The rearing of farmed animals is a vital component of global food production systems, but its impact on the environment, human health, animal welfare, and biodiversity is being increasingly challenged. Developments in genetic and genomic technologies have had a key role in improving the productivity of farmed animals for decades. Advances in genome sequencing, annotation, and editing offer a means not only to continue that trend, but also, when combined with advanced data collection, analytics, cloud computing, appropriate infrastructure, and regulation, to take precision livestock farming (PLF) and conservation to an advanced level. Such an approach could generate substantial additional benefits in terms of reducing use of resources, health treatments, and environmental impact, while also improving animal health and welfare.

The growing role of genetics and genomics in animal production

Selective breeding (see Glossary) of animals to better suit specific environments, management systems, and different market needs has played a key part in the livestock industry for centuries and is responsible for the wealth of farm animal genetic resources that we observe globally today. Over the past 100 years, significant technological advancements have been made that have had an important role in accelerating the rate of development and shaping what has become a key part of the livestock industry (Figure 1). Advances in reproductive techniques initially facilitated distribution of high-merit genetics and a higher selection intensity to be used for breeding. The parallel improvements in breeding value estimation, computing methods, and selection accuracy, initially through the application of quantitative genetic approaches and, more recently, through also using genomic tools, have helped ensure that the rate of genetic improvement has continued to increase over time. These developments played a large part in dramatically improving the efficiency of livestock production. For example, between 1957 and 2005, growth rates in broiler chickens increased by 400%, while food conversion ratio was concurrently improved by 50% [1]. Over a similar period, the average milk yield for North American cows also increased by 400% through a combination of improved management and genetic improvement, with the latter having a major role [2]. With international genetic evaluations having been routinely run for dairy cattle for more than 25 years, similar rates of improvement have been achieved in several countries around the world. The improvements achieved have also contributed to significant reductions in greenhouse gas emissions per unit product across a range of farmed species [3–5]. Despite the significant advances already achieved, the livestock sector is still under increasing pressure to reduce costs, use of resources, its environmental impact, and the use of antimicrobials and antibiotics, while conserving biodiversity and maintaining high levels of animal welfare [6–11].

The primary focus for applying genetic and genomic knowledge to-date has been to harness and accelerate the naturally occurring process of evolution to meet the requirement of defined scenarios or goals. As measuring technologies have been improved, naturally occurring genetic variation...
has been found in the majority of animal characteristics of interest. Such a powerful approach offers real opportunities to improve production systems, but equally, if used inappropriately (e.g., though poorly defined breeding goals), can reduce the effectiveness of production systems and pose a threat to animal welfare.

As new tools and approaches have been developed, they have allowed not only the rates of progress to be accelerated, but also lessons to be continually learnt and the approaches adapted to make best use of them in the context of other agricultural innovations. For example, many early breeding programmes primarily focussed on improving production, which resulted not only in good rates of progress being achieved, but also welfare concerns being raised [12]. Over time, as more data have become available, breeding goals have been increasingly broadened to include a range of animal characteristics, with a growing emphasis on improving health, fertility, survival, and welfare [13–15]. The importance of responsible, sustainable, balanced, and transparent breeding approaches has been recognised through the establishment of industry-led code of conduct initiatives, such as Code-EFABAR. The process of learning, adapting, and improving the approaches being used is ongoing.

Over the past two decades, there has been a rapid acceleration in the development of genomic tools of relevance to livestock species. It is now possible to generate a level of genomic detail that would have been difficult to imagine previously. Many new tools are continually being developed that have the potential to support more accurate and effective selective breeding, but, when considered alongside and combined with other technological developments, they increasingly also offer potential opportunities to generate additional benefits through nonbreeding applications, such as to support more effective conservation and precision tailoring of management and health treatments for individual animals and groups.

Here, we review important technological advances that are of relevance to a range of livestock species, particularly over the past 5 years. We also discuss some of the opportunities and challenges that lie ahead in terms of delivering positive industry impacts from their use, across a range of livestock sectors for genetic improvement, precision farming, and conservation.

**Use of genomic tools**

At the start of the genomics era during the 1980s, the main focus for applying the technology in livestock breeding was the development of standalone genome marker tests, particularly for inherited diseases (e.g., the **Halothane** gene in pigs [16,17]) and parentage. The focus then shifted toward combining quantitative and genomic approaches to identify genomic **variants** with large effects on characteristics of interest (quantitative trait loci; QTL) for use in **marker-assisted selection** (MAS). However, the uptake of MAS was limited, since few QTL were reliably detected across populations, and those detected generally only accounted for a small proportion of the variation in the overall breeding objective [18]. The realisation that hundreds, if not thousands, of individual genes were likely involved in the expression of most traits of commercial interest has shaped many of the developments that followed.

Over the past 15 years the primary focus has been on implementing and refining methods for **genomic selection** (GS) (Box 1). Rapid concurrent advances in the availability and cost of generating genomic information, and in computing and analytical approaches to GS (Box 2) have facilitated a continual increase in the density of genomic information that can be used for breeding value prediction, and the amount of data that can be evaluated simultaneously (Box 2).

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**Glossary**

- **Bayesian method**: statistical theory in which the probability for a hypothesis is updated as more evidence becomes available.
- **Computational intelligence**: form of computer model based on the methods by which humans learn.
- **Copy number variation (CNV)**: occurs when the number of copies of a gene varies from one individual to the next.
- **CRISPR/Cas9**: two-component system used for targeted gene editing. A specific strand of DNA is located with high accuracy and then altered.
- **Data mining**: analysis of large databases with the aim of generating new insights.
- **Epigenomic/epigenetic**: studies of changes in organisms caused by modification of gene expression rather than by modification of the genetic code.
- **Epistasis**: interactions between genes that effects their expression.
- **Genetic improvement (in livestock)**: definition of production-relevant traits and establishment of programmes to gradually improve to meet a specific goal.
- **Genome editing (GnEd)**: process of changing an organism’s DNA at specific locations by using one of a group of techniques.
- **Genomic best linear unbiased prediction (GBLUP)**: statistical technique that takes account of genomic information and phenotypes to generate relative estimates of genetic merit.
- **Genomic selection (GS)**: marker-assisted selection in which genetic markers over the entire genome are used to estimate the effects of all loci and predict genetic values of untested populations.
- **Genotyping**: technology that detects small genetic differences at defined locations on the genome.
- **Genotyping by sequencing (GBS)**: also known as next-generation genotyping. Detection of SNP variations in DNA by sequencing a series of genomic regions.
- **Halothane gene**: named after the discovery that pigs carrying two copies of the specific variant of a gene underwent physiological stress and died when exposed to halothane anaesthesia.
- **High density (HD) (SNP chips)**: chips designed to detect variations at a high
Use of whole-genome resequencing

With the development of next-generation sequencing and subsequent reductions in costs, interest in using whole-genome resequencing as an alternative to SNP chips for genotyping to support GS in breeding programmes has increased. The main advantage of using resequencing is that it allows capture of a wider range of variation specific to the population of interest, as opposed to variation defined through a subset of common SNPs typically selected based on information collected on other populations. Use of genotyping by sequencing (GBS) as a viable cost-effective alternative was initially tempered by the realisation that, compared with genotypes obtained from SNP arrays, the quality of genotypes obtained with GBS tended to be lower when only low depths of genome coverage were used. While the quality increased with a higher depth of coverage, so did costs. The use of imputation (Box 3) to generate full sequences offered a means to help reduce the impact on genotype quality [36]. As well as characterisation of common variants typically included on SNP chips, use of whole-genome sequencing (WGS) offers several additional benefits, including characterisation of rare variants and other sources of variation, such as structural variations and copy number variations (CNVs).

Accurate imputation to the whole-genome level to help capture these additional sources of variation requires the availability of good reference populations. Several population-based initiatives are underway to help achieve that (reviewed in more detail elsewhere [44], the most well-known of which has been the 1000 Bull Genomes Project [45], which now includes whole genomes for over 6000 animals, with an average coverage of ~12× (H. Daetwyler, pers. comm. 2022).

With such populations now becoming available, interest in using a low coverage (also referred to as low-pass) WGS (typically <1×) and imputation approach in commercial breeding programmes is gradually building. Few results have been published to date for livestock, but results from research on a small, mixed-breed beef cattle population (77 animals) are encouraging, with a high level of agreement generally being achieved between imputed genotypes and genotypes called from the SNP arrays and transcriptome sequences [46]. Similar positive results have also been achieved for pigs [47] and in human studies [48,49].

While the availability of large numbers of imputed WGS data is expected to result in higher prediction accuracy, the likely magnitude of that benefit is still the subject of some debate. The results of some studies have suggested that the use of WGS will result in only a small increase (≤5%) in prediction accuracy compared with using high-density SNP arrays [50–53]. Several reasons have since been proposed as to why these results should not be considered indicative of the potential benefits that should be expected in general across a range of traits, such as level of relatedness between training and prediction populations, size and composition of reference populations, potential sequencing, and imputation errors. Some studies have reported improved results by fitting only selected variants from the WGS with the aim of increasing the importance of causal variants or SNPs in high LD with them in predictions. One of the main challenges in doing so is choosing appropriate approaches or criteria to help identify suitable variants to include without introducing bias. Several methods and approaches have already been proposed, including using multibreed training populations (Box 4) to help identify suitable SNPs [52–55].

Further work is required to determine how best to capture the most value from using WGS in different scenarios and populations. However, at the very least, its use offers the ability to generate prediction accuracies that are, as a minimum, equivalent to using HD arrays for some traits and higher accuracies for others, and with the potential for even more benefits as genomic resources and evaluation methods are developed further.
Increasing the robustness and accessibility of GS

One of the challenges with implementing GS is the need to periodically retrain the evaluation models due to a gradual breakdown of linkage disequilibrium (LD) between SNPs and QTLs as a result of recombination (Box 1). Although not a major concern when the phenotypes of interest are routinely recorded (i.e., production traits for dairy cattle), it can have a significant impact on the cost of GS implementation when recording is done only periodically through specific initiatives or projects, which is commonly the case for many traits and populations.

The development of methods and approaches to mitigate this affect has received some attention. The use of WGS, nonlinear models (Box 2), and multibreed training populations (Box 4) have all been found to offer some benefits, with the combination of all three offering the greatest level of mitigation in most scenarios. The use of multibreed training populations can also have a key role in supporting the implementation of GS in small populations, which is a common challenge for many breeds. The use of nonlinear models can also have a beneficial effect in improving prediction accuracies when using such populations [18].

Improving our understanding of genome function

Despite livestock research communities being small compared with those for humans, good progress has been achieved in generating many important genomic resources for farmed animals. Reference genome sequences have now been developed for most major livestock (poultry, cattle, pig, goat, and sheep) and several aquaculture species, the development of which has been reviewed elsewhere [44,68]. Although more work is needed to further improve the quality of each reference sequence, the initial research efforts leading to their publication established an important foundation from which to generate a range of other genomic resources (e.g., low-, medium-, and high-density SNP arrays). It also established a strong platform from which to continually increase our understanding of the nature and function of the genomic variations present within each species (Box 5).

Through various projects and coordinated initiatives, such as the 1000 Bull Genomes Project [45], the number of animals resequenced has gradually increased. It has allowed the identification of several tens of millions of SNPs for various characteristics of interest and has supported a growing understanding of the genomic variation that exists both within and between populations and the functionality of different parts of the genome. As the quality and annotation of reference genome sequences for various species continues to improve, more will undoubtedly be learnt. The use of nonlinear models to take such information into account in evaluations has already been shown to increase prediction accuracy [57,69], but the potential benefit would be expected to be even greater as more detail is uncovered. New methods to facilitate the analysis of large and complex data sets using nonlinear models and to enable single-step analysis are clearly needed [18].

Most existing approaches for implementing GS still only consider the additive effects of SNPs. While expected to capture the majority of genetic variation either directly or indirectly [84], there is evidence to suggest that also directly accounting for nonadditive effects, such as dominance, inbreeding depression, epistasis, and imprinting, could be beneficial [85–87]. One area of growing interest is the detection and analysis of gene networks to help improve modeling of variation due to epistasis [88–92]. As more detail on the genetic architecture of various traits is developed, and more data become available (a major limitation for effective research on nonadditive effects to date), the interest and opportunities to capture value from refining breeding schemes (for within-breed selection and crossbreeding) to take account of nonadditive effects is likely to increase.
Increased data collection, integration, and mining

Due to the size of populations required for viable statistical significance, most of the work described herein has been conducted using data collected on commercial farms, company-owned nucleus farms, or multiplier units rather than on research farms. New methods for data collection and collation on-farm and post-farm gate (e.g., in slaughterhouses) have been gradually evolving for several decades, and various important advances have been achieved as a result. For example, genetic evaluations for dairy cattle are now routinely conducted for resistance to mastitis (using somatic cell scores and direct observation records), and increasingly for metritis and ketosis using on-farm data [93,94]. An increasing willingness to share data, for clearly defined purposes, collected in different parts of the supply chain or as part of government-led animal health testing, has already generated real benefits. For example, genetic evaluations for cattle are now routinely conducted for carcass traits using slaughterhouse data [95–97], and for bovine tuberculosis (bTB) resistance in the UK using data collected as part of a national surveillance and culling programme [98].

Despite these innovations having been ongoing for some time, the rate of development has accelerated over the past decade due to a growing interest in developing and adopting new agritech data collection systems (e.g., sensors, cameras, microphones, gas analysers, accelerometers, and on-farm disease diagnostics) and internet-connected methods to further improve the sustainability of agricultural production, commonly referred to as PLF. The primary aim of PLF is to assist the...
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Box 1. Genomic selection

GS was first proposed in 2001 [19], and its implementation made feasible as medium and high-density (HD) SNP-chips (typically >50,000) became commercially available (see Figure 1 in the main text). The concept is based around exploiting the LD between causative variants/QTLs and the SNPs in an HD array, and “training” the model by estimating individual SNP effects using a representative subset of animals (ideally several thousand) that have both relevant phenotypes and genotypes. The adoption of GS has had a transformative effect on breeding programmes, particularly for dairy cattle, for which the adoption was most rapid, resulting in an increase in 50–100% in the rate of genetic improvement being achieved for most traits, and 300–400% for some with a low heritability, such as fertility, longevity, and resistance to specific diseases [18,20,21]. GS is now routinely used in breeding programmes for a range of livestock species, including cattle (dairy and beef), pigs, poultry, sheep, and goats [18,22,23], and for several aquaculture species [24,25].

As well as increasing the accuracy of evaluations for animals with genotypes and data, GS also allows genomic predictions with good accuracy to be generated for genotyped animals with little, if any, phenotypic data themselves or on their relatives. This is a particularly attractive benefit for traits that are traditionally difficult to measure, due to being sex limited (e.g., milk production or litter size), expressed late in life (e.g., lifespan), or difficult or expensive to measure (e.g., meat quality or disease resistance traits). For example, historically, accurate breeding value estimates were not available on young dairy bulls until ~7 years of age (when their daughters started to milk) but can now be generated shortly after birth, or even at the embryo stage, and for a fraction of the cost of traditional progeny testing.

After initial training of the models, good prediction accuracies can be achieved using GS for some time. However, the prediction accuracy typically reduces over successive generations, requiring periodic retraining [26–28]. The reason for the reduction is a gradual breakdown of LD between SNPs and QTLs due to recombination and is expected to be most rapid when using arrays with lower SNP densities [29]. Most commercial arrays were designed to include a limited number of SNPs that were commonly found across a range of populations and breeds, when considering phenotypes for only a small number of traits, that also provided good genome coverage. Therefore, a gradual breakdown of LD over generations is not unexpected, particularly when the arrays are being used to analyse traits and breeds not considered in the original design.

Box 2. Evaluation methods for genomic selection

The evaluation procedures applied to GS have evolved rapidly as advances have been made with statistical models and computing methods, and the number of genotyped animals has increased. Initially evaluations for genotyped and non-genotyped animals were conducted separately and then blended together, but now a concurrent evaluation using a single-step genomic best linear unbiased prediction (ssGBLUP) approach is preferred, because it allows more optimal use to be made of all the available data, reducing the risk of double counting and bias [30,31]. Although more computationally demanding, good progress has been made in increasing the efficiency with which evaluations can be conducted. For dairy cattle, single-step genomic evaluations for populations of >862,000 animals each with 79,000 SNPs genotyped are now routinely being run [32].

In using GBLUP approaches, all SNP effects are assumed to be well represented by a single normal distribution. This assumption leads to BLUP estimates of SNP effects that are a linear combination of the observed phenotypes [18]. Although high selection accuracies have been achieved using this approach, it is generally accepted that it does not accurately represent the biological background of traits. It is more likely that the size of effects will vary between SNPs and with traits, with a small number of SNPs typically closer to the causative variant(s) having a high, medium, or low effect on the trait of interest, but most will have none. As a result, there has been a growing interest in using nonlinear approaches to more accurately model SNP effects. These methods, often referred to as Bayesian methods, use prior distributions for SNP effects, and several different approaches have so far been proposed (e.g., Bayes A, B, C, and R), using one or multiple prior distributions of varying types [18,33].

Although increases in prediction accuracy over GBLUP methods have been achieved by using nonlinear models, the level of benefit depends on whether the simulated and real-world data and between traits [18,34]. Typically, their use increases prediction accuracies when SNPs with large and extreme effects are present, but are less beneficial for highly polygenic traits. However, the benefit appears to be more consistent when higher SNP densities are used, and generally highest when using WGS.

Use of nonlinear methods can also help mitigate against the effect of LD breakdown over successive generations because it allows less emphasis to be placed on SNPs with small effects that are likely to be located further away from the causative variant [33].

Despite the expected advantages, the use of nonlinear models in commercial evaluations has been limited to date, primarily due to higher computational requirements, making it difficult to analyse the large data sets that are now routinely available, but also since their use does not currently lend itself to a single-step approach [18].
management of individual animals by continuous real-time monitoring of health, welfare, production/reproduction, and environmental impact [99]. While many benefits can be realised through data collected solely on farms, the potential added benefit from collecting and integrating data from other important industry stakeholders (e.g., veterinary practices, government-run disease testing programs, etc.) should not be overlooked. The potential to add value has already been clearly demonstrated by the successes achieved with carcass traits and bTB resistance in cattle [98].

The growing volume, array, and quality of phenotypes being collected provides tremendous opportunities for animal breeding both to further increase the range of traits that can be

Box 3. Imputation

Over time, a range of SNP arrays with varying densities and levels of genome-wide coverage have been developed for many species (see Figure 1 in the main text). While the use of a higher SNP density was shown to result in higher selection accuracies in GS, the substantially increased cost relative to using low-density chips presented a barrier to their widespread use. Imputation was proposed as a method that could help capture many of the benefits without incurring the full cost of genotyping all individuals using a high-density (HD) chip. As part of the imputation process, statistical models, pedigrees, and a reference set of haplotypes (typically HD genotypes on relatives) are used to infer missing genotypes for individuals only genotyped using lower density chips [37,38]. The approach has since become popular, with several supporting software packages now available (e.g., Beagle [39], Fimpute [40], and AlphaImpute [38]). Given that the accuracy of imputation is influenced by several factors, the optimisation of analytical approaches and genotyping strategies has also been extensively researched. As a result, genotyping strategies in large breeding schemes often involve the use of three or more densities of SNPs [41,42] and imputation for non-genotyped animals from genotyped relatives is now also possible [38].

Given that commercial livestock breeding schemes are typically pyramidal in structure, such techniques offer a means to easily adopt a stratified approach to genotyping, whereby individuals at the top of the pyramid are genotyped to a HD or are whole-genome sequenced, those in the middle are medium-density genotyped, and individuals lower down the pyramid genotyped at low density. Using this approach allows a two (or more)-stage imputation process to be adopted, which helps to overcome some of the challenges of imputing directly from low density to HD or WGS [18,43].

Box 4. Use of multibreed/crossbred training populations in genomic selection

One of the reasons for the rapid uptake of GS in dairy cattle breeding is that one breed (Holstein) accounts for a high proportion of the national herd in many countries. In addition, good-quality phenotypes were routinely collected through well-established progeny testing schemes, and semen from key ancestors were frequently available in gene banks, which allowed high-density (HD) genotypes to be generated for them. As a result, it was possible to generate large training populations relatively easily. The requirement for large training populations makes successful implementation of GS a more difficult challenge for breeds or populations in which the number of available phenotypes for a trait of interest is small due to either small population sizes or recording difficulties. Consequently, the potential value of multibreed training populations, (including or excluding the breed to be evaluated) for across-breed prediction has been, and continues to be, of considerable interest. Their use has also been of interest as a potential method for helping to reduce the level of LD decay over generations when implementing GS, by helping to eliminate or reduce the impact of SNPs in long range LD with causal variants [18].

Our understanding of how multibreed populations can be used to have an important role in the implementation of GS has developed over the past decade. Typically, where large training data sets are available (e.g., for Holsteins), the use of multibreed training sets adds little value to directly increasing prediction accuracies [52]. However, where numbers are limited, the use of multibreed populations can help increase accuracy, but the level of accuracy is influenced by several factors, such as the size and structure/composition of the training set, and level of genetic relatedness to the population to be predicted, including whether the breed of interest is included. The results are also influenced by the SNP density being used, being more robust when using higher densities [56–63]. While additional work is needed to determine the optimal composition of training sets for different scenarios, it is clear that the use of multibreed training populations will have an important role in future GS programs for many breeds and species, particularly those with small numbers of animals or phenotype records.

Much of the research to date has focused on data from dairy populations, in which the predominant interest is applying GS within pure-bred populations. However, for many species, crossbreeding is a key part of typical commercial production systems. Consequently, there is growing interest in investigating the benefits of including crossbreds in the reference populations, with some benefits being reported [62–67]. However, more research will likely be needed to determine the optimal composition of reference populations for prediction and imputation in various types of crossbreeding system.
considered for selection and to improve the accuracy of selection. It also offers opportunities to further enhance PLF by adjusting management practices to take account of the genetic makeup of the animal or cohort, through a process of advanced phenotype prediction.

To fully harness the potential benefits of PLF, several major challenges need to be overcome. For example, suitable data infrastructure (including strong broadband access in rural areas) will need to be developed that can support effective data sharing in real time, along with advanced analytical methods for the increasingly complex multidimensional data sets that will become available [21,100–102]. Techniques, such as data mining, computational intelligence, machine learning, time series, and pattern recognition, are already being used to successfully analyse complex data sets from livestock systems and are likely to become increasingly important as more data are collected [103–107].

Despite the wide range of data that could be collected, many of the major challenges to be overcome to achieve effective industry adoption will be common across application areas and across livestock sectors. Given that many livestock sectors are highly fragmented and resources are limited, much could be gained from the establishment of a clear long-term vision and strategic plan at a national level that has strong buy-in from industry, academics, and government organisations. The availability of such plans may also facilitate the establishment of effective public–private partnerships to support development in key areas [104]. The importance of developing effective data-sharing protocols and strategies so that all contributors and users of the data can develop confidence in the system cannot be understated. As we move forward, technologies, such as blockchain, may also offer an additional means to help build confidence and trust [108].

Box 5. Increasing our functional understanding of livestock genomes

Particularly following the establishment of the Functional Annotation of Animal Genomes (FAANG) project in 2015 [70–72], our understanding of the functional nature of animal genomes has been gradually improving. The establishment of FAANG was inspired by the success already achieved with the human Encode project [73], but aimed to generate comprehensive maps of functional elements for a range of domesticated animal species. It now includes activity related to several livestock and aquaculture species.

FAANG work initially focussed on using a specific set of transcriptomic and epigenomic assays to define functional regions of the genome in tissues, including coding and regulatory sequences, with the latter increasingly being recognised as accounting for most of the genetic variation underlying complex traits [44]. As progress has been made, the focus has been widened to also include understanding the effect of genetic variation on genome function, with the aim of supporting improved genomic predictions and ultimately toward improved phenotypic predictions to support more informed management of animals by combining the results with other sources of data [72]. The consortium is not alone in working toward this objective; for example, results from a large-scale study for cattle, covering relevant tissue/cell types and candidate genes for 45 economically important traits, was recently published [74].

Pangenomes

It is increasingly recognised within the genomics community that a single reference sequence cannot fully describe the genomic variation that exists within a species [75]. As a result, there is a growing interest in establishing pangenomes for various species, with progress already having been made for a number of species, including microorganisms, plants and humans [75–78]. The recent establishment of the Bovine Pangenome Consortium [79] is likely to engender further progress in this field for cattle [79–82].

The general aim is to describe all the genes and variations present within a species by focussing on two subdivisions: the core genome, which is present in all genomes; and the accessory genome, which is present in a subset of the genomes within a species. Although highly complex, the use of a graph-based framework offers a means to effectively capture, visualise, and interrogate the information being generated [83], and has already been used for cattle [80]. The availability of pangenomes will be particularly useful in helping to better characterize and understand the impact of structural variations, such as inversion, duplications and CNVs, as well as epigenetic effects, which in turn would be expected to help increase the accuracy of prediction both within and between breeds.
The most appropriate level at which to develop a national strategy will depend on the specific circumstances in each country. For example, the US Department of Agriculture (USDA) published a new blueprint for genome research in livestock for the period 2018–2027 [21]. For countries in which adoption of PLF approaches is still at a relatively early stage, it might be appropriate to consider developing strategic plans to support widespread implementation of PLF approaches more generally, and to include the use of genomics within that, at least within certain livestock sectors, if not across sectors.

Next phase of development: genomic passports?

Much of the work conducted to date has focussed on genotyping or sequencing for the sole purpose of using this information to improve the accuracy of selection in breeding programs. Under those circumstances, the potential gain in prediction accuracy may often not be sufficient to justify the cost of genotyping many individuals, particularly to a high density. However, if we consider that access to genomic information could be used to support not only precision breeding, but also improved traceability and precision management of animals throughout their life, then this opens new possibilities when considering how future genomic profiling could be managed and funded for use in livestock production systems [109]. Historically the use of genetic tests to aid management has been low, in part due to the long delay (typically several weeks) between sampling and results becoming available.

If genomic tests were to be more routinely used, then ideally: (i) an animal would only be DNA sampled once during its life, at an early stage; (ii) the resulting genomic profile would be sufficient for any future applications that may be of interest, and could be uniquely linked to the animal for at least the duration of its life; (iii) the information would be easily accessible in real time, but only under managed conditions; and (iv) the genomic profiling and access cost would be low enough to facilitate its use on commercial farms.

The use of low-pass sequencing and imputation may already offer a means to achieve (ii) and may help go some way toward achieving (iv), particularly if the sequencing was carried out as part of a coordinated high-volume, high-throughput programme that included most, if not all, of the national population of a given species. Recent advances in cloud computing may also offer a means to meet at least partly (iii).

The perceived acceptable cost for use on commercial farms would likely depend on the commercial value of individuals within a species, and the anticipated number of times that access to the genomic profile would be of interest during the life of the animal, which would, in turn, be expected to increase with average productive lifespan. While the cost of WGS is still expected to reduce over time, acceptable costs may already be within touching distance for cattle.

In some countries, such as the UK, traceability systems for cattle are already well established. Typically, owners are required by law to tag calves with a unique ID (increasingly using an electronic tag) and register them on a central database within a few days of birth. The unique ID, owner, and farm of residence is then recorded as part of a cattle passport system. Subsequently, any sale or transfer of the animal during its life also needs to be recorded on the live system. If, in addition, the calf was DNA sampled at the point of tagging and the genomic profile linked to its unique passport on a cloud-based system, it could offer an ideal platform for supporting genome-enabled PLF for cattle. By linking to a traceability system, it also offers a potential means for cattle owners to control permissions, at least partly, for access to the genetic profile of the animal. Ensuring that cattle owners feel that the genomic information could not be accessed to disadvantage them without their knowledge is likely to have a vital role in developing a strong foundation for the ongoing
development and success of the system [109]. Provided a strong foundation could be established, the potential benefits that could be available would be expected to increase over time as further improvements in genomic resources and predictive models are made. Given the core importance that such a database could have, the rapid rate of technological advances and growing number of potential industry applications, establishment and running of a WGS database on a national or regional basis may be well suited to a public–private partnership.

Once available, this information could be used for a variety of applications (e.g., parentage verification, more secure traceability, mating optimisation, or determining the suitability of the animal for specific management, markets or disease treatment options; see [109] for a more comprehensive list) and would also help ensure that genetic predictions for various characteristics could be available for the whole cattle population rather than only those that are in, or related to animals that are in, structured performance recording programmes. While the increase in the number of animals for which genomic information is available might only be modest for dairy cattle populations, it would likely result in a large increase for most beef cattle populations, in which the level of performance recording is typically low and typically confined to only pedigree animals. This may also make GS approaches more accessible to a wider range of breeds, using single or multibreed training populations of various compositions as required, provided suitable phenotypes were available. Standardising the collection and access to genomic information would allow a greater development focus to then be put on collecting suitable phenotypes as needed and developing the suitable infrastructure and collaborations to do so.

Combined with appropriate phenotypes, the WGS database could also provide a valuable source of information for further research, breeding, and the development of genomic tests for various applications, such as to determine the suitability of animals for various production systems or target markets, feed, or health treatments. Given that most tests would likely focus on results for a relatively small number of SNPs or SNP combinations, once developed, this could offer significant advantages in terms of lowering computational requirements, making real-time generation of results for on-farm use more feasible. The information could also be combined with other data as appropriate to predict phenotypes more accurately and thereby further strengthen support for real-time decision-making and increase the potential benefits that could be achieved from adopting PLF approaches for cattle (Figure 2). If successful, the approach could also serve as a good exemplar to help scope what might be possible for other livestock species as and when unique identification and electronic IDs for individuals are more routinely used and recorded.

Although the results of the recent study on using low-pass sequencing and imputation for beef cattle are encouraging [46], the data sets used were small. More research would be needed to determine the appropriate depth of sequence coverage to use for existing cattle populations that would offer the best balance between constraining costs and meeting the likely broad range of possible future needs.

With WGS routinely available for large cohorts of animals, this could provide a strong platform from which to further extend the potential benefit from precision approaches using genomic tools, for example through tailoring feeding or health treatments to suit the genomic make-up of not only the animals themselves, but also the microbiomes and parasites that they interact with (Box 6).

**Genome editing**

During the early part of the genomics era, there was considerable excitement over the availability of tools that would enable manipulation of livestock genomes to introduce new sequence
variations, primarily identified in other species, that could generate novel and beneficial effects for various applications. The tools available at that time were limited in their specificity and, consequently, the transgenes were integrated randomly into the genome, resulting in unpredictable transgene expression [134,135]. The use of transgenic approaches is still actively researched in some areas (e.g., biopharmaceutical production and biomedical research) and potential benefits for agricultural production continue to be investigated [135–137]. However, their use in food production has generally been limited due to consumer scepticism over safety, welfare, and ethics, with high regulatory barriers or outright bans having been subsequently introduced in many countries [135]. To date, only one transgenic food product has been marketed to the public (The Aqua Bounty AquAdvantage salmon in the USA, with regulatory approval now also gained in Brazil), but only >25 years after its initial production [137,138]. Similar early excitement surrounded the potential value of using cloning in livestock production, fuelled by the development of Dolly the sheep using somatic cell nuclear transfer (SCNT). However, commercial application challenges have also emerged in some global regions (such as the European Union (EU), where commercial use of the technology to produce livestock is banned) following concerns over potential negative impacts on animal welfare [139].

Over the past 20 years, interest in genome editing (GnEd) to generate beneficial effects has been reignited following the discovery of programmable nucleases, such as zinc finger nucleases (ZFNs) [140] and transcription activator-like effector nucleases (TALENs) [141], which offered a means to edit genomes more precisely than was previously possible. The growth in interest accelerated further following the discovery of CRISPR/Cas9, which was simpler and offered more versatility compared with alternative methods. In each case, the basic concept is the same: the nuclease is used to introduce a double-strand break into the DNA at a targeted location, and the repair is undertaken by the mechanism of the cell itself, either without any additional influence (nonhomologous end joining: NHEJ) or is guided through provision of a repair
Box 6. Understanding host–microbiome and pathogen interactions
As genomic technologies have advanced, they have facilitated more detailed characterisation of the genome of not only an individual animal, but also that of the microbiomes and parasites that interact with it. By using metagenomics approaches, it has been established that microbial communities of the rumen and gut are highly complex (often including bacterial, fungal, protozoal, and viral communities [110,111]), dynamic, and influenced by the host’s genomics. The composition of these communities also has a significant effect on high value characteristics, such as feed efficiency and environmental emission (e.g., methane production in ruminants) and the health of the animal. These interactions have been explored in several farmed species, including poultry [112–114], pigs [115,116], cattle, sheep and deer [111,117–122]. As further advances are made with in-vivo (e.g., rumen boluses) and external sensors, on-farm diagnostics, and our knowledge and prediction models improve, it offers real opportunities to build-in a high level of individual tailoring into our feeding and treatment decisions.

Animal health
Genetic variation exists in and between animal populations in their resistance to a range of diseases [123–125]. However, other than selective breeding to increase the average level of resistance within populations for a relatively small number of diseases, little use has been made of that knowledge. This has been largely due to difficulties in collecting suitable data, including the level of infection in individuals with the parasite(s) of interest [126,127]. Advances in high-throughput and pen-side diagnostics are gradually increasing the speed and accuracy with which the presence of specific parasites species can be detected on farms, as well as the level of genomic detail that can be generated for them [128–132], opening the real possibilities of personalised medicine for livestock and populations. Should real-time access to the genomic profiles of individual animals on-farm be enabled, it could offer an opportunity to take account of the genetics of the parasite, the individuals infected, and the surrounding population. Optimal use could then be made of the isolation, treatment, and prevention measures available to minimise the need to use antimicrobial, antiparasitic, and antibiotic treatments, without compromising welfare.

When combined with other developments in PLF, it also offers a means to routinely generate valuable and informative on-farm data to support enhanced disease surveillance and on-going research in animal health, the generation of which has been both challenging and highly costly to date. If collation with data collected at veterinary practices was also possible, along with greater integration with data collected through national health programs [98], highly valuable source data to support on-going research could be generated for existing and emerging diseases in livestock. It could also offer a strong platform through which to harness further developments in multi-omic technologies [133].

template (homology-directed repair; HDR), in which one or more new bases are deliberately introduced at the cut site. When considered alongside the growing quality of genomic resources and functional knowledge, the reason for the excitement in the field is evident. In the context of agricultural applications, part of the excitement is due to the realisation that, as a result of the higher level of precision with which genome edits can be made, GnEd offers an approach that can be clearly differentiated from the transgenic approaches that still face high regulatory barriers.

Since the initial discovery of genome editors, numerous projects have been undertaken to edit a range of targets across most farmed species of livestock and aquaculture (see reviews and references therein by [134,142–144]). Further development and refinement of both the technology and application approaches to improve the accuracy and efficiency of the editing process have continually been underway [145]. The volume of research in this area has been extensive given the wider range of disciplines, in addition to livestock breeding, (e.g., human health, plant breeding, etc.) in which gene editing has potential applications. It has also supported not only improvements in the efficiency with which single edits can be introduced, but also a gradual increase in the number of edits than can be introduced simultaneously [146–148].

Remaining challenges
While many successes have already been achieved, several challenges still need to be overcome before GnEd can be considered as an efficient/cost-effective tool that can be routinely used in animal breeding and conservation.
Remaining challenges: incorporating GnEd into existing breeding programs

When the efficiency of the editing process is low, effective use of GnEd in successful commercial breeding programs would be challenging, particularly for less fecund species (Box 7). When combined with the challenges and costs associated with the development of suitable editing targets, it is likely to ensure that GnEd does not replace the use of GS anytime soon for improving most traits. However, GnEd could have a very important impact in situations similar to the examples outlined in Box 8 (see also Box 9), where good progress using GS is unlikely to be achieved, the traits of interest have a high value, and are under monogenic control.

In the case of edits that confer resistance to specific diseases, some additional thought may need to be given to how the edited animals could be best used in commercial populations, particularly where homozygous-edited animals are expected to have a higher level of resistance compared with heterozygotes. If the edited animals were used in breeding programs in which mating with nonedited animals was routine and disease challenge likely, this may lead to the infective agent more easily developing a means to overcome the resistance conferred. Obviously, if the carrier status of all animals within the population was known or could be easily checked (e.g., using a genomic passport), then ensuring that matings were only conducted between homozygous carriers could be more easily managed. Genus, a commercial company based in the UK, is in the process of developing the capacity to commercialize one of the edits conferring resistance to Porcine Reproductive and Respiratory Syndrome virus (PRRSv) in pigs [157]. Their commercialization plan is focused on generating homozygous carrier animals for sale that have been generated through a process of initially generating founders using GnEd (a process expected to take ~3 years) and then crossing and backcrossing into existing commercial populations. It is expected that development of sufficient animals to support their commercial sale will require six or seven generations of breeding once the founders have been produced. Given that the aim is to fix the edited allele in the breeding

Box 7. Remaining challenges: technology

Risks associated with insertion of non-intended sequences at target editing sites, off-target effects, and mosaicism have all been raised as concerns in recent years [149–151]. While further improvements are still needed, it is important to recognize that, as a result of the rapid rate of development, several options already exist that can help reduce the risk in each of these areas. For example, while use of NHEJ can be prone to errors/random insertions, the use of HDR offers a means to reduce their incidence. The use of vectors has previously resulted in accidental insertion of carrier DNA at the target site [152,153], but it is now possible to carry out genome editing without using carrier vectors, primarily through use of microinjection or electroporation. Recent improvement in genomic resources have also aided the selection of appropriate target sites and design of guide templates to increase specificity. Several improvements to the CRISPR/Cas9 system have recently been developed that offer benefits for specific edit sizes, particularly for editing point/single base mutations (e.g., CAS9 Nickase, Dead CAS9, Base editors, and Prime Editors). The ability to edit poultry primordial germ cells (PGCs), combined with the use of sterile hosts (discussed in Box 10 in the main text), also offers a means to reduce the risk of mosaicism in chicken. While still a concern when editing mammalian zygotes, several potential solutions are being investigated including shortening the longevity of the Cas9 and conducting GnEd on single cells (see [144,145] for more detailed reviews).

The majority of the most recent advances have been achieved through the use of CRISPR, which, given that it was discovered less than a decade ago, makes the rapid rate of on-going developments even more remarkable, and highlights the benefits of using an underlying technology that has a range of potential application areas.

Editing efficiency

Although success rates of over 90% have been reported, the efficiency of the editing process in animals generally remains relatively low (typically <25%) [137,145]. This affects the ease with which GnEd can be used in existing breeding programs, particularly for species that produce only a relatively small number of embryos. The challenge is even more difficult when the aim is to introgress the edits into existing commercial selection programmes that are achieving high rates of genetic gain for other traits. In the absence of high efficiency and high-throughput editing methods, the integration process will inevitably lead to a reduction or even temporary reversal of the high rate of progress that was being achieved, with the level of disruption being proportional to the number of live animals born from edits successfully made in high genetic merit embryos.
Box 8. Remaining challenges: target selection and validation

In addition to the development of the editing technology, one major challenge for the successful application of GnEd in livestock production is the identification of suitable editing targets. In the literature published to date, one or more of three general approaches have been used: (i) characterisation of naturally occurring genome variations between domesticated animals or breeds within a species that exhibit a phenotype difference of interest; (ii) genome comparisons between closely related domesticated or wild species that display a phenotype of interest; and (iii) identification of a gene/sequence believed to have a key role in a biological process of interest, and the disruption (knock out) of which could generate a desirable phenotype.

Given the successes now being achieved using GS, the primary industry interest in using GnEd in livestock breeding has tended to be around two main areas: improving welfare and resistance to diseases, the latter particularly for targets where more traditional selective breeding or other prevention approaches (e.g., vaccines) have not been effective. The most high-profile successful editing targets to date have been the introduction of a polled phenotype into the Holstein breed of cattle, and resistance to Porcine Reproductive and Respiratory Syndrome virus (PRRSv), which is currently endemic among pig populations in many parts of the world (see Box 9 in the main text). These targets were identified using approaches (i) and (ii). The highest profile use of approach (ii) has been an ultimately unsuccessful attempt to convey resistance to African Swine Fever virus in pigs (ASFv) (see Box 9 in the main text).

Although the initial attempt to convey resistance to ASFv was unsuccessful, a combination of approaches (i) and (ii) has since been successfully used to generate an edit that results in chickens that are resistant to infection from a subgroup Avian Leukosis virus (ALV-J [154]). The editing target (a cell surface receptor, as in the case of PRRSv) was initially identified through genome comparisons between susceptible (e.g., domestic chicken, jungle fowl, and turkeys) and resistant species (most galliform birds). The three-nucleotide deletion in the coding sequence for one residue of the receptor resulted in the knock out of one amino acid, which was sufficient to confer resistance to infection from the virus.

As the genomic resources available and the level of knowledge relating to sequence function continue to improve (see Box 5 in the main text), this will support an increased efficiency in the selection and refinement of target sites using each of the three approaches. Even so, it is likely that identifying suitable targets will continue to be challenging and costly, particularly when the costs of validation are also factored in.

population, it essentially requires a two-stage selection approach to be adopted, whereby breeding candidates are first screened on their allele status and then on their merit for other traits.

Box 9. Case studies in genome editing: polling, PRRSv and ASFv

Both polled and horned phenotypes occur naturally in many cattle breeds, but there is a low frequency of the polled variant in the Holstein breed, the most dominant dairy breed globally. The absence of horns offers a significant welfare benefit because they are typically removed mechanically to aid the management of cattle in indoor systems or during winter housing. While introgression of the genome variant using traditional means (cross and backcrossing with known carriers) would be possible in time, the use of GnEd offers the ability to introgress quickly and without negatively impacting (through linkage drag) the high rate of genetic progress in milk production and other traits that has been achieved within the breed over the past few decades. GnEd has been successfully used to introduce one of two known naturally occurring polled alleles. Although the simplest of the two known alleles, the ‘Celtic’ allele, is still a fairly complex variant involving a duplication of 212 bases, and an additional deletion of another ten bases [155].

Previous research identified that the primary entry route for PRRSv infection in pigs was through alveolar macrophage cells, and that one cell surface receptor (CD163) had an essential role in transporting the virus into the cells. Resistance to PRRSv has successfully been achieved using two separate GnEd approaches to disrupt one of nine extracellular domains of CD163 [156,157]. The most targeted approach involved deleting the entire coding sequence (315 bases) for the domain [157]. The specific domain was chosen because, other than being important for PRRSv infection, it was believed not to have any other biological function. Whether the same knockout effect could be achieved by introducing an even smaller edit in the domain is not clear. A similar process of identifying candidate editing targets based on understanding of the mode of biological interaction between the animal and the disease pathogen has also been investigated for several other diseases [158].

In an attempt to confer resistance to ASFv, candidate editing targets were identified through comparison of genome sequences for domestic pigs (highly susceptible, with a high mortality rate) and African warthogs, which have natural resilience to the disease. The targets identified involved a difference of 15 bases, resulting in three amino acid changes in the RELA gene. That the sequence variations in the gene could account for the resilience was considered plausible because it was known to encode a major component of the NF-κB transcription factor family, which in turn has a critical role in activating specific immune cells. Despite being initially promising [159,160], the introduced edits unfortunately did not confer resilience in subsequent validation trials [161].
An alternative strategy, called ‘promotion of alleles by genome editing’ (PAGE), has been proposed as an effective means to combine both GS and GnEd, whereby high genetic merit sires are first selected using GS and then, before dissemination, their genome is edited for several causative variants [162]. To be successful, this would require a high editing efficiency and an effective process for identifying causative variants. Ideally a heterozygous status for the allele would also confer a performance advantage to allow a rapid increase in frequency across the population using existing GS selection approaches or, alternatively, an effective genome-screening process would need to be in place for commercial populations. Although the relevant technologies are not yet at that level, the advances discussed in this review would suggest that some, if not all, of the elements required might be possible in the not-too-distant future, particularly if the genomic passport approach was adopted.

**Remaining challenges: funding research and development**

Even if a positive regulatory environment were to be developed (see following text), the costs associated with the successful development and commercialisation of edited animals will likely be significant. For commercial companies to invest in the use of the technology, they will need to be confident that they can secure a financial return. Although it is already possible to secure patents in relation to GnEd, they are typically granted for the resulting animals rather than the edit itself. This makes patent protection complex in sectors or systems in which crossbreeding is typically practiced. Where relatively long development and scaling-up periods are required (as in the example in the preceding text), securing good commercial returns before the patent expires may be even more challenging. However, there are variations in the business models that are typically used for commercialisation of elite genetics between livestock sectors and, as a result, greater control over new genetics may be easier in some sectors (e.g., pigs, poultry, and aquaculture) than in others. The ability to routinely generate and supply sterile edited commercial stock to customers, as might be feasible in time for some aquaculture species (see following text), could also have a dramatic effect on the level of control that companies could have and, thus, their appetite for investing.

In some cases, such as in the developing world, securing financial returns may be even more difficult, but the technology may still offer the potential to make a significant difference to smallholder farms, particularly those that are battling endemic disease challenges. In those circumstances, it would likely require public or other sources of funding to support relevant research. It is interesting to note that the Gates Foundation is already supporting several research projects in this area, with one jointly funded with UKAid [137].

**Other uses for GE; inducing sterility**

For mammalian species, most of the reproductive technologies in industry use today are based on initial breakthroughs that were made several decades ago (Figure 1). However, the techniques and approaches being used have gradually improved over time to increase success rates and reduce costs of use (e.g., embryo transfer, semen sexing, in vitro fertilisation, embryo culture, and biopsy; see, for example, [163–166]). These technologies have a key role in not only genetic improvement programmes and production (e.g., sexed semen), but also conservation. Many of the advances made, particularly in embryology and in vitro culture, have also had a key role in facilitating the development and adoption of the other technologies contained within this review.

However, progress with reproductive technologies in poultry has historically been comparatively slow. While the use of artificial insemination was possible, fertility using frozen semen was poor and no efficient methods were available for conserving female genetics [167].
This posed a particular challenge for conserving poultry breeds or lines, requiring the maintenance of live flocks.

Recent developments first reported in chickens have offered a solution. Within an early-stage developing embryo, primordial germ cells (PGCs) are present that, depending on the sex of the individual embryo, will eventually differentiate into sperm or ova. By first extracting these cells from fertilised eggs at day 3 of incubation, it has been possible to successfully culture, proliferate, sex, and cryopreserve these cells. Regeneration of the cryopreserved genetics has also been successfully achieved by thawing and then inserting these PGCs back into a developing embryo at the same stage of development as when they were extracted [167,168]. When using this approach, gonads from the resulting bird contain cells from both the transferred and hosts cells, and any resulting progeny would likely need to be genotyped to accurately determine their genetic lineage.

The development of these techniques with PGCs has paved the way for more efficient GnEd in chicken, because they offer several advantages over other methods that have been used previously [169]. However, the availability of sterile host male and female birds could have a significant benefit on the efficiency of reconstituting conserved or edited PGCs. By using GnEd, sterile host birds have now been successfully produced, initially using TALEN-mediated disruption of the DDX4 allele [170].

Successful use of the sterile host female to reconstitute pure-bred rare breed hens from thawed cryopreserved female PGCs was also demonstrated [171]. When the reconstituted hens are then inseminated with semen from males of the same rare donor breed, the progeny produced carry only genetic material from the cryopreserved rare breed. Although an important step, two hurdles remained for efficient commercial application of the technology. The first that sterile hosts for male PGCs were still required, and the second that generating a flock of DDX4 knockout females could involve a lengthy process and would need to be repeated each time because the genetic lineage could not be propagated.

A potential solution to both challenges has now been successfully generated in the form of transgenic male and female birds that can be induced to be sterile by introducing a drug into the developing embryo [172]. This would allow a live flock to be maintained and offer a significantly shorter timeline for regenerating conserved lines or generating a significant number of edited birds for other applications. The success was achieved by transferring an inducible caspase9 (iCaspase9) gene directly into the chicken DAZL locus using a GnEd approach. The utility of the approach was then demonstrated by introducing both the iCaspase9-binding compound and genome-edited cells concurrently into iCaspase9 embryos. The gonads of the resulting transgenic (G1) birds were then formed from only the introduced PGCs. When the G1 birds were then mated, 100% of the resulting progeny were from the edited lineages and did not include the iCaspase transgene. The model was successfully used to regenerate birds from two traditional breeds and two separate lines of genome-edited birds with targets related to feather phenotypes [171].

The obvious question regarding the use of the iCaspase approach is whether the use of transgenic birds could be easily accommodated within a commercial system without having to overcome significant regulatory hurdles. This will likely be easier to tackle once the regulatory requirements for genome-edited animals becomes clearer in various countries. However, two positive aspects seem to be (i) the fact that the iCaspase9 transgene is not transmitted to the progeny, and (ii) the edited progeny (non-transgene carriers) could easily be shipped as fertile.
eggs without needing to transfer the transgenic birds themselves out of the high biosecurity unit in which they would likely reside.

The successful use of GnEd to develop sterile host animals has not just been confined to chickens, as discussed in Box 10.

**Regulatory approaches and developing public trust**

Given the greater level of specificity that genome editors offer compared with the genomic technologies previously available, it has been generally accepted that the regulatory frameworks that had been in place over the past few decades are no longer adequate and need to be revised. As a result, the development of more suitable frameworks has been the focus of considerable debate and activity in recent years, with several national governments having either already amended, or being in the process of amending, their regulations (Box 11) or are undertaking a review (e.g., EU). Typically, (although not exclusively), the reviews have considered the application of the technology in plants and animals in parallel (along with applications in microorganisms and/or humans in some cases). A high-level overview of the current status of reviews for GnEd regulations plant and animals can be found online.

The key question generally being considered as part of the reviews has been whether the use of GnEd technology should automatically mean that developers would need to follow existing genetically modified organism (GMO) regulations. The definition of living modified organisms (LMOs) contained within the Cartagena Protocol [180,181] has typically been a key, but often not the only, consideration, particularly in countries where the regulatory responsibility for GMO is covered by more than one governmental department. Where reviews have been completed, the position adopted in nearly all cases has been that they should not need to follow GMO...
regulations, provided certain criteria are also met, but different criteria and approaches have often been adopted (Box 11).

Although these high-level frameworks provide a level of guidance for developers, it is generally accepted that highly detailed regulations will be difficult to achieve, at least in the short term. This is partly due to the rapid rate with which the editing technologies and application areas are evolving, but also recognising that there are several areas in which more evidence will be needed before a general consensus and agreement can be achieved. For example, how to clearly define; what would be considered novel combinations, which would likely need to include a clear understanding of what genome variations could arise naturally (including, additions, subtraction, and structural variations); and what new genome combinations could have been achieved using traditional breeding methods within a reasonable timeframe, which would likely need to include a clear definition for crossable species. The evidence presented over the coming years by developers to regulatory bodies for new applications of the technology is likely to play a large part in how the thinking process will evolve. The knowledge gathered through ongoing development of pangenomes for various species will also likely have a key role.

Box 11. Examples of regulatory approach and commercial applications of genome editing

Argentina (the first country to complete their review in 2015) determined that GMO regulations would not apply to new plant and animal products provided that no new genes were introduced and that there were no “novel combinations of genetic material” [182].

The UK announced plans to exclude genome-edited plants and animals from GMO regulations where the genomic change could have been achieved through traditional breeding or arisen naturally.

In Japan, animals and plants developed using site-directed nucleases are not considered GMO, provided there are no insertions of extracellular processed nucleotides in the host genome (effectively limiting the use of HDR to the insertion of small number of nucleotides [183]. Companies are also encouraged to voluntarily notify regulatory bodies when any GnEd product is in development or being considered for marketing [137].

In Australia, products derived through the use of site-directed nucleases are not regulated as GMOs provided that no templates were used to direct the repair [184].

In Canada, the regulatory approach adopted for GMO in general (which also applies to use of GnEd) is more focused on outcomes rather than on use of the technology itself, and regulatory restrictions are not applied provided no novel traits were produced.

In the USA, different regulatory approaches have been adopted for gene-edited plants and animals. The USDA concluded that gene-edited crops with mutations that could have occurred in nature would not be considered GMO. However, the regulations for animals are overseen by the US Food and Drug Administration (FDA), which has determined that intentional genome alterations in animals destined for the food chain would be regulated as new veterinary drugs and be subject to extensive testing requirements [185,186].

Commercial applications in animals

In 2021, the first food product from GnEd animals to gain regulatory approval globally was marketed in Japan. Regional Fish Institute Ltd, a Kyoto-based start-up, in collaboration with Kyoto and Kiniki Universities, developed GnEd red seabream and tiger puffer fish populations with increased edible muscle as a result of myostatin knockouts [137,187]. Seven GnEd products across cattle, pigs, and fish are also under regulatory review in Argentina, with the GnEd tilapia (developed by AquaBounty) already having been deemed exempt from GMO regulation in Argentina and Brazil [137,188].

Interest from large multinational animal breeding companies is also growing. Genus are working through the regulatory application process in the USA for the edited PRRSv-resistant pigs [135]. Other companies, such as Hendrix Genetics, Cobb Vantress, and Benchmark Genetics, are also actively engaged in research with a focus on applying GnEd technology.
To accommodate the current level of uncertainty, most countries have established, or intend to, a review process that developers can engage with to ascertain whether any new products being considered would be considered GMO [182]. Although extremely helpful, this could lead, at least in the short term, to additional international variations in regulatory requirements. As has been noted by others previously [182], if international variations in regulatory requirement persist, they could have negative implications for international trade and, thus, the development of at least some level of regulatory harmonisation internationally would be desirable.

Although not the only way of conducting GnEd, a significant proportion of the proof-of-concept studies published to date have used a SCNT step [144,145], the use of which is currently banned in the UK and EU. Developing a clear distinction between the use of the two technologies will likely be a key part of gaining public trust within those regions.

Building consumer trust
While the development of appropriate regulatory frameworks is an important step, it should not be seen as an endpoint. Rather, it should be viewed as the start of a new opportunity to build and maintain public trust in the use of advanced breeding technologies. Given the experience of reactions to the use of transgenesis and cloning (in some global regions), it is vital that its importance is not overlooked. For the animal sector, providing visible reassurance that any

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**Box 12. Benefits for conservation and maintaining biodiversity**

Although only briefly mentioned so far, all the technologies presented can have an important role in improving conservation schemes. The ability to cryopreserve PGCs and use them to efficiently reconstitute healthy populations is a major step forward for the conservation of chickens, both for biobanking rare breeds and for protecting high-value elite genetics from disease outbreaks, and preliminary evidence for potential applications in other avian species is also emerging [189].

Good genomic tools are now available to assign parentage more accurately, particularly in mixed mating groups, and the level of inbreeding and heterozygosity within a breed, population, or between individuals can be quantified more accurately (at the DNA level as opposed to estimated only from pedigrees) and managed as appropriate through more detailed mate allocation programs.

With the development of pangenomes, the specific nature of genomic differences within and between breeds can also be characterised in more detail, allowing more emphasis to be placed on conserving specific genomic characteristics of interest where appropriate.

Many geographically concentrated breeds are believed to have adapted over generations to meet specific geographical, management conditions, or market needs. However, little is often known about the genomic variation that underpins that adaptation, which makes effective conservation of the characteristics of interest more challenging. Some details are starting to emerge [190–194] but the development of a national WGS database, coupled with advanced phenotyping as the use of PLF methods continue to develop momentum, could allow a greater understanding to be established. Once better understood, it could also allow an assessment to be carried out as to whether those specific adaptation variants may be beneficial in other circumstances and, if so, whether the variants of interest could be best introgressed into other populations through establishment of a structured crossbreeding program or by using GnEd.

Good tools are also now available to identify causal mutations more easily for inherited diseases and to manage them appropriately as and when they arise. If such a disease appears at a high frequency in small populations and threatens their survival (e.g., if a population goes through a genetic bottleneck), then GnEd offers a means to correct that inherited disease so that population numbers can be recovered more easily.

In assessing how new technologies can best add value to conservation schemes, it is important to recognise that many existing programs for livestock rely heavily on coordination through nongovernmental organisations or volunteer groups with a strong focus on maintaining live (in situ) populations across multiple smallholder farms [195]. To have a positive impact, any new technology would need to add value and help evolve existing approaches rather than look to completely replace them, and also be accessible to existing groups.
introduced edits will not result in negative impacts on the welfare of the animal will be key to building trust with consumers. How that is best achieved may vary between countries and sectors, because it will likely depend on what assurance initiatives and schemes are already in place, and whether they can be adapted to suit. However, it should not be assumed that enough reassurance can be provided through only regulatory frameworks. In some regions, such as the EU, industry-led voluntary codes of conduct for animal-breeding companies relating to welfare have been in place for some time (e.g., Code-EFABAR). Whether adoption of such schemes will be sufficient or whether additional measures will also be needed to help build consumer trust remains to be seen. In that regard, it is encouraging to see initiatives such as the Coalition for Responsible Use of Gene Editing in Agriculture, being established, which hopefully will have a positive impact. However, it is also vital that clarity is established for a range of stakeholders over how the technology can, and will, be used in different scenarios, which is then respected so that trust can also be established and maintained.

Going forward, it is likely that genome editors and HDR will be increasingly important tools for producing transgenic animals for various applications. It will be important to clearly differentiate use of the technology for both applications to avoid confusion. In the context of plant breeding, referring to GnEd as part of applying ‘new breeding technologies’ has been advocated and has gained momentum, but has not as yet been widely adopted for describing applications in farmed animals.

**Concluding remarks**

In this review, we provide a broad overview of the existing use and recent developments in relation to genomic tools of relevance to livestock. Although not always explicit, we also provide suggestions of how and where the use of the different technologies could be used to generate a positive industry impact, particularly in relation to precision breeding, farming, and conservation (Box 12), along with some opportunities to increase the level of benefits that could be achieved. A number of challenges that will need to be overcome for these benefits to be fully realised have also been highlighted (also see Outstanding questions).

Over the past two decades, we have seen a rapid rate of development in genomic tools for various livestock species, and that high rate of development is ongoing. Many of the technologies presented have already been adopted by industry and have resulted in increases, not only in the rate of genetic progress for routinely measured traits, but also through the use of GS for traits that have previously been more difficult or costly to measure. The latter advantage is particularly important because it offers the ability to better tailor or further broaden selective breeding goals. As data on more measures of health and welfare are captured, they can then be considered as tools for monitoring, or indeed as breeding goals in their own right.

A high level of genomic detail can now be generated at a relatively low cost for most species, and the costs of doing so are still decreasing. Our understanding of the consequences of specific SNP variations in isolation or combination is also growing rapidly. This will likely result in a continual improvement of the accuracy and precision with which different tools and approaches can be applied. Where the specific genomic variation underpinning a characteristic of interest can be clearly identified, the use of GnEd offers an additional powerful tool that can be used, but only provided existing regulatory hurdles and public concerns can be addressed. Even then, it is likely to be used only in specific scenarios in which the genomic tools already in use are not effective, rather than replace them.

As we move forward, the increased use of genomics, alongside ongoing developments in sensors, diagnostics, data collection, analytics, and cloud computing, to support advanced precision

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**Outstanding questions**

- Can single-step nonlinear methods be developed that can be used to efficiently analyse large data sets?
- As WGS becomes more routinely used, the adoption of nonlinear modelling offers several advantages, but only if the increases in accuracy are additional to those currently being achieved.
- Can genomic-based prediction methods be adapted to account effectively for nonadditive effects?
- Nonadditive effects are rarely directly accounted for in current genetic evaluations for livestock, but are expected to have an important role in accounting for variation for some traits.
- What is the optimal composition of reference populations in which the primary interest is to improve imputation and prediction accuracy for crossbred animals?
- Most research to date has focused on the establishment of reference populations for pure-bred animals, but many commercial production systems are based around optimising crossbred performance.
- Can national strategies be developed to support the establishment of suitable infrastructure to enable effective industry-wide implementation of PLF, in which use of genomics is included as a core element?
- There are clear opportunities to benefit from greater use of genomics in livestock production, but to capture them in a cost-effective manner will require this to be set as a clear objective in ongoing development, and suitable infrastructure and accompanying training and policies are required.
- What is the optimal average genome sequence coverage to use as part of a national genetic passports scheme for livestock?
- Dramatic reductions in the costs of accessing sequence information could be achieved for some species through the establishment of national programmes based around a standard sequencing approach and imputation.
- The choice of sequencing depth to
livestock production, is a key opportunity area. The impact potential will likely vary between species, but if appropriate infrastructure can be developed to support the establishment of genomic passports, it could deliver a significant impact in species such as cattle, not only in improving efficiency, but also in reducing environmental impact and the use of disease treatments while still improving the health and welfare of animals. By facilitating the ability to spread sequencing costs across multiple uses and populations, that same infrastructure could also have a significant role in increasing the accessibility and use of genomic information across a greater number of breeds than is currently the case. In doing so, the potential benefits from the increased use of genomic tools to support conservation and selective breeding could also be increased (see Outstanding questions).

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Declaration of interests
None declared by authors.

Resources
www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost
vhttps://njdbickhart.github.io
iiihttps://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/
www.1000bullgenomes.com
iwww.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost

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25. Boudry, P., et al. (2021) Current status and potential of genomic selection to improve selective breeding in the main aquaculture species would ideally balance cost against the level of accuracy, which will likely be required for future applications. This can only be determined with time and successive data collection to optimise the process both economically and biologically.

How can the genomic sequence of an animal and cohorts be best combined with other information and used to optimise production systems and the management/treatment of individuals?

Is it possible to routinely identify causative variants that can be targets for GNEd?

Although several targets have been identified, many could be regarded as low-hanging fruit. New approaches for data collection, analysis, and high-throughput early-stage testing of candidate targets may be required to ensure that suitable targets continue to be identified.

Can transgenic birds have an effective role in the livestock industry if the risk of the transgene entering the food chain is minimised?

Currently, there is little use of transgenic approaches in food production due to high regulatory barriers, but the technology could have a key role in supporting sustainable food production in some sectors without transgenic animals entering the food chain.
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