used (at 1.5 years for bulls

according to Pryce & Daetwyler 2012). Such a reduction in the generation interval would drastically speed up the genetic improvement of breeds in spite of the lower prediction accuracy, and prediction accuracy would moreover increase over time in an appropriately designed breeding program (Lillehammer et al. 2011). Many breeding programs have therefore embraced genomic selection. Still, BovReg and similar projects (see https://www.fabretp.eu/eu-projects.html) aim to improve the state of genomic science and to exploit its practical implications in breeding programs. So what are the lacunae in genomics and its application to animal breeding that science can try to address?

One current limitation concerns the availability of data on certain genotypes and phenotypes. Data is widely available on common breeds and commonly recorded phenotypes, which allows making accurate breeding predictions for those breeds and those phenotypes. However, for rare breeds and for phenotypes that are not assessed and recorded frequently, insufficient data may be available to predict the effects of breeding decisions accurately (Biscarini et al 2015). Collecting data on uncommon breeds and uncommonly measured phenotypes would be an obvious solution. However, the costs of such data collection may be prohibitive (Biscarini et al 2015), and some phenotypes of interest (e.g. phenotypes relating to methane emission or animal welfare) are difficult to measure or still lack a commonly accepted definition (Seidel et al 2020).

Another limitation is that genomic selection currently operates as a 'black box': although certain phenotypic traits are known to be *correlated* to certain genotypic variants, the *causal* relation between phenotype and genotype remains unclear. In case the correlation is strong, knowing the genotypes of young animals allows predicting their phenotypes with high accuracy, but the weaker the correlation, the higher the chance that predicting the phenotype of future generation animals will be less accurate. In addition, some traits of interest are known to be correlated negatively with other desired traits; high milk yield is for example known to be associated with both a lower fertility and a lower resistance to mastitis in Holstein dairy cows. Here too, part of the solution may be to collect more phenotypic and genotypic data. Larger sets of data could help to correlate phenotypes more reliably to particular genotypic variants and to

identify subpopulations for which negative associations between desirable phenotypes do not hold. However, the availability of large data sets of phenotypic and genotypic data may not be sufficient to make accurate genomic predictions. Phenotype and genotype may sometimes be weakly correlated not because their correlation has been calculated on the basis of limited phenotypic and genotypic data; the fact that phenotype is not determined by genotype alone may be the issue instead. As phenotype is determined by genotype *plus* factors regulating how the genotype is expressed phenotypically, a weak correlation between genotype and phenotype may be due to variation in those regulatory factors. Some factors regulating gene expression are part of the genotype and can therefore be found by correlating genotypic and phenotypic data. Regulatory genomic regions are sections of DNA which do not code for proteins but which increase or decrease the functioning of genes; there are typically many regulatory genomic regions which each have a small effect on the expression of traits of interest for breeding. This means that the contribution of particular regulatory regions can be observed only in large sets of phenotypic and genotypic data, and increasing the number of entries in such data sets could therefore help to find regulatory regions, which would in turn help to find stronger phenotype-genotype correlations. Other factors regulating gene expression are not part of the genome, however. In particular, gene expression is sensitive to environmental factors, and some phenotypic effects of environmental influences are transmitted between generations epigenetically (i.e. without any change in the DNA sequence). Understanding the biological mechanisms that explain the epigenetic heritability of phenotypic traits could therefore help to make more accurate predictions of what phenotypic traits breeding animals will transmit to their offspring. This is where the limitations of genomic science for animal breeding show and where other 'omics' sciences may offer complementary insights. For example, the field of transcriptomics researches how DNA is transcribed into different kinds of RNA, which influences how DNA is expressed phenotypically and involves hereditary aspects. Other omics sciences are metabolomics, which maps collections of small molecules in cells to determine basic chemical processes going on in cells, and proteomics, which maps the collection of proteins in (part of) an organism and studies their functions. Together, such omics sciences offer a multi-level understanding of the

biological processes that determine how genotype is expressed phenotypically, as shown in figure 1 (from Seidel et al 2020).
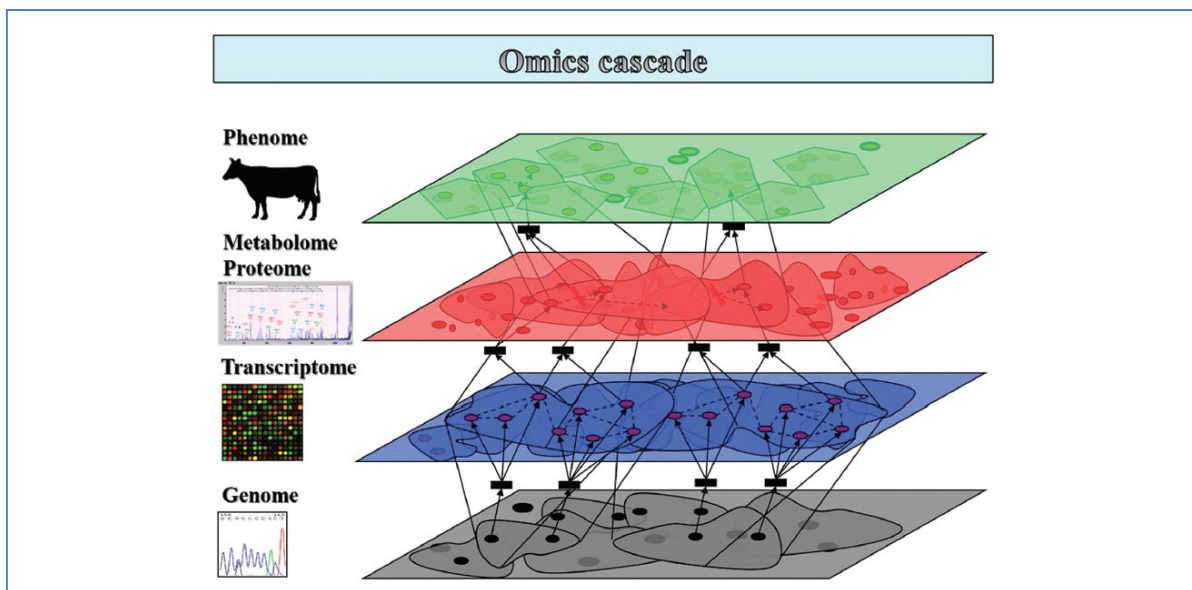

Figure 1: The omics cascade In systems biology approach is linking several levels of biological information of a certain phenotype. Source: Seidel et al 2020, adapted from Schwerin, unpublished.

Advances in these omics sciences could lead to innovations in livestock breeding. Once it is sufficiently understood how phenotypes of interest in breeding are co-determined by epigenetic factors, tools could be developed for selecting animals with favourable (genetic and) epigenetic profiles.

Both genomics and other omics sciences play important roles in the BovReg project. One of BovReg's major aims is to integrate existing data sets matching genotype and phenotype data. Aggregating entries from several data sets will increase statistical power when determining genotype-phenotype correlations, which means that new or stronger associations between genotypes and phenotypes could be found. BovReg draws on other 'omics' sciences to study how the expression of phenotypes of interest to cattle breeding is regulated by epigenetic factors. A variety of techniques (RNA-seq, CAGE, ChIP-seq, ATAC-seq, Hi-C seq, ChIRPseq) is applied to 24 tissues collected from cows and bulls from three different breeds or crosses kept in different environments to map characteristics regulating expression of the genome for the main traits of interest in the project (work package 2). Further epigenetic effects will be studied (in work package

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5) by mapping DNA methylation in these 24 tissues and in cell lines. The epigenetic effects of malnutrition or heat stress will be studied specifically by an experiment exposing parent animals to different environmental conditions and investigating the epigenetic and phenotypic characteristics of their progeny (work package 5). The results of these investigations are integrated with existing data on phenotypes, genotypes and factors regulating the phenotypic expression of genotypes (work package 4), on the basis of which tools for biology-driven selection (i.e. selection based on genomic features plus biological parameters supplied by other omics sciences) are developed (work package 7).

The main practical aim of the BovReg project is thus to improve cattle breeding by enabling biology-driven selection, which goes beyond genomic selection by including further biological parameters that can be used to predict phenotypic results of breeding decisions. Biology-driven selection still draws heavily on genomics, however, and improving genomic prediction is also part of BovReg. The distinction between genomic selection and biology-driven genomic selection is not maintained explicitly in the remainder of this report. Unless noted otherwise, the sections below assume that the legal, policy, and societal perspectives discussed apply similarly to both selection approaches. The current report offers a broad account of the societal context of innovations in cattle genomics, which has received little scholarly attention so far, and can serve as a background for more discriminative analyses of legal, policy, and societal aspects of either selection approach.

Conclusion

Genomics reduces the generation interval and is embraced in many breeding programs as a way to speed up the genetic improvement of cattle. The use of genomics in breeding still faces some limitations, however: a limited amount of data is currently available on some breeds and phenotypes; some phenotypes are difficult to measure or define; and there is a lack of knowledge on factors regulating the phenotypic expression of the genotype, which limits the accuracy of predicting phenotypes on the basis of genotypic information. Science can try to improve cattle breeding by generating more genotype-associated phenotypic data, integrating existing data sets matching genotypic

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and phenotypic data, or improving the state of knowledge on factors regulating gene expression. In addition, knowledge gained in other 'omics' sciences may enable making selection decisions based on a wider range of biological parameters (biology-driven genomic selection).

B. Opportunities of advances in omics sciences for cattle breeding

While some parts of BovReg engage with cattle biology on a fundamental level, the project as a whole is meant to inform cattle breeding practice by offering tools enabling biology-driven genomic selection. BovReg scientists we have interviewed do not expect a revolution in cattle breeding based on a single project, though. Further research projects are going on and will be needed, including projects addressing the same traits BovReg focuses on (biological efficiency, disease susceptibility, and robustness) and projects addressing other traits. We will therefore present more general views on how cattle breeding could benefit from advances in genomic science and other omics sciences, according to BovReg scientists and according to representatives of cattle breeding organizations.

It should be noted that BovReg scientists and breeding organization representatives also offered some critical views on (particular aspects of) cattle breeding and (biology-driven) genomic selection. We have taken these views into account in our analysis of the societal context of genomic selection (see section F) and will consider them again in our ethical analysis (deliverable 8.2). The last paragraph of the current section also presents a critical perspective on the advantages and opportunities claimed for genomic selection. This perspective was offered by a representative of a breeding organization that rejected the use of genomic selection in cattle breeding.

As explained in the previous section, opportunities for genomic selection could be increased by generating more phenotype data (provided that it is coupled to genotype data). An alternative approach, taken by the BovReg project, is to make better use of existing data on cattle genotypes and phenotypes by combining existing data sets. This will increase statistical power when determining genotype-phenotype

correlations, which might lead to new or improved applications of genomic knowledge in cattle breeding. First, regulatory genomic regions might be found with small effects on the phenotype. If a significant number of these regions are found, their effect on phenotypes of interest can be taken into account in genomic prediction, which will increase prediction whose daughters had generally favourable variants in cattle populations. This would allow improvement of traits that are already bred for using genomic selection (e.g. milk yield) or breeding for new phenotypes that are determined by many genomic regions which each have a small phenotypic effect. Second, relatively small subgroups of animals might be identified for which negative associations between traits of interest prove not to apply. This might help to redesign breeding programs so that common tradeoffs between traits of interest may be avoided. For example, if a sufficiently large subpopulation of Holstein cattle could be found that perform well on both milk yield and fertility, it might be possible to design breeding programs that improve milk yield without compromising fertility or vice versa. Another example could be to identify and spread genotypes that combine high milk yield and quality with high meat yield and quality, thus making the dual-purpose use of cattle more interesting economically. Third, combining data sets might enable breeding for phenotypes that are not recorded routinely (e.g. feed efficiency or methane emission). If several data sets contain data on such phenotypes, combining them may help to discover correlations to genotypes that could not be found in the individual data sets. It would then become possible to start breeding for those phenotypes. Lastly, large data sets hold potential for improving cattle breeding on the female side. Because cows kept on farms typically have only one calf per pregnancy and have few calves in their lifetime, phenotype testing of their progeny does not allow drawing reliable conclusions on these cows' genetic merit for breeding. Moreover, dairy cows need to calve each year to keep lactation going. Dairy cows can be inseminated with semen from a beef bull to produce calves for veal production rather than calves for milk production, but a significant number of cows must have calves intended for milk production to maintain the on-farm population of dairy cows. Dairy cattle breeding has for these reasons progressed mainly by selecting bulls whose daughters had generally favourable phenotypic profiles. Large data sets correlating genotypic and phenotypic data will not remove all the limitations on selectively breeding with cows, but will enable predicting the results of selection choices

more reliably. In particular, the results of inseminating specific cows with semen from specific bulls can be estimated with higher probability, which means that mating advice can be tailored to the traits of specific cows. Projects like BovReg thus support the development of 'precision' breeding practices.

Because the combined data sets will include data from several breeds, genotype-phenotype associations might also be found that apply across breeds. If favourable genotypes occur with sufficient accuracy in breeds for which these associations were previously unknown, it would become possible to propagate the associated phenotypes in those breeds. This holds potential for the improvement of minority breeds, which is one of BovReg's explicit aims. In particular, farming uncommon breeds could become more viable economically if genotypic variants known to be correlated with production traits (e.g. milk yield and quality) in majority breeds can be propagated in uncommon breeds. But it might also be possible to improve main breeds by selecting for genotypic variants that are known to be correlated with favorable phenotypes in less common breeds. Such breeds often have various advantages relative to for example Holstein-Frisians, and if associated genotypes can be found that also occur with some frequency in the more common breed, it might be possible to spread those advantages there. A final option that might be facilitated by combining data on several breeds would be to switch to cross-breeds. If certain genotype-phenotype correlations are known to apply irrespective of breed, it would be possible to make somewhat accurate breeding predictions when parent animals from different breeds are selected.

Insights from other omics sciences could help to improve breeding mainly through the identification of further biological markers (e.g. certain transcriptome or metabolome profiles) that prove to be correlated to phenotypes of interest. Provided that these markers are heritable and that the requisite technologies allow breeders to screen animals for the presence of these markers on a sufficiently large scale, selective breeding could be used to propagate beneficial marker profiles among cattle populations. The relative frequency with which phenotypic traits of interest occur should increase as a result. In addition, knowledge of the epigenetic effects of environmental stress could help to breed animals that are more resilient to such stress. More insight on the effects of metabolic stress or heat stress on future generations of

cattle could help to breed cows that are more resilient against the effects of climate change. For regions that will presumably be facing a hotter climate, for example, cattle could be bred that can cope with such conditions. Finally, further knowledge on epigenetics could help breeders to provide their customers with important management information: knowing the epigenetic profiles of their cattle, breeders could give more accurate predictions of how their animals respond to certain environmental conditions.

All in all, understanding the biological factors underpinning phenotypic traits would allow breeding for those traits more effectively, in a more balanced manner (i.e. without compromising on other important traits), and more sustainably in the face of climate change. This includes the traits that BovReg focuses on: biological efficiency (operationalized as nutrient conversion and greenhouse gas emission), disease susceptibility (mastitis resistance), and robustness (fertility). However, the integration of knowledge on genotypes, phenotypes, and factors mediating the phenotypic expression of genotypes might also enable or improve breeding for other traits. For any phenotypic trait that is recorded (and coupled to genotypic data) in a sufficient number of entries, genotype-phenotype correlations could in principle be established, and if these correlations prove to be sufficiently strong, they could be taken into account in genomic selection. Knowledge on what regulates the phenotypic expression of genotypes may also enable selection for a wider range of phenotypic traits. Indeed, the knowledge produced by genomics and other omics sciences would according to some interviewees allow establishing a "broad toolkit" for livestock breeding. They meant that breeding programs could address a wide set of traits, and that breeders could switch priorities relatively quickly, for example if societal demands on breeding were to change.

Further traits for which phenotypic data is recorded routinely, and which could thus be correlated to genotypic data easily, are health (in particular the absence of lameness), productivity (milk and meat yield), and longevity (operationalized as the span in which a dairy cow yields a sufficient amount of milk). There are also some routinely recorded behavioural traits that could be correlated to genotypic data. For example, the ease with which cows let themselves be handled is assessed (on a five-point scale) regularly by farmers (Chang et al 2020). Genotypes have already been found that correlate with ease of handling and other so-called temperament traits, which means

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that these traits could already be bred for using genomic selection. However, there are also traits on which phenotypic data is insufficiently available, or which still lack a commonly accepted definition. The lack of a common definition of animal welfare was stressed in several of the interviews we held. Although some traits that are measured frequently and that have an accepted definition have welfare implications (e.g. resistance to mastitis), there is no common view on what animal welfare entails and, therefore, no agreement on what phenotypes breeding programs aiming to improve animal welfare should be spreading. A similar problem was mentioned for robustness: although robustness (operationalized as fertility) is one of BovReg's key traits, it was considered a difficult concept to define and operationalize adequately.

It may be noted that some of the breeding goals discussed hitherto (in particular increased mastitis resistance, fertility and longevity) are particularly relevant for dairy cattle breeding, while others (for example reduced environmental impact) are also relevant for beef cattle breeding, even if these breeding goals may be associated with somewhat different phenotypic traits in dairy and beef cattle. Like many of our interviewees, the current section did not distinguished strictly and systematically between dairy cattle breeding and beef cattle breeding. This was motivated not only by the fact that several breeding goals are relevant in both dairy and beef cattle breeding, but also by the fact that breeding programmes using (biology-driven) genomic selection may try to improve dual-purpose breeds. Still, it should be clear from the previous analysis that some breeding goals are particularly relevant for milk production, while other breeding are important more generally.

These opportunities for cattle breeding were proposed by BovReg scientists and breeding organization representatives who were, overall, optimistic about genomic selection and biology-driven selection. We also interviewed a representative of a breeding organization that opposed the use of genomic selection (and biology-driven selection) in cattle breeding. A main objection of this interviewee was that genomic selection takes breeding decisions by optimizing expected breeding outcomes based on a narrow set of traits. Selection decisions are based only on those traits which the genomic selection paradigm recognizes as important and for which correlations with genotypes are known. Animals are selected whose offspring are expected to perform

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excellently on those traits, but this attempted optimization ignores that an animal's performance depends on the 'weakest link' in her traits, and this results in all kinds of problems. Ranking animals based on their scores for a narrow set of traits also threatens to narrow the genetic base of herds: it invites buying only semen from the highest ranking bulls worldwide, which would quickly lead to inbreeding. Underlying this interviewee's objections to genomic selection seemed to be a criticism of how genomics represents animals. On this criticism, genomics reduces animals to collections of (epi)genetic traits that can be used as inputs for calculations – calculations recombining the (epi)genetic traits of parent animals to predict the characteristics of the next generation. This reductionist approach threatens to leave out important characteristics or oversimplify how they are interrelated. The interviewee was therefore sceptical of the supposed advantages of genomic selection and argued for a breeding approach based on a more holistic (non-reductionist) view on animals.

Conclusion

BovReg scientists and breeding organization representatives hold that developments in the omics sciences offer a range of opportunities for cattle breeding. These opportunities are summarized in table 1. We also encountered some more sceptical views on the advantages of genomic selection and biology-driven selection, however.

Table 1: potential opportunities for cattle breeding due to biology-driven selection	
Part A: Breeding practice improvements	**Part B: Potential breeding goals**
Reducing the generation interval	Feed efficiency
Improving the accuracy of estimated breeding values (EBVs)	Greenhouse gas (methane) emission
Breeding for traits determined by many genomic regions	Disease susceptibility
Breaking negative correlations between traits	Robustness

Breeding for phenotypes that are not recorded routinely	Health
Improving selection on the female side	Productivity
Enabling precision breeding	Longevity
Improving minor breeds/dual purpose breeds/cross-breeds	Behaviour
Diversifying breeding programmes	Welfare?
Establishing a broad toolkit for future breeding programmes	

C. Legislative context: EU legislation on breeding

In 2016, the European Parliament and Commission issued a Regulation (2016/1012) which aims to set down a complete EU legal framework on the breeding of purebred animals for farming purposes, and which came into effect on 1 November 2018. In accordance with its comprehensive aims, it includes rules covering various aspects of the breeding sector, including for example the entry of breeding animals in breeding books and breeding registers, performance testing and genetic evaluation, and standards for certificates which describe the characteristics of particular breeding animals.

Notably, this Regulation requires breeding programmes to be approved by a competent authority and set conditions for approval (chapter II, section 2). A breeding programme qualifies for approval only if its aim is to improve, preserve, create, or reconstruct a breed, if its selection and breeding objectives are described in detail, and if it complies with requirements described in one of the Regulation's annexes (annex I, part 2). However, that annex only provides directions on the information to be provided to the competent authority and on the number of animals and breeders that must be involved in the breeding programme. The purpose of the Regulation was not to delineate what counts as 'improving' a breed, offer guidance on the breeding objectives that should be pursued, or the technologies which may be applied.

The only restrictions are in Directive 98/58/EC concerning the protection of animals kept for farming purposes, which states that "natural or artificial breeding or breeding procedures which case [sic] or are likely to cause [more than minimal or momentary] suffering or injury to any of the animals concerned must not be practised" (annex, 20). A proposed Directive 2013/0433 would have forbidden the use of cloning for farming purposes, based mainly on animal welfare grounds, but the Directive proved controversial and has never been passed. The only EU legislation that currently applies to animal cloning is Regulation 2015/2283. This Regulation determines that pre-market approval based on a food safety risk assessment is required for importing or selling food "produced from non-traditional breeding techniques". The European Court of Justice judgment C-528/16 placed genome editing under the same regulatory requirements of genetically modified organisms (which are covered in Regulation 1829/2003). According to this, the commercial use of genetic modification and genome editing in cattle is allowed provided that applicants can demonstrate that there will be no adverse effects on human health, animal health, or the environment. There is no specific legislation regulating the use of genomics in breeding, however. Preamble 11 to Regulation 2016/1012 indeed shows a favourable attitude towards genomics, which is believed to "hold considerable potential to address concerns in society and achieve the objectives of sustainable animal breeding in terms of improved resource efficiency and the enhanced resilience and robustness of animals" (Regulation 2016/1012 preamble 11).

Conclusion

Although breeding programmes must aim to improve (or preserve, create, or reconstruct) a breed, what counts as an improvement is beyond the remit of EU legislation. The only regulatory constraint on breeding innovations is that (more than minimal or momentary) suffering or injury should not be caused to any animals involved.

D. Policy context: the EU's Common Agricultural Policy and its values and objectives

Agriculture is a major topic in EU law and policy. Already in the 1957 'Treaty of Rome', which established the European Economic Community and set regulations for the functioning of its internal market, agriculture is identified as a domain for which certain specific regulations and policies should be developed (article 38). The Treaty calls for a common agricultural policy which serves to increase agricultural productivity, to ensure a fair standard of living for the agricultural community, to stabilise markets, to assure the availability of supplies, and to ensure that supplies reach consumers at reasonable prices (Article 39). These objectives should be pursued by establishing a common organization of agricultural markets, which may involve regulating prices, aiding the production and marketing of specific types of products, making storage and carryover arrangements for surplus products, and stabilizing imports or exports (Article 40). The first Common Agricultural Policy (CAP) became effective in 1962 and was the first common policy adopted by the EEC.

CAP has been repeatedly redeveloped to address emerging concerns (see Figure 2). In parallel, many regulations have been ratified which specify and formalize the policies set forth in CAP.
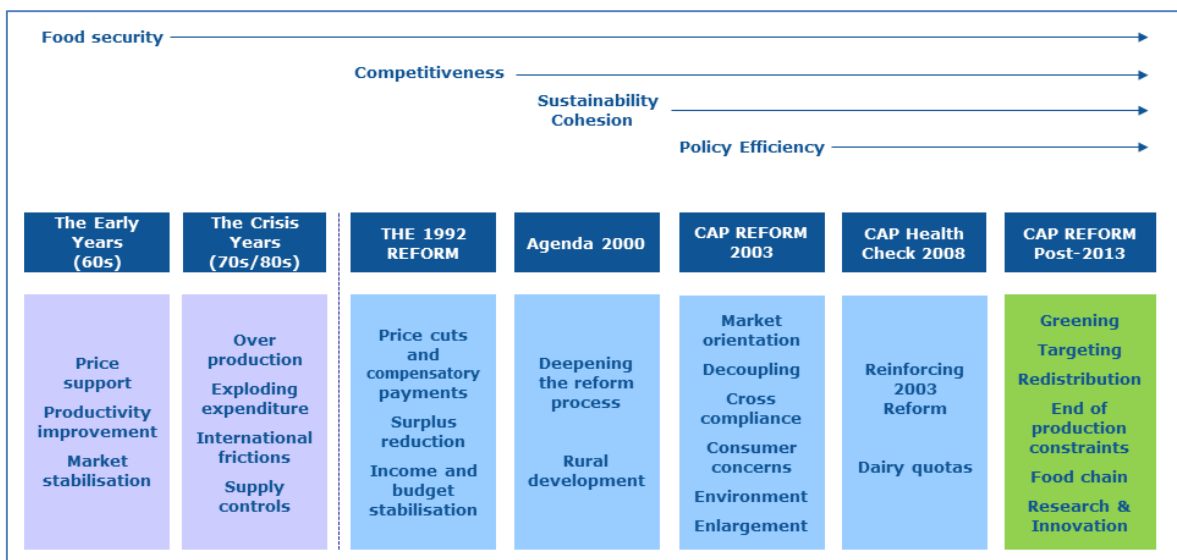

Figure 2: Historical development of the Common Agricultural Policy (Source: Sterly et al. 2018)

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In general terms, the scope of CAP has been widening: it initially addressed only food security and the economic performance of agricultural markets, but nowadays also covers environmental problems and other broad societal issues to which agricultural policy can make a contribution (Sterly et al. 2018).

In its first formulation in 1962, CAP was designed to improve food security by strengthening the agricultural sector's economic position (European Commission 2018). Policy instruments that could be applied to match this goal included price supports, investments to improve productivity, and market stabilization measures (European Commission 2018; Sterly et al. 2018). Over time, however, these measures led to overproduction of some agricultural products, escalating expenditures on support for agriculture, and frictions with external trade partners (European Commission 2018; Sterly et al. 2018). These problems were initially addressed by employing market interventions meant to counterbalance overproduction, but eventually motivated reforming CAP in 1992 to establish a more market-oriented agricultural sector (European Commission 2018; OECD 2011; Sterly et al. 2018). At the same time, CAP came to include agri-environment and afforestation schemes (OECD 2011), thus responding to environmental concerns as for example voiced at the 1992 Rio Earth Summit. In subsequent years, price supports were gradually reduced further and supplanted by direct payments that were decoupled from productivity, environmental and animal welfare requirements were set for farmers receiving direct payments, and rural development goals were included (European Commission 2018; OECD 2011; Sterly et al. 2018).

While economic goals remain part of CAP, emphasis has thus been shifting towards sustainable farming and contributing to social goods. The 2014-2020 CAP explicitly "plac[es] the joint provision of public and private goods at the core of policy" (European Commission 2013: 5) by setting up schemes that reward farmers for public goods they provide for society, but still focuses at environmental public goods (for example landscapes, farmland biodiversity, and climate stability) and rural development. The range of public goods to which CAP is expected to contribute is widened further in EU documents on the future of food and farming (European Commission 2017; European Parliament 2018). According to the European Parliament's

report, for example, CAP "should be designed to enable the EU farming and forestry sector to respond to justified citizens' demands regarding not only food security, safety, quality and sustainability, but also environmental care, biodiversity and natural resources protection, climate change action, rural development, health and high animal welfare standards, and employment" (European Parliament 2018). These forward-looking documents alternatively frame CAP's importance for public goods in terms of the United Nations Sustainable Development Goals (SDGs, see Figure 2): while some SDGs may receive focal attention (especially SDGs 2, 5, 12, 13 and 15), CAP is expected to contribute to most of them (European Commission 2017; European Parliament 2018).

Figure 3: the intended contribution of the European Union's Common Agricultural Policy to the United Nations' Societal Development Goals (source: European Commission 2017a)

While formulations of CAP's main aims vary and thus seem to point to somewhat different sets of underlying values, CAP has clearly come to adopt a broad normative basis, recognizing not only economic values but also various environmental, social and ethical ones. Aiming to incorporate such broader goals, CAP after 2020 will comprise three general objectives and nine more specific objectives (see Figure 3). These objectives will be pursued by three types of policy instruments: direct payments and market measures (pillar I) and rural development (pillar II).

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GENERAL OBJECTIVES	FOSTER A SMART AND RESILIENT AGRICULTURAL SECTOR	BOLSTER ENVIRONMENTAL CARE AND CLIMATE ACTION	STRENGTHEN THE SOCIO-ECONOMIC FABRIC OF RURAL AREAS
Policy area	Pillar I		Pillar II
Specific objectives	Support viable farm income and resilience Enhance market orientation and increase competitiveness Improve the farmers' position in the value chain	Contribute to climate action and sustainable energy Sustainable development management of natural resources Contribute to the protection of biodiversity, preserve habitats and landscapes	Promote employment, growth, social inclusion and local development Attract young farmers and facilitate business development Improve response of agriculture to societal demands on food and health, including safe, nutritious and sustainable food, as well as animal welfare
	Foster knowledge, innovation, digitalisation in agriculture and rural areas		

Figure 4: Summary of proposed objectives and related instruments of the CAP post-2020 (source: Sterly et al. 2018)

Both the European Commission (2017) and the European Parliament (2018) consider (technological) innovation in agriculture key to meeting CAP's objectives. Accordingly, support for innovations needs to increase, while the uptake of agricultural technologies by farmers should be improved (European Commission 2017). The European Commission's recent 'Farm to Fork' strategy also emphasizes the importance of research, innovation, and technology development for a sustainable, healthy, and inclusive food system (European Commission 2020). Expectations seem to be especially high where smart farming technologies are concerned (European Commission 2020, European Parliament 2018, STOA 2016), but .breeding is also mentioned as an area where innovation can serve the multiple goals of agriculture (European Commission 2017: 12).

The EU thus regards agricultural innovation favourably. Moreover, particular innovations can be evaluated from an EU policy perspective using CAP as a normative framework: one may consider to what extent an innovation squares with CAP's objectives and underlying values. In the section that follows, we will consider how

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possible applications of bovine omics knowledge, as produced for example in the BovReg project, relate to those objectives and values.

Conclusion

The set of values and objectives behind the EU's Common Agricultural Policy (CAP) has been widening: CAP now includes economic, environmental, societal, and ethical objectives. Innovations can be evaluated from a general EU policy perspective by considering how these innovations connect to CAP's values and objectives.

E. Connecting BovReg's opportunities for cattle breeding to CAP

In section B, a number of opportunities were identified that biology-driven selection might offer for cattle breeding (see table 1), based on interviews with BovReg scientists and breeding association representatives. In section D, it was suggested that innovations in cattle breeding could be evaluated from an EU policy perspective by considering their connection to wider policy objectives. The current section connects the potential breeding opportunities identified in section B to the policy objectives identified in section D. By considering to what extent these breeding opportunities further the economic, environmental, social, and ethical values underpinning CAP, this section shows how they could be supported from an EU policy perspective.

How (biology-driven) genomic selection relates to CAP's values and objectives depends on the trait under consideration. Some traits of interest in cattle breeding relate mainly to economic values, which applies in particular for improving productivity. Breeding goals that arise from other values (for example environmental or ethical values) can also be important from an economic perspective. For example, breeding animals to be more resistant to prevalent diseases has potential economic advantages. Infectious diseases can lead to severe economic losses if a herd has to be culled for epidemiological reasons or when disease outbreaks lead to a fall in productivity. Cows suffering from mastitis or lameness are less profitable for farmers, because of their

lower milk yields and higher veterinary costs. Thus farming herds with a lower prevalence of mastitis and lameness also has economic benefits.

Improving the longevity, fertility, and overall robustness of dairy cows can be economically advantageous as well. It takes about two years before cows start lactating and they must give birth each year to continue lactating. Milk yields drop if cows are not able to cope with environmental disturbances, such as heat stress. Improving longevity, fertility or robustness should mean that the overall duration during which cows do not give milk is reduced and that a larger share of the herd is producing. In each of these cases, an economically beneficial breeding goal is associated with (except perhaps in the case of fertility) non-economic values, and in particular to animal health and welfare, which are recognized as socially and ethically relevant by CAP. Finally, improving the welfare of animals can be economically advantageous, if enough consumers demand it and are willing to pay for more animal-friendly products.

Some traits of relatively recent interest in breeding relate to environmental values. In particular, in the context of climate change, the environmental impact of cattle farming could be reduced by breeding for reduced methane emission. Special sensors are sometimes installed in indoor farming units to measure the amount of methane excreted by cows, and this phenotypic information is correlated to genotypic (and possibly other omics) data. Any correlation found could perhaps be used to breed cows who emit relatively little methane. There does not seem to be any direct economic interest for farmers in keeping such cows, but CAP does offer some financial incentives to mitigate the environmental impact of agricultural businesses, and limiting the effects of climate change does serve long-term economic and ethical interests.

Another trait of interest for environmental reasons is feed efficiency. If more feed efficient animals are bred, less feed is required to meet the demand for animal products. This would reduce the environmental impact of the production of feeds for cattle (e.g. concentrates), where this involves long-distance transportation, land use changes or in some cases deforestation. This would therefore reduce the environmental footprint of dairy and beef production. Rather than breeding cows that need less feed overall, another option might be to breed cows that can feed efficiently on types of feed with a smaller environmental impact, for example roughage or even waste foods.

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Improving feed efficiency also brings economic opportunities: a cow that requires less (expensive) feed per unit of milk or beef produced is, other things being equal, less costly to keep. Finally, even disease resistance, health, longevity, and fertility have some connection to environmental values. If fewer cows are ill, infertile, or still too young to lactate, fewer cows would be needed to meet demand for dairy products, thus reducing the climate impact of cattle farming to some extent.

In summary, some traits (e.g. health, disease resistance and longevity) that are economically interesting also connect to other societal and ethical values, and there is a long-term societal and ethical interest in limiting climate change. It is somewhat unclear whether biology-driven selection will also facilitate incorporating other socially or ethically valuable breeding goals that do not also have significant economic or environmental potential. Animal welfare is recognized as an important societal and ethical value, which suggests that CAP would support developing such breeding applications even if these do not bring economic benefits. However, as discussed in section 2, there is no consensus on how to define animal welfare and no welfare phenotypes are recorded routinely. Some scientists and breeders whom we interviewed inferred that 'improving welfare' cannot be included as a general breeding goal in breeding programmes. Even if some specific welfare traits can be identified, it remains up for discussion whether these should be included as separate breeding goals. Breeding already addresses animal welfare – at least to an extent – by targeting health problems such as mastitis and lameness, and some welfare problems might require changing farming practices rather than breeding goals. Whether animal welfare improvements could and should be incorporated in breeding indices would have to be assessed on a case-by-case basis. A minimal requirement would be that specific welfare-associated phenotypes are found to be heritable.

Most traits of interest in breeding for which biology-driven selection might have added value can thus be connected to CAP's broad normative basis. Breeding for behavioural traits might seem to be an exception, but even here connections to CAP's underlying values can be made. One behavioural trait of interest is a cow's ease of handling, which is regularly scored by farmers on a five-point scale. Similarly, milking robots keep track of the frequency with which cows visit them, which provides not only

input for on-farm management decisions, but also for selection decisions in breeding programs adapted to the use of milking machines. Breeding for ease of handling and for robotic milking agreeability would make management easier and could be supported by referring to CAP's broad economic objectives. Whether this breeding goal would also be societally and ethically desirable is debatable however (e.g. Holloway 2007). Breeding cows that are less stressed during human handling could be defended from an animal welfare perspective. But some would raise the objection that such a breeding goal was premised on debatable production systems, and might be perceived as unacceptably adapting animals to their living conditions, instead of adapting the living conditions to the animals.

Some of the opportunities that (biology-driven) genomic selection offers for cattle breeding do not concern specific breeding goals, but instead relate to the efficiency of breeding irrespective of the traits bred for (see table 1). For example, improving the accuracy of estimated breeding values (EBVs), breaking negative correlations between traits, improving selection on the female side, and reducing the generation interval do not refer to specific traits. While such opportunities may in practice be particularly relevant for certain specific traits – for example traits for which EBVs are currently still relatively unreliable or for economically significant traits that are negatively correlated to other economically significant traits – they are in principle applicable more widely. This is why some of interviewees stated that (biology-driven) genomic selection could establish a 'broad toolkit' for cattle breeding. These potential opportunities for breeding can thus be connected to CAP's underlying values by referring to their significance for breeding goals that CAP would support. On the other hand, such broadly applicable opportunities for breeding might also enable controversial uses in cattle breeding. For example, while genomic selection allows reducing the generation interval by enabling the selection of younger animals to parent the next generation of breeding animals, this approach is most efficient when advanced reproductive techniques (egg collection, IVF and embryo transfer) are used. These techniques may not be completely unproblematic from a societal or ethical perspective, even if there is more over controversy on cloning, classical genetic modification, and genome editing (see the next section). Thus, although the values underlying CAP might

support some implications of innovations in cattle breeding, some other implications may be more contentious from an EU perspective.

Some other opportunities for breeding connect strongly to certain of CAP's specific aims. The ability to diversify breeding programs allows breeding and keeping animals that fit local conditions and diverse farming systems. This would directly promote biodiversity insofar as phenotypic and genotypic diversity among cattle breeds is concerned. Moreover, insofar as this would facilitate keeping animals in diverse natural landscapes, biodiversity would be indirectly promoted for a wider range of species: farming suitable animals in natural landscapes would help to protect those landscapes (for example against deforestation) and the plant and animal species that depend on them.

Another explicit aim of CAP that could be promoted by diversifying breeding programs is rural development. Breeding programs could be aimed at improving the viability of farming minor, local breeds. This would, at least to an extent, counter economic incentives to replace such breeds by higher-yielding breeds such as Holstein-Frisians. This might help rural areas to maintain their characteristic breeds, farming practices, landscapes, and artisanal products. Moreover, if the profitability of local farming practices can be increased, that should stimulate the economies of rural areas.

Finally, increasing and improving organic farming has been stated as an aim for CAP (European Parliament 2018). Without going into details here, (biology-driven) genomic selection can support this aim by breeding animals that suit organic farming conditions. This may include, among others, increasing the efficiency of feeding on roughage and improving robustness against environmental stressors that animals face in outdoor systems.

Conclusion

The current section considered how opportunities for innovation in cattle breeding, enabled by (biology-driven) genomic selection, connect to values and objectives underpinning the EU's Common Agricultural Policy (CAP). We conclude that CAP suggests broad directions for innovation in cattle breeding: at a general level, CAP

approves of innovations in cattle breeding insofar as these help to realize its economic, environmental, social, and ethical objectives.

However, CAP offers no sufficient frame to deal with the societal dimensions of (biology-driven) genomic selection. It does not provide overt guidance on what objectives to prioritize in breeding – that economic considerations were historically primary does not mean that they should trump considerations that were incorporated later, for instance. Neither does CAP settle how competing values should be weighed when particular breeding innovations are considered. For example, if some breeding innovation is economically advantageous but socially or ethically controversial, perspectives may differ from country to country and CAP is not competent to lay down whether or not this innovation should be pursued. CAP thus leaves ample room for discussion on the desirability of particular breeding innovations. Moreover, even if a detailed policy perspective on (biology-driven) genomic selection in cattle breeding could be derived from CAP (or its ancillary policies), this should not exclude other perspectives from consideration. The next section explores (possible) societal perspectives on genomic selection in farm animal breeding. It does so by revisiting debates on related technologies and drawing lessons for the public acceptability of genomic selection in cattle breeding.

F. Lessons from previous public debates on (bio)technologies

There seems to be little public debate specifically on the acceptability of using (biology-driven) genomic selection in farm animal breeding. While there are some academic publications addressing ethical aspects of genomic selection (Coles et al 2015, Twine 2007, 2010), the concerns voiced are not echoed in wider public debates. Animal advocacy NGOs whose representatives we interviewed did not have official positions on these selective breeding approaches, for example, and some of them even stated that they were unfamiliar with genomic selection. NGO concerns do address breeding technologies are focused on other technologies, such as genome editing and classical genetic engineering.

However, even if other agricultural biotechnologies have been more in the public eye, it does not follow that the use of (biology-driven) genomic selection in cattle breeding raises no controversial societal issues at all. Representatives of animal advocacy NGOs stated that the use of genomic selection in livestock breeding was not among their organizations' main priorities, but did raise some worries when they were informed about this topic. Thus, the lack of public discussion could perhaps be explained by the necessity to prioritize issues in public debate or a general unfamiliarity with genomic selection rather than unqualified public acceptance. (See also the first lesson below)

From a responsible research and innovation (RRI) perspective, which aims to ensure that the views and values of a wider range of publics inform decision-making on new technologies, these considerations call for public engagement on genomic selection in animal breeding. Three different types of motivation for doing public engagement are suggested by Sykes & Macnaghten (2013, cf. Stirling 2005). An *instrumental* motivation means that engaging publics would have certain desired consequences, like building public trust in the breeding sector or avoiding negative public perceptions of genomic selection). A *substantive* motivation is that critical discussions with lay publics could lead to better decisions (for example because lay people brought relevant local knowledge or identified wider social and ethical issues not considered by scientists or breeders). A *normative* motivation is that citizens ought to be involved in decisions that concern them, for reasons of democracy, equity, equality, or justice. Regardless of which of these motivations applies, research and innovation should be genuinely responsive to the general public's views.

Taking an RRI approach, Work Package 8 of the BovReg project seeks to anticipate possible societal, ethical and other impacts of genomic selection, and to engage with lay publics by means of a Democs card game. Outputs from these two tasks will feed into the creation of an ethical framework that can be used to inform further research and innovation in cattle breeding.

As stated, the remainder of this report anticipates lay views on (biology-driven) genomic selection. The approach is to see what lessons can be drawn from the social science literature with regard to previous public debates on (bio)technologies, with a

focus on GM food. Such an exercise is inherently speculative. Accordingly, the current section does not pretend to offer a reliable guide to public views, nor to make actual public engagement redundant.

Another methodological limitation of the current section is implied by the second lesson discussed below: it is often difficult to separate public debates on different technologies. Separate technologies may in practice be interrelated, and lay publics may see connections between technologies that experts consider irrelevant or do not consider at all. This complicated deciding which public discussions to review in the current section. The approach chosen here is to review social scientific literature presenting general lessons from public engagement on a wide range of technologies, to illustrate these lessons with reference to public discussions on genetic modification (GM) in food production, and to consider how genomic selection compares to GM with respect to the lessons discussed. Public discussion genome editing, although relevant in the current context, is much less developed and will be referenced only occasionally. Throughout, the focus is on qualitative rather than quantitative empirical research. The point of this section, accordingly, is not to quantify how people generally feel about genomics and other technologies. Rather, the aim is to understand concerns and perceptions that shape peoples' attitudes to technologies and to consider how these concerns and perceptions might be relevant for genomic selection.

First lesson: the amount of overt controversy does not necessarily reflect or predict the general public's views

Overt public controversy typically flares up after NGO campaigning or media coverage of some particular scientific development or event. These played an important role in shaping the trajectories of public controversy about genetic modification (see PABE 2001). GM foods were introduced in Europe in 1996, but initially did not arouse public opposition. In the UK, tomato paste from a GM tomato was sold openly and clearly labelled in supermarkets, which did not spark public controversy. In Germany, biotechnology had been politically controversial since 1985, due to campaigns from the Green Party, but public and media interest weakened in the early 1990s. Public opposition to biotechnology was also limited in France during the early 1990s, and

French public policy had generally been supportive of biotechnologies. By the end of 1996, some international NGOs started to campaign against GM foods more intensively, but general public concern was not aroused until the 'Five Year Freeze' campaign in the UK in late 1998. This came to a head with a series of newspaper 'exposees' against GM in February 1999, which led to controversy about the technology across much of Europe. This led to call for an EU-wide moratorium on authorizing further GMOs to enter the market. Supermarkets started withdrawing GM products soon after.

Public perceptions of GM were investigated by means of a series of focus group discussions held between September 1998 and October 1999 (PABE 2001). During this period, public controversy started in Italy, intensified in France and the UK, remained stable in Germany, and remained very limited in Spain. Yet the views and arguments expressed by focus group participants in the different countries and at different times were remarkably similar. People generally proved to be ambivalent about GM and offered arguments both in favour of and against GM. Thus, neither positive nor negative views of GM were accepted uncritically, irrespective of the level of media coverage or NGO campaigning (PABE 2001, cf. Grove-White et al 2000).

A lesson to be drawn here is that the views of the general public should not be inferred too easily from the absence or presence of overt public controversy, but should be addressed specifically. Both quantitative (e.g. Eurobarometer 2000, 2010, Frewer et al 2013) and qualitative empirical methods have been used to research these views. The focus of this section is on qualitative empirical research, in particular focus group research, aimed at discovering and understanding lay perspectives on (new) technologies.

Second lesson: the social acceptability of genomic selection may be influenced by previous experiences and by societal views on other technologies

A second lesson is that it is difficult to separate debates on different technologies. Public responses to new technologies are informed by experiences in public debates concerning previous technologies or events. For example, GM controversy arose in the UK against the backdrop of the outbreak of BSE in cattle and the transmission to

humans via the food chain, in the form of a new variant of Creutzfeld-Jakob (CJD) disease (PABE 2001). The UK government's assurances that British beef was safe were discredited in the public eye when the link from BSE to CJD was demonstrated by researchers in Edinburgh. When scientists and the UK Government gave assurances that, despite repeated objections against GM, there was no health risk from eating foods of GM origin, their credibility with the public was already compromised. The GM controversy might in turn shape public attitudes towards genome editing. Advocates of genome editing argue that genome editing should be more palatable to the public than GM, as it does not necessarily rely on transferring genetic material from one species to another, which stood out as particularly controversial in GM debates. It has been pointed out that some potential edits would lead to variants already occurring in some breeds or subpopulations, and some have argued that edits that do not involve the insertion of DNA from another species should not be subject to GMO legislation. This argument has however been rejected in a Judgment by the European Court of Justice (C-528/16), and it remains to be seen whether genome editing differs significantly from classical GM in public perception.

An important question for the societal acceptance of genomic selection may be whether it will be perceived as continuous with conventional breeding approaches or whether the public will link genomic selection to genetic engineering techniques. The latter is suggested by our experience that some NGO representatives whom we recruited for interviews initially conflated genomics with genome editing. An empirical study into consumer attitudes towards using genomic selection in tomato breeding (Van den Heuvel et al 2008) also found that people initially interpret genomics as similar to classical GM. Focus group participants (with the exception of low-educated young people) did however revise their understanding and view towards genomic selection during discussion. Towards the end of the focus group discussions, most participants considered genomic selection more acceptable than GM. However, although they considered genomic selection the breeding technology of the future, they still favoured traditional selective breeding. Even if educated publics will associate genomic selection with traditional selective breeding rather than GM or genome editing, however, it does not follow that it is thereby completely unproblematic from a societal perspective.

While Van den Heuvel et al (2008) found that traditional selective breeding was considered an accepted breeding practice for tomato's, its use in farm animal breeding has had some controversial results, for example the generation of fast-growing broilers. Moreover, even if people consume animal products and do not protest against husbandry and breeding practices openly, it does not follow that they have no qualms about those practices. Studies suggest that many people feel ambiguous about the consumption of meat, for example, but repress psychological tension by mechanisms such as strategic ignorance (Onwezen & Van der Weele 2016; Van der Weele & Driessen 2019).

Public acceptability of other technologies is also relevant in another way. Technologies are in practice thoroughly interrelated: applying one technology may require or at least 'invite' the use of other technologies (cf. Ihde 1990, Verbeek 2006). This is also the case for breeding technologies. For example, some applications of genome editing in livestock have used somatic cell nuclear transfer (SCNT), a core technique in some applications of cloning. Genomic selection is in practice applied in combination with reproductive techniques that reduce the generation interval (egg collection, IVF, and embryo transfer). This means that societal views regarding those technologies are implicitly relevant to attitudes towards genomic selection, and the same applies insofar as genomics will facilitate and be facilitated by genome editing.

Some may argue that genomic selection should be evaluated as an independent technique that does not *have* to be used in tandem with more controversial techniques. This argument could be contested, however, insofar as genomics *in practice* often involves the use of these other techniques, and so cannot be completely separated from them. NGO representatives whom we interviewed feared that genomic knowledge would facilitate genome editing but were unaware of interrelations of genomics with other techniques. One NGO representative did object to egg collection and embryo transfer in a different context but did not connect their usage to genomic selection. Given animal advocacy NGOs' general preference for more natural breeding approaches, however, they might well oppose genomic selection programmes that in practice require advanced reproduction techniques.

In sum, public perception of genomics could be influenced by controversies around other technologies. This might in part be explained by a lack of familiarity with genomics, in which case educating the public about genomics and its differences with for example classical GM and genome editing might change attitudes among some groups. It should not be assumed however that all societal objections against genomic selection can be removed through this approach. Even if publics generally end up associating genomic selection more with traditional selective breeding than GM or genome editing, for example, people might have (latent) qualms about both traditional selective breeding and genomic selection. Public concerns over 'abnormal' broiler chickens arose out of applying classical selective breeding to growth rate. Moreover, genomic selection may in practice be intertwined with the use of other technologies – notably reproductive techniques such as egg collection, IVF, and embryo transfer – that might attract public scrutiny.

It should finally be noted that lay concerns about technologies may not focus on the technical aspects of these technologies. Participants in a series of focus group discussions on GM foods were conscious of their lack of technical understanding of GM and based their views mainly on common sense knowledge about non-human organisms (for example about the behaviour of pollinators such as bees), human fallibility, and the behaviour of institutions (PABE et al 2001). This suggests that technical differences and similarities between genomics and other breeding technologies may not be decisive for public attitudes towards genomics. As lay people consider the wider societal context of technologies, they may notice other differences and similarities between genomics and other technologies. This leads to the next lesson.

Third lesson: the social acceptability of (bio)technologies depends on broad public concerns

A third lesson is that public attitudes towards technologies tend to be based on wider perspectives than scientific assessments of those technologies are. Publics may therefore have (or develop) concerns about genomic selection that scientists would dismiss as irrelevant or would not consider at all. Social scientists have investigated public responses to (new) technologies, the concerns behind those responses, and to

what extent public attitudes differ from scientific and regulatory perspectives. In what follows, we present some of the main conclusions from this strand of research and consider to what extent these apply to genomic selection.

In reviews of focus group studies on a range of technologies, Sykes & Macnaghten (2013) and Macnaghten & Chilvers (2014) note that lay people generally consider most domains of research and innovation beneficial (in particular medical research to create new cures, environmental and energy research to promote sustainability, innovations offering environmental solutions, and innovations consolidating their country's leading role in science and technology). However, these reviews also identify five areas of major public concern, which we will consider in turn. They will each be applied both to classical GM used in food production and to genomic selection in animal breeding.

First, focus group participants addressed the purposes of certain domains of scientific inquiry and the motivations of those involved (Sykes & Macnaghten 2013, Macnaghten & Chilvers 2014). They critically questioned whether particular innovations were necessary, in whose interest they were developed, and whether there were alternatives. Although science was considered very important in dealing with 'big challenges' such as global warming, serious diseases, energy problems, and food security, people were not always convinced that science was conducted for the right reasons. This also affected public responses to GM (Grove-White et al 2000, PABE 2001). Although the development and spread of GM foods was presented as increasing food security (by improving yields, nutritional properties, and resistance to environmental stressors), European publics doubted that GM foods were necessary and that the world's neediest would indeed benefit. There was a concern that the commercial corporations which developed and supplied GM foods would reap the benefits instead.

This concern might also influence public responses to genomic selection in animal breeding. Genomic selection has been advocated as a way to improve food security, reduce environmental impact and improve animal welfare within the livestock sector. Lay publics might acknowledge the importance of these aims but prefer to look for alternative approaches, such as reducing the consumption of animal products and keeping animals in less intensive agricultural systems. According to this view, the

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development and application of genomic selection might be interpreted as an attempt to avoid reforming consumption patterns and production systems, and thus as an attempt to secure vested interests rather than address the underlying causes of current problems in animal husbandry, which would require systemic changes. Our interviews suggest that this is indeed how animal advocacy NGOs typically view genomic selection in cattle breeding. However, our interviewees also held that dramatic changes in consumption and production patterns were not forthcoming and believed that genomic selection can make a positive contribution in these non-ideal circumstances, provided that its uses promote the interests of animals.

A second concern related to the issue of trust. Sykes & Macnaghten (2013) and Macnaghten & Chilvers (2014) state that participants of the focus group discussions reviewed usually trusted the motives of scientists but distrusted the motives of government and industry. However, even science was considered vulnerable to industry interests, especially in fields where a close proximity between government and industry was suspected. In the public controversy about the commercialization of GM crops, industry and government were perceived to actively support GM, which to critical publics suggested that GM would be assessed and regulated with insufficient care (Grove-White et al 2000, Jasanoff 2016). In focus group discussions about GM, the behaviours and motivations of industry and government were not considered unexceptional or unsurprising, however (PABE 2001). Past experience about the behaviour of institutions and lay knowledge on human fallibility had taught focus group participants to expect such behaviours and motivations.

Perceptions about the influence of industry interests could also shape public attitudes towards genomic science. A close collaboration between academics and breeders may be necessary for developing both the science and the practice of animal breeding, but might suggest that genomic science is steered significantly by commercial interests. This is could be aggravated by the perception that traits which are prioritized in research also have economic significance. Some of our NGO interviewees at least suspected that genomic science would primarily serve the economic interests of breeders rather than the interests of, for example, farm animals. To be sure, not all economic objectives may be assessed negatively – improving farmers' incomes might for

example be considered a laudable goal. Lay publics may also accept that making profit is an important aim for breeders: past experience suggests that people accept that industry has economic goals but mistrust corporations that are not upfront about those goals (cf. PABE 2001). The main worry seems to be that economic goals will in practice trump societal or ethical considerations, thus driving breeding into unacceptable directions for commercial reasons. Another public concern (see the fifth public concern below) is *who* will benefit financially: farmers in low-income countries, for example, or large breeding companies.

Third, focus group participants often felt powerless in the face of technological developments (Sykes & Macnaghten 2013, Macnaghten & Chilvers 2014). Even if people were consulted about their attitudes towards new technologies, they held that they were not included in decisions on which technologies to develop and for whose benefit; they believed that they were 'kept in the dark' about such decisions. This was also the case when GM foods were being commercialized in Europe, where people felt that the decision that GM foods should be developed and spread had already been made without hearing the public (Grove-White 2000, Sykes & Macnaghten 2013). Generally speaking, people felt that scientists form a closed community that it is difficult to gain access to and that there is a cultural resistance among scientists to open up science to the public's views and values (Sykes & Macnaghten 2013, Macnaghten & Chilvers 2014). A solution to this feeling of powerlessness would be to include the public in the earliest phases of technology development, provided that the innovation trajectory is genuinely responsive to public views, which might in some cases mean being prepared to halt research and innovation completely (Stilgoe & Macnaghten 2013). The general public is still rarely included in 'upstream' decisions on the direction of science and technology, however (Macnaghten & Chilvers 2014), and this also applies for genomic selection. Some scientists whom we interviewed felt that transparency about the use of genomic selection in cattle breeding was limited: they held that open-access information was incomprehensible to the public and saw few efforts to engage lay people actively. Although NGO representatives whom we interviewed were unfamiliar with genomic selection and biology-driven selection, it was not clear in our interviews whether they felt they had been 'kept in the dark' about their use in cattle breeding. It is also yet

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unclear to what extent people would object to being left ignorant about genomic selection. Presumably, feeling 'kept in the dark' about a technology is worse when people associate that technology with serious risks, societal concerns, or ethical issues.

Fourth, people were concerned about the speed and direction of innovation processes (Sykes & Macnaghten 2013, Macnaghten & Chilvers 2014). In a first variant of this concern, people believed that commercial pressures pushed for a quick development and commercialization of technologies, which would mean that the (social and ethical) impacts of the technologies would be assessed with insufficient care. In a second variant, technologies were perceived as disrupting natural processes without careful consideration. These perceptions raised a broad set of social and ethical issues, including concerns about unforeseen, uncontrollable and irreversible consequences and a perceived loss of naturalness. Both variants of the concern about the speed of direction of innovation can also be traced in the controversy over GM foods. As industry and governments insisted that GM foods were safe because there was no evidence that GMOs carried any risk, the general public met those reassurances with scepticism and suspected both industry and government of inappropriately promoting the technology rather than taking the time to consider the technology with sufficient care (Grove-White et al 2000, Sykes & Macnaghten 2013). It was felt that the set of risks taken into account was too narrow and that there was insufficient attention to uncertainty and social consequences. On a more ontological level, focus group participants expressed the concern that creating GMOs was inappropriately 'messing with nature' (Grove-White et al 2000, PABE 2001, Sykes & Macnaghten 2013). Although they recognized that humans have been manipulating nature for centuries, GM was considered a manipulation of a qualitatively different kind (PABE 2001).

There could also be some concerns about the speed and direction of genomic selection in animal breeding. Although genomic selection does not instantly introduce new genetic variants, as GM would, it is in some respects quicker than traditional genetic selection. Genomic breeding programs have a reduced generation interval compared to breeding programs based on traditional selection: judging the genetic merit of bulls no longer relies on assessing the performance of their daughters, which means that younger bulls can be used to breed the next generation of breeding animals

(see section A). Genetic gain can be increased further by harvesting eggs from top breeding cows, fertilizing these eggs *in vitro*, and transplanting fertilized eggs into a number of cows that function as surrogate mothers. Genomic breeding programs thus strive to make faster progress towards breeding goals. However, this also means that undesirable characteristics, including unforeseen effects that become apparent only after some lag time, could potentially spread more rapidly among herds. If genomic selection involves narrowing the set of bulls used to breed the next generation of cows in farms and bulls in breeding programs, as one breeding organization representative whom we interviewed objected, a kind of inbreeding would result that could further speed up (and lock in) the spread of undesirable characteristics. The risks associated with increased speed was acknowledged widely among breeding scientists and breeders, who recognized the importance of maintaining sufficient genetic diversity. However, the critical breeding organization representative believed that there was in practice a pressure for farmers to select only the highest-ranking bulls, thereby narrowing the genetic base of their herds. One NGO interviewee proposed that genomic selection would tempt breeders to pursue new or different breeding goals without due consideration. These concerns, whether they are valid or not, addressed the speed and direction of genomic selection programmes.

To some extent, genomic selection might also be associated with a loss of naturalness in animal breeding. Although genomic selection was considered more natural than GM in Van den Heuvel and colleagues' (2008) study, it was considered less natural than conventional breeding. Insisting that genomic selection results in similar animals to conventional breeding, considering that both involve spreading variants already present in the population, may not be completely persuasive; lay people's judgments of naturalness might not be based on the properties of the 'products' of breeding but on the nature of the processes involved (Bruce & Bruce 1998). In genomic selection, this process may involve the use of reproductive techniques that people might consider unnatural (for example egg collection, IVF, and embryo transfer). Note however that from this perspective, even traditional selective breeding is to some extent unnatural: cows are matched to bulls based on human choices and inseminated with a straw of semen that may have been imported from another continent. The

perceived 'naturalness' or 'unnaturalness' of a breeding technology may be a matter of degree and may depend on what it is contrasted to: genomic selection might for example be 'natural' compared to GM but 'unnatural' compared to letting a bull roam and mate cows on one's farm. At any rate, the concept of 'naturalness' shapes people's responses to technologies in important ways and is likely to inform views on genomic selection.

Fifth, people raised (further) ethical concerns about new technologies. A main ethical concern, according to Sykes & Macnaghten (2013) and Macnaghten & Chilvers (2014), was whether innovations were thought to bring a genuine social benefit. When people did consider a technology highly beneficial for society, they were willing to accept trade-offs with other ethical values. People also expressed concern about the social distribution of benefits and costs. Generally speaking, they feared that the benefits would befall the rich and powerful rather than the poor and vulnerable, who would at the same time be affected disproportionately by the disadvantages of new technologies. In the controversy over GM foods, as stated earlier, the general public did not see much social benefit in GM. People believed that GM was not necessary and that the benefits would befall the corporation offering GM seeds and animals rather than smallholders or the world's poor and hungry. Accordingly, they were generally unwilling to accept the perceived uncertainties and downsides of GM foods. Whether lay publics will see a genuine social benefit in genomic selection, compared in particular to traditional selective breeding, is yet unclear. Who benefits from the uptake of genomic selection and who loses out is an important question here. Because genomic selection depends on expert knowledge, big data and advanced technologies (including software tools for genomic prediction and reproductive techniques that help to reduce the generation interval), the uptake of genomic selection will expectedly benefit breeders who can afford to make large investments in their breeding programs. This has already led to consolidation into a small number of large companies, which outcompeted or acquired many smaller companies and cooperatives, in pig and poultry breeding. This process has been much slower and less decisive in dairy cattle breeding. Cows on dairy farms need to calve to lactate and produce a new generation of cows in the process. Main 'genetic resources' in cattle breeding are therefore kept on dairy farms rather than

concentrated in the hands of a few breeding companies. This constraint does not apply to beef cattle breeding, however, which means that beef cattle breeding may be more amenable to centralization than dairy cattle breeding. Still, our interviewees typically feared that a centralization would also take place in dairy cattle breeding, in part due to the high budgetary requirements of breeding programs based on genomic selection. This would mean that smaller breeding cooperatives and companies would be pushed out of the market and, according to some interviewees, that farmers would become dependent on a small number of powerful suppliers. Farmers would on this view not benefit from the (further) uptake of genomic selection in breeding programmes. Other interviewees instead argued that farmers would benefit from the increased performance of their animals due to genomic selection. Views on whether consumers would benefit also diverged; one NGO representative, for example, saw no significant benefit for consumers because high-quality animal products were available at low prices already.

Conclusion

Drawing lessons from previous public debates on technologies, this section considered how lay people might perceive (biology-driven) genomic selection in cattle breeding, and identified a number of potential issues.

It was first noted that the views of the general public cannot be inferred directly from the presence or absence of overt public controversy. Thus, although the use of genomic selection is not currently a matter of visible public interest, it does not follow that genomic selection is wholly without problems from citizens' perspectives. Perspectives on genomic selection should instead be researched specifically by means of public engagement.

Second, it was noted that the social acceptability of genomic selection may not be independent from peoples' views on and experiences with other technologies. An important question for the societal acceptance of genomic selection may be whether it will be perceived as continuous with conventional breeding approaches or whether the public will associate genomic selection with genetic engineering techniques.

Associations with other technologies may to some extent stem from a lack of understanding of the technologies involved. But people may also see similarities not in the technical aspects of these technologies, but with respect to their institutional contexts or societal implications. Furthermore, genomic selection may in practice require or invite the use of other technologies (for example egg selection, IVF, embryo transfer, and genome editing). Societal views with regard to those technologies are then (at least implicitly) relevant for views on genomic selection.

Third, this section addressed five broad types of concerns that focus group participant have raised with regard to technologies: (1) the extent to which the technology is considered necessary and beneficial; (2) trust in scientists, industry, and policy-makers; (3) a sense of powerlessness to influence research and innovation; (4) the speed and direction of research and innovation; (5) further ethical concerns including the social significance of the technology and the distribution of its burdens and benefits. Each of these concerns may have some relevance for genomic selection. It would probably make a difference, however, to what aims genomic selection is applied; an important question for the general public is whether technologies are developed for the right purposes, benefits the right people, and takes other ethical considerations into account properly. In addition, how research and innovation are pursued may make a difference. People could become particularly critical if they would come to suspect that commercial interests drive omics science and cattle breeding, if they would feel powerless to influence the direction of research and innovation, and if omics science and its application to cattle breeding would in their view progress too hastily.

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4. Conclusions

This report addressed the context of innovations in cattle breeding, in particular innovations possibly enabled by (biology-driven) genomic selection.

Section A and B considered the scientific context: the state of knowledge in genomics as applied to cattle breeding, current knowledge gaps and the limitations these set for cattle breeding, and opportunities that biology-driven genomic selection is expected to offer. It was concluded that biology-driven genomic selection is expected to make cattle breeding more efficient in several ways (for example by reducing the generation interval and improving the accuracy of breeding predictions), to enable some different breeding approaches (for example making cross-breeds or improving minor breeds), and to incorporate additional breeding goals (for example reduced emission of methane).

Section C then addressed the legal context of cattle breeding innovations in the EU. It concluded that although breeding programmes must strive to improve (or preserve, create, or reconstruct) a breed, EU legislation does not regulate what counts as an improvement. The use of cloning, genetic modification, or genome editing in cattle breeding is prohibited, but genomic selection is allowed. There seems to be no legal ground to object to the breeding innovations that (biology-driven) genomic selection is expected to enable, except if (more than minimal or momentary) suffering or injury is caused to the animals concerned.

The policy context of cattle breeding innovations was addressed subsequently, in sections D and E. Focusing again on the EU, the values and objectives underlying the Common Agricultural Policy (CAP) were first identified, which was followed by an analysis of how potential cattle breeding innovations connected to these. CAP's underlying values and objectives typically support the cattle breeding innovations that biology-driven selection will expectedly enable, but CAP only suggests general directions for research and innovation and leaves ample room for discussion on the desirability of particular innovations.

Finally, section F addressed societal views on (biology-driven) genomic selection. Although there is barely any societal discussion on the use of genomic selection, it does

not follow that genomic selection raises no societal concerns whatsoever. Public perception of genomic selection may not be independent from attitudes towards other technologies, and although people often see potential benefits in (new) technologies, they typically also have a range of concerns. People could presumably become critical of innovations in cattle genomics if they feel that these innovation offer no societal benefit or are unnecessary, if they would come to suspect that commercial interests drive omics science and cattle breeding, if they would feel powerless to influence the direction of research and innovation, or if omics science and its application to cattle breeding would in their view progress too hastily. Public attitudes may hence depend on both the direction and the process of innovation in cattle breeding.

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