



Department
for Environment
Food & Rural Affairs



**A REVIEW OF CURRENT AND NEW TECHNOLOGIES FOR BOTH
GENETIC IMPROVEMENT AND BREED CONSERVATION OF UK FARM
ANIMAL GENETIC RESOURCES**

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Produced by members of the Defra expert committee on
Farm Animal Genetic Resources (FAnGR)

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Executive Summary

Farm animals are fundamental for our food security, rural economy, and in managing our diverse landscapes. The selective breeding of animals to be better suited to management in specific environments, production systems and to meet different market needs has played a key part in managing livestock populations for centuries, and is responsible for the wealth of farm animal genetic resources that we observe today.

The UK has a long and proud history of pioneering developments in animal breeding approaches and the innovations achieved has led to the creation and growth of many of the leading international breeding companies in what has become a globally important industry.

The rate of advancements has accelerated over the last 60 years, and a variety of high-tech methods are now commonly used for most livestock species to identify the best animals to use for breeding. As well as helping to increase the accuracy of selection, recent advances have also allowed genetic improvement to be considered for a continually increasing range of characteristics, including measures relevant for improving product quality, animal health and welfare (thus reducing antimicrobial use), as well as reducing the environmental footprint of livestock production. Many of the new tools now available also offer the means to better manage and conserve our existing biodiversity.

Developments in animal breeding methods and tools are on-going, and as each advancement is made it potentially offers a range of opportunities for the UK industry. In this paper we aim to help stakeholders navigate through recent developments, and highlight the potential role that they can play in different scenarios, including mitigating the effects of global challenges, recognising that some are already available for widespread use while others are still at the research and development stage. As part of the review we consider technology developments in the following areas: Agri-tech, Reproductive technologies, Cryopreservation and Biobanking, Modelling social genetic effects, Animal Genomics, and other uses for Genomics.

Advancement in Agri-tech have already resulted in improved detection and measurement methods, and the ability to more easily integrate data collected for different uses. The rate of developments is also accelerating. This offers exciting opportunities to further improve livestock breeding programmes, but some livestock sectors are better placed than other to harness the potential benefits being offered.

Greater integration of data collected across livestock sectors (*e.g.* by farmers, veterinarians (public and private), and in abattoirs) could do much to help many sectors to further develop and thrive. An industry-led long-term sector development plan, standard methods for data collection, and appropriate mechanisms for data sharing and maintaining confidentiality would be key steps to help harness the opportunities on offer. This would be particularly important for the UK beef and sheep sectors where data collection is currently poor and highly fragmented. The UK Government, Devolved Administrations and Levy Boards need to work collectively with the livestock industry to achieve this.

Although variations between species exist, many reproductive and cryopreservation technologies are now at an advanced development stage and offer the industry effective means to improve rates of

genetic improvement, production efficiency (*e.g.* through use of sexed semen in cattle), and biobanking.

For the first time, tools to allow biobanking of female as well as male genetics are available for poultry. Extraction and cryopreservation of cells from early stage embryos have been shown to be suitable for long-term storage for chickens and results in healthy birds when reconstituted. However, further research is required to establish whether it can be applied to other poultry species.

There have been major advances in genomic techniques in recent years and that development is expanding rapidly. A range of tools are now available to allow detection of many of the natural variations in DNA that account for the genetic differences between animals and breeds. By combining them with advanced statistical models they can be used to (i) increase the accuracy of selection; (ii) allow easier genetic improvement of difficult to measure characteristics; (iii) detect and eliminate causes of inherited diseases; and (iv) improve management of biodiversity for conservation. Genomic tools have already been widely adopted for breeding dairy cattle and can also offer real benefits in other species.

A very recent development is the ability to edit individual genes within an animal embryo from one naturally occurring polymorphism to another. Current research interest is in using this technique to introduce variation known to confer resistance to specific diseases, where current breed populations have little or no natural resistance and no effective prevention and treatment strategies are available. Two specific diseases under investigation are porcine reproductive and respiratory syndrome virus (PRRSv) and African swine fever virus (ASFv). Both are a major concern for animal health and welfare because they result in high levels of disease and mortality. The technology is also being investigated as a possible means to improve welfare, such as by removing the need for dehorning in cattle or castration in pigs. It may also offer a means to correct inherited diseases in endangered populations, but it would be important to fund more exemplar projects to demonstrate its effectiveness in addressing these important challenges.

Being very open, canvassing public support, and developing an appropriate regulatory framework to underpin some of these technologies will be vital. This is especially the case for gene editing. It will be especially important to make clear that gene editing simply involves editing a gene from one naturally occurring polymorphism in the species in question to another: it does **not** involve the introduction of any 'foreign' gene from another species.

To derive maximum benefit from these various technologies it is vital not only that appropriate levels of funding for both fundamental and applied research continue to be provided, but that Devolved Governments, Research Councils, Levy Boards (as potential funders) and farmers cooperate closely to define research priorities and to ensure the effective transfer of research into practice.

Introduction

Farm animals are fundamental for our food security and in managing our diverse landscapes. They also underpin much of our rural economy and cultural heritage.

The UK has a long and proud history of being at the cutting edge of advances in animal breeding. This pioneering spirit, along with the varied landscape that can be seen throughout the UK, has resulted in the wealth of Farm Animal Genetic Resources (FAnGR) that we can observe today.

The innovations achieved in the UK led to a once thriving export market for UK genetics, and also the creation and growth of many of the leading international breeding companies in what has become a globally important industry.

Developments in animal breeding methods have been on-going for centuries, but the rate of advances has accelerated dramatically over the last 60 years. A variety of high-tech methods are now commonly used for most livestock species to identify the best animals to use for breeding, based on accurate estimates of their genetic potential across a range of characteristics of interest. When advances in genetic improvement methods were combined with advances in reproductive technologies, such as semen and embryo collection and freezing, it has resulted in a high value global industry. Progress continues to be made, particularly in improving the accuracy of 'breeding value' estimates using genomic tools and generating breeding values for desirable characteristics that have been elusive to date due to measurement difficulties. As each new advance is made, they potentially offer a range of opportunities for the UK industry, both for use in genetic improvement and in conservation of our biodiversity. To correctly identify these opportunities, it is first important to develop a clear understanding of how they can add value, while also recognising that the opportunities may not be equal across all farm animal species and breeds, due to varying biological, sociological and economic challenges.

In this paper we review a range of new technologies that could offer opportunities to generate real benefits and value when applied to genetic improvement and/or conservation of existing farm animal genetic resources in the UK and beyond. In reviewing each technology, it is important to highlight that as with many tools already successfully being used, they all have the potential to be very helpful, but only if used appropriately. Inappropriate use could equally threaten the maintenance and development of any farm animal genetic resources (*e.g.* it could result in high levels of inbreeding or proliferation of undesirable genetic conditions).

This paper is not intended to be an exhaustive list of all the new technologies that may have useful applications in animal breeding, but is rather a review of many of the main technology areas in which significant advancements have been made in recent years, and areas where the UK has existing capability (industry and/or scientific) that would allow adoption/implementation or where further development is considered feasible. As with any rapidly advancing industry, there will be continued developments in scientific knowledge and increased understanding over time which will lead to refinements to existing technologies as well as the development of new ones. With this in mind, it is intended that the information presented here will not only provide a useful snapshot of the current status, but also offer a strong base of understanding that can help better understand how any future advancements in these technology areas may add further value, and why they may have been

developed. This review is intended to be accessible to a wide audience, and therefore where references have been cited we have given preference to those that are easy to access for all.

As well as potential benefits from new technologies, there is also growing interest in the extent to which genetic selection may provide opportunities to breed animals with increased resistance to disease, thereby leading to a reduction in antibiotic use on farm, as well as in reducing emissions from livestock production systems. In view of that interest, we will also briefly consider the opportunities already being presented by existing tools and approaches, and then consider if and how many of the new technologies reviewed could potentially add further benefits.

Throughout the paper, the term 'breeds at risk' is used to refer to both rare breeds, and minority (numerically small) breeds used in mainstream agriculture.

At the end of the paper we will also make a number of recommendations as to how the UK industry could best take advantage of the opportunities being presented by these technologies.

New technologies in context - a brief history of developments in animal breeding methods

Breeding expertise was initially based around identifying animals with similar desirable characteristics and mating them together. Developments over time have included recording of ancestry/pedigree for individual animals, formation of breed societies, measuring and recording of characteristics that we wished to improve, and then combining this information with advanced computing methods and models to generate individual estimates of an animal's genetic value for breeding for specific characteristics (often called Estimated Breeding Values [EBVs] or Predicted Transmitting Abilities [PTAs]), which took account of differences in the way animals were reared and managed at different locations. As further advancements were made, this allowed direct comparisons of 'breeding value' to be made between animals located in different parts of a country, and then in different countries around the world, particularly for dairy cattle.

Today genetic selection is commonly used to improve a wide range and growing list of characteristics in most farmed animal species, such as growth rate, feed efficiency, milk and meat quality and quantity, skeletal soundness, egg quality and reproductive success. Selection for multiple characteristics simultaneously within a breed is achieved through use of selection indices, with individual weightings for traits in the index determined and optimised based on their level of genetic variation, genetic associations between them and, typically, the likely impact of change in each on the overall economic value of the animals within the production system or systems of interest. As computing methods have advanced, this has allowed more sophisticated models to be used to determine economic values for index development as well as models to determine levels of genetic similarity between animals so that levels of inbreeding and biodiversity can be managed for conservation, or managed alongside the pursuit of genetic improvement across a broad range of characteristics. As it has become possible to measure an increasing number of characteristics, this has allowed selection on a broader range of traits, but also offered the ability to more closely monitor and guard against potential unintended negative consequences through intensive selection on one or a small number of characteristics, a concern that was sometimes raised in relation to early breeding programmes.

Current status of breeding to improve disease resistance and environmental impact

Disease resistance

Genetic selection for improved disease resistance has been used as an effective tool to aid management of a number of livestock species for many years. For example, in the UK, selection to improve mastitis resistance and longevity (for which resistance to diseases will be a contributing factor) has been done by the industry for more than 15 years, and for increased resistance to Bovine Tuberculosis (bTB) since 2016. Genetic selection for improved resistance has also been taking place in sheep for diseases such as foot-rot, mastitis and intestinal parasites.

While effective, the biggest challenge has always been to get useful records on sufficient numbers of genetically related animals, as data collection can often be slow, difficult and expensive (as has been the case in the UK with the sheep diseases mentioned), with greatest progress made often through use of associated proxy measures, *e.g.* use of milk Somatic Cell Counts as a proxy for mastitis resistance in dairy cattle. Good progress in reducing the need for veterinary interventions has also been achieved in the UK through genetic selection on characteristics such as calving ease (dairy and beef cattle), locomotion (primarily through improvement in feet and leg structure), and fertility in dairy cattle. In countries such as the USA, estimation of breeding values in dairy cattle for reduced incidences of additional conditions such as displaced abomasum, milk fever, metritis, ketosis and retained placenta is also now routine.

Genetic variation in resistance to various diseases is also known to exist in pigs and poultry, but collection of useful records on selection candidates or close relatives is difficult given that elite breeding animals, particularly those managed within large breeding companies and cooperatives, tend to be managed in high health status units where exposure to diseases of interest in commercial farm environments tends to be very rare. As a result, the potential benefits offered through use of genomic tools (as discussed later) has been of particular interest. As with cattle, genetic selection to improve structural soundness of legs and feet which can reduce welfare and increase susceptibility to diseases has been conducted for decades in both species.

Where good records can be collected, genetic variation in resistance has been observed for most endemic diseases, and therefore genetic selection can play a key role in managing such diseases. As resistance to related diseases are often based on similar cellular mechanisms, selection for improved resistance for one disease may well have associated benefits for resistance to other diseases.

However, with the exception of a very small number of diseases, the proportion of the total variation accounted for by genetic variation between animals tends to be low. As a result, even where good records can be collected the rate of genetic progress that can be achieved tends to be low for most disease characteristics. It is also important to recognise that there is a wide range of disease challenges, each with their own predisposing factors, and many diseases are sporadic in nature, thereby making collection of sufficient numbers of good quality records even more challenging. Collectively, these make breeding for increased disease resistance extremely difficult, but developments in detection and routine data capture through advances in Agri-tech (see below) may help capture more benefits over time.

Reducing environmental impact

The main focus of the majority of genetic improvement programmes in livestock to date has been to breed animals that improve the efficiency of production and thus profitability of the farming system. In general, the focus has been on increasing production levels per animal, increasing number of offspring per female and improving survival rates, and for pigs and poultry also improving the efficiency of feed use. All of these objectives would also be expected to contribute to reductions in Green House Gas (GHG) emissions per unit product (*i.e.* per kilo of meat or litre of milk produced).

A Defra-funded modelling study completed in 2008 estimated that the genetic improvement achieved within the UK industry in the previous 10 years had contributed to reductions of 1.3%, 1.2%, 0.8% and 0.8 % per unit product of GHGs (quantified in carbon dioxide equivalents based on changes in emissions for three primary GHGs) for each year of selection in laying hens, broiler chickens, pigs and dairy cattle respectively ⁽¹⁾. The study also concluded that the annual rates of reduction would be expected to continue as further genetic improvement was made. In addition, it suggested that the rate of reduction would likely increase if/when the use of new technology that was able to increase the rates of genetic improvement became available.

The positive impacts had been achieved primarily as a result of three main factors:

- (i) the genetic improvement in production levels through increases in growth rates (given fixed slaughter weights), egg number and weight, litter size and milk yields;
- (ii) the high level of uptake of genetically improved animals through to the commercial level in each sector;
- (iii) for pigs and poultry, genetic improvement in food conversion efficiency.

Individual feed intake recording has been typically on-going within commercial pig and poultry breeding companies since the mid 1980's, and good rates of genetic improvement in food conversion efficiency have been achieved.

In dairy cattle, a positive impact was also being seen from genetic improvements in cow lifespan, even though this characteristic had not long been included in UK selection indices.

As part of the modelling study, the impact of GHG emissions through genetic improvement in sheep and beef cattle were estimated to be minimal, due partly to the relatively low use of high genetic merit animals at the commercial level, and also a lack of genetic improvement in food conversion efficiency.

Over the last five years, recording of feed intake to support genetic improvement of feed use efficiency in beef cattle has also started in the UK, with the establishment of the Beef Feed Efficiency Programme being a major component. The programme is a novel approach that was conceived after a review of approaches used in other countries around the world ⁽²⁾. It is focused on a network of three industry-based recording centres to monitor feed intake and growth rates in commercial cattle that will be

¹ Defra Project Report AC0204 (2008): *A study of the scope for the application of research in animal genomics and breeding to reduce nitrogen and methane emissions from livestock based food chains;*

² Defra Project Report IF0207 (2012): *Developing options to deliver a substantial environmental and economic sustainability impact through breeding for efficiency of feed use in UK beef cattle;*

open for use by any breed, with the information collected being used to generate EBV's for purebred animals within the respective breeds. Work to establish the network started in 2015 and was supported by public funding from Defra and the Scottish Government, with administrative support to run the programme provided by AHDB. Once the units were set-up the initial focus was on refining recording protocols and approaches with industry input and generating the required information on genetic variation for measures of interest and associations with other characteristics using two breeds as exemplars (Limousin and Aberdeen Angus). A key component to the successful establishment of the project was the recent availability of advanced electronic individual feed intake recording equipment for cattle.

The project has now entered its second phase (with public funding support secured for 3 years from Defra), and will focus on continued refinement of the approaches for data collection, analysis and routine generation of EBVs to allow genetic selection of more feed-efficient animals. Additional work will also be done to record meat quality characteristics on feed intake evaluated animals, with the aim of also including such measures in future selection programmes.

New Technology Areas

1. Opportunities through Agri-tech

The rapid developments in detection (sensors and disease diagnostics), electronic data capture, storage, integration, sharing, processing and analysis that have been achieved over recent years have had a dramatic effect on society. In Agriculture, these developments are often characterised under 'Agri-tech' or 'precision farming', and while still at a relatively early stage in terms of applications in animal production, there have been a number of significant advances made already (*e.g.* sensors such as Video Image Analysis (VIA) of carcass quality in abattoirs, wireless wearables to detect oestrus and lameness, and wireless rumen boluses to detect acidosis and temperature fluctuations due to disease in cattle), and the level of interest and activity from developers and investors is growing rapidly world-wide. As the scale of developments in these areas continues to gather momentum it offers tremendous opportunities to improve farming productivity and reduce emissions through improvements in the management, health and welfare of animals.

Improved detection methods

It is likely that the largest market growth in the livestock sector will be in detection methods for characteristics of interest for managing animals, including their health, as opposed to measurement solely for breeding purposes. However, it is important to recognise that data collected primarily for management use has formed the main source of data for much of the genetic improvement successes that have been achieved in recent decades (*e.g.* growth rate, milk yield, longevity, age at first calving, calf survival, carcass classification and bTB status).

Consequently, such growth could offer a valuable source of additional data for enhancing genetic improvement programmes. However, if there is a proliferation of technology providers that all use different approaches to detect and measure the same or similar characteristics, then it may not be possible to directly compare and combine different datasets. This could potentially limit their use in genetic improvement breeding programmes. This issue may be particularly important for industries

where datasets are usually collated from across a number of independent small to medium scale farms, as is commonly the case for cattle and sheep.

Ensuring steps are taken to harmonise the structure and format of data collected from these new detection methods across the industry, or sectors of the industry, could have a big effect on their overall value for genetic improvement purposes.

Data sharing and integration

Some success has already been achieved in the UK through data sharing and integration, such as in the generation of breeding values (PTA's) for dairy cattle using data collected through the British Cattle Movement Service, PTA's for dairy bulls for increased bTB resistance (which results in a small but significant reduction in the incidence of bTB in their daughters), and EBV's for carcass characteristics of beef cattle from data recorded in abattoirs ⁽³⁾ (a project supported by AHDB and HCC). The UK national genetic evaluations for dairy cattle are also conducted routinely through the integration of data collected on farms through three recording services companies.

As the use of individual electronic identification (EID) grows for many livestock species, opportunities to gain even further benefits will continue to emerge provided new data systems and business models are built in ways that will allow the potential benefits that could be gained from data sharing and integration to be considered and explored. For example, a wealth of data is already being collected in abattoirs on disease incidence and condemnations (*e.g.* by Food Standards Agency officers), and by veterinarians and farmers on disease incidences and treatments on farms. As the use of electronic recording systems becomes more routine, the quality and quantity of similar data collected on farms would be expected to increase. If collation on a routine basis were possible, such data could offer substantial benefits for:

- disease surveillance (generating benefits for the whole industry, particularly if linked to farm-level diagnostics and veterinary practice data);
- management (day to day and developing more informed herd and flock health plans to reduce antimicrobial use);
- benchmarking (*e.g.* farm productivity and animal health);
- new genetic improvement programmes and the better characterisation of the value of the genetic resources.

The use of on-farm software is already common on many UK dairy and pig farms and is becoming more popular on other types of livestock farms. With this growing demand, the industry is also seeing an increase in the number of on-farm software providers. An increased uptake by UK farmers should be actively encouraged as it could provide a key step in helping the industry take best advantage of the opportunities being offered by Agri-tech developments. However, long-term success will likely depend on limiting the number of times farmers and other data providers will need to input the same data for different purposes (*e.g.* on-farm management, traceability *etc.*), which will require effective connectivity and data sharing between different systems. If developed effectively, the farmer's own

³ http://beefandlamb.ahdb.org.uk/wp-content/uploads/2013/04/carcasetrait_evaluations_final_report.pdf

software system could be a key part in pushing out data for use by collaborators or public bodies, and for pulling in data for on-farm use from similar sources. It is important to also recognise that the availability of more on-farm detail on the performance of various animals may also help demonstrate the value of improved genetics and thus help stimulate demand and increase the level of industry wide benefits that is captured through genetic improvement.

Concerns over commercial sensitivities will undoubtedly play an important role in determining how much and how frequently data are readily shared in the future. These concerns can likely be managed more easily where long-term relationships have been developed in supply chains that include a relatively small number of stakeholders, as is common in the pig and poultry sectors, where some successes have already been achieved. However, the challenges will be greater in more fragmented and dynamic supply chains, as is common with beef and sheep production. In those circumstances, appropriate development of UK wide data hubs, aligned with clear rules on how various data sources could be used, may offer the means to overcome several concerns over data sharing and help build sufficient trust to allow many of the potential benefits to be realised. An overview of typical structures and current levels of data sharing in the main UK livestock sectors are shown in Appendix 2.

Development of industry-led long-term visions of how data collection and sharing could be effectively used to benefit the industry and various stakeholders within it, could be of benefit for all UK livestock sectors to help guide appropriate future investment, but will be particularly important for sectors with more fragmented data collection. For the beef and sheep sectors in particular where current levels of data recording are minimal, including consideration of the role that UK wide data hubs could potentially play in achieving that vision would be important, and would likely also play an important role in building trust and helping to establish a road map to help realise that vision. Establishing standard approaches for recording data on specific characteristics across the industry (including in on-farm software systems, and detection methods as already mentioned) could also greatly facilitate the ease with which data can be combined, and thus potentially have a major effect on reducing development costs and increasing overall benefits. Historically in the livestock industry, the International Committee for Animal Recording (ICAR) has played a key role in helping achieve a level of harmonisation across countries, particularly for recording in dairy cattle. Whether ICAR will continue to be able to cover most areas as the growth in detection methods continues and can extend its activity to cover other ruminants in sufficient detail remains to be seen. It is important to acknowledge that, currently, data collection across the UK in the beef and sheep sectors is highly fragmented and becoming increasingly so (see Appendix 2).

Development of a long-term vision and a coordinated approach to data collection and development across the Devolved Administrations and wider UK industry could have a big effect, not only in harnessing the value that can be provided through genetic improvement, but also on capturing value from data for a wide range of applications and from adopting new technology, all of which are likely to be key elements in helping the sectors thrive.

As further technological developments are made, there is little doubt that the amount of data available will increase, as will the level of complexity that will need to be navigated to derive real cost-effective benefits for livestock breeding and conservation. Current and on-going advances in data analytical approaches, such as machine learning (*e.g.* automated real-time analysis and detection), are and will likely continue to play an important role in helping to achieve that goal.

As well as offering a valuable source of data for improving on-farm productivity, environmental impacts, animal health and welfare, and genetic improvement, developments in Agri-tech as described above also offer a great opportunity to better characterise and understand the true differences between the UK's wide range of farm animal genetic resources, both for informing optimum breed choice for different farming systems and genetic improvement to meet the challenges ahead, but also to help explain and promote the value of our genetic resources for the purpose of selling breeding animals and genetics internationally. The level of information on characteristic differences between various breeds currently available is relatively low, being mainly focused on appearance, some production characteristics (*e.g.* growth rates, milk production, lambing rates) and geographical areas in which they are primarily kept. Further developments in Agri-tech offer the means to increase the level of detail available, but also should offer the means to record and genetically improve characteristics that previously could not be recorded easily or not recorded at all.

2. Reproductive technologies

Included within this category are artificial insemination (AI), semen freezing, semen sexing, multiple ovulation and embryo transfer (MOET), freezing of embryos and ova, and *in vitro* fertilisation (IVF).

Some of these (AI, semen and embryo freezing, MOET) are used widely in mainstream animal breeding, but their success and application varies across the species. For example, the use of frozen semen is widely applied and very successful in cattle, but in other species, such as sheep, goats, pigs, horses and ponies, pregnancy rates are significantly lower with frozen semen, with the result that fresh/chilled semen is often the method of choice for conventional breeding purposes. Nevertheless, even in these species, semen freezing can have a significant role in breed conservation (see section on Biobanking).

As well as conventional systems of semen collection, it is also worth noting that very limited volumes of semen can also be collected from the epididymis immediately after death or castration of a key male animal. This can be especially important for breed conservation purposes.

Fresh/chilled boar semen remains viable for several days, facilitating its transport without the need to first cryopreserve it, thereby allowing cervical AI to be commonly used by keepers of traditional pedigree pig breeds in the UK.

In addition, the ease with which AI can be carried out in different species varies, and this partly explains differences in adoption rates. For example, in cattle, goats and pigs, AI is trans-cervical, allowing semen to be deposited directly into the uterine lumen. However, in sheep this is not yet possible, requiring a laparoscopic approach through the abdominal wall to permit deposition of semen directly into the uterus which is essential to generate acceptable conception rates with frozen semen. Development of a welfare-friendly technique that allows effective trans-cervical AI in sheep could dramatically increase the benefits from its use for genetic improvement and breed conservation.

Semen collection and freezing are also possible in chickens and turkeys although again fertility using frozen semen is significantly lower than for fresh semen.

Semen sexing

The sexing of semen using flow cytometry was first introduced for cattle some 30 years ago. As well as removing dead and immotile sperm from the sample, this process resulted in semen samples that were >90% sperm of the desired X (female) or Y (male) chromosome types. In theory this allowed breeders far greater control over the sex of the offspring being produced compared with unsexed semen. However, at that time, the pregnancy rates achieved with frozen sexed semen were only around 70% of those achieved with unsexed semen, resulting in low rates of uptake in commercial production, although it was used by breeding companies in the generation of IVF embryos of the chosen sex.

Over the last decade, significant improvements have been made to sorting processes, making them more efficient and more benign for the sperm cells. As a result, commercially available sexed semen (4 million sperm per dose) now produces similar pregnancy rates in both heifers and cows when compared to unsexed semen (15 million sperm per dose) as long as AI is undertaken close to the time of ovulation, suggesting that the sorting process reduces the time required for capacitation of sperm in the female reproductive tract to facilitate fertilisation. Furthermore, the technique is now being used by many international cattle AI companies worldwide, to sex sort semen from a wide range of high genetic merit sires. These improvements have significantly increased the uptake of AI using sexed semen in commercial cattle production, especially in dairy herds where it allows producers to selectively breed their heifer replacements from the best genetic merit cows in the herd and largely avoids the production of unwanted low beef quality dairy breed male calves. The lower genetic merit cows can then be mated with beef sires to produce offspring with improved meat quality. It has been estimated that rates of genetic improvement in dairy herds can be increased around 2.7-fold using this approach, and if combined with genomic selection (see Genomics section) this can increase to around 4.8-fold.

The potential advantage of using sexed semen in terms of genetic improvement will be greatest for dairy cattle, where a large proportion of the genetic improvement is driven through highly selected males, and the highest genetic merit females can be used to produce them. However, there are also significant benefits that can be captured through its use at the commercial level in both dairy and beef cattle production. In addition to reducing the number of unwanted purebred dairy bull calves mentioned above, it can also be used to improve the efficiency of producing replacement females and increasing volumes of meat produced per beef suckler cow, both of which can help increase efficiency and environmental benefits per unit of meat produced

As well as providing benefits in mainstream cattle breeding, conservation organisations should also be encouraged to work with commercial cattle breeding companies offering these techniques to collect and biobank sexed semen as well as sexed embryos from breeds at risk as this could help improve the efficiency of any breed recovery programme.

It has also been shown that AI using sexed ram semen can result in similar or better pregnancy rates compared with conventional frozen semen, and indeed may improve fertilization rates in superovulated donor ewes within an embryo transfer system. It has been suggested that these improvements result from the fact that AI in sheep uses a laparoscopic approach in which semen is deposited directly into the uterine lumen close to the fallopian tubes.

However, significant challenges need to be overcome before semen sexing can become routine for either horses or pigs. The use of cryopreserved semen in horses results in high levels of early embryonic death, no matter whether unsorted or sexed semen is used, and this limitation needs to be overcome.

The major challenge in pigs is that the number of sperm required for conventional cervical AI (2.5 – 3.0 billion) would require very long sorting times to produce a single dose. Current research is therefore investigating whether this can be overcome by either laparoscopic AI or specialist catheters that can be passed through the cervix to facilitate deep intrauterine AI to deposit reduced numbers of sperm at the tips of the uterine horns. If these techniques prove successful, sexed semen could be used by the major pig breeding companies in their nucleus and multiplier herds. In addition, such techniques may also result in significant improvements in pregnancy rates following the use of frozen semen. This would be of major benefit for biobank samples (see below).

Semen sexing in poultry is irrelevant because in birds, contrary to mammals, it is the female that carries the two different sex chromosomes which will determine the sex of the chicks: male birds carry two copies of the same sex chromosome, and therefore produce only one type of sperm.

MOET, IVF and embryo freezing

Multiple ovulation and embryo transfer (MOET) is a process whereby a donor female is given a course of hormones to promote superovulation which results in increased numbers of eggs being released by the ovary. The female is then inseminated, and the embryos are flushed from the uterus a few days later. The resultant embryos can then either be transferred fresh to a recipient female or else frozen for future use/biobanking.

The application of MOET is both successful and of far greater importance in ruminant species than in pigs because of the much smaller litter size of ruminants. Indeed, using the highest genetic merit females within the herd/flock as embryo donors within a MOET programme can significantly increase rates of genetic improvement.

However, the induction of multiple ovulation in equids is more problematic, because of the different structure of their ovaries. MOET is also not possible in avian species, necessitating a different approach for biobanking purposes (see section on Avian primordial germ cells).

A related, but different approach used in cattle is *in vitro* fertilisation (IVF). With this approach, a veterinarian uses an ultrasound guided needle via the vaginal wall to aspirate ova from ovarian follicles. These are then matured *in vitro* for 24 hours before semen is added to achieve fertilisation. Following development in an incubator for 7 days, suitable quality embryos (approx. 30%) are either transferred into recipient animals or cryopreserved for later transfer.

The use of IVF offers some advantages over MOET because:

- more ova per cycle can be collected;
- ova can be collected more frequently (every two weeks);
- ova can be collected from young, virgin heifers (from 10 months old onwards);

- embryos can be produced with less sperm, which may be particularly useful for conservation where the number of doses or quality of semen available is low;
- individual ova can be fertilized from separate males, which can help increase biodiversity if the availability of ova is a limiting factor;
- embryos can be screened for genomic traits of interest prior to implantation into the recipient surrogate.

All these factors can help increase the rate of genetic improvement that can be achieved. Furthermore, if a particular sex is preferred, then this can be achieved by combining IVF with sexed semen. However, the system needs to be managed with care because there is evidence that in a very small proportion of cases foetal oversize may occur.

Across pigs and ruminant species, the ability to successfully freeze embryos is not only useful for the international movement of genetic resources in mainstream breeds but can also play a significant role in breed conservation (see section on Biobanking). In contrast, the freezing of equine embryos is far more challenging, likely due to their larger relative size. However, recent successes have been achieved by using slow freezing, or vitrification (a novel freezing technique in which the production of damaging intracellular production of ice crystals is prevented).

When combined with performance recording and genomic tools (see later) to identify superior genotypes these different reproductive technologies can help significantly increase rates of genetic improvement for a wide range of traits. This capability increases their usefulness for both mainstream breeds and breeds at risk.

3. Biobanking and related cryopreservation technologies

Cryopreservation of semen, embryos, ova, and somatic cells (for cloning – see later section), as well as avian primordial germ cells (see later section), could all have a significant role in breed conservation via biobanks. When used appropriately, these can safeguard against population and genetic diversity losses due to unforeseen events that could threaten a breed's survival ⁽⁴⁾.

The preferred tissues for biobanking are semen and embryos. However, this is only possible in species where these tissues can be frozen and/or MOET is successful *i.e.* cattle, sheep, goats, pigs and to a lesser extent equine species. In some species, pregnancy rates using frozen semen are significantly lower than when fresh or chilled semen is used, but this difference is not sufficient to preclude biobanking frozen semen from these species.

Cryopreservation of ova can also provide an additional safeguard against the loss of breeds at risk. This may be necessary when it is not possible to freeze embryos. However, there can be additional problems associated with this technique. IVF using cryopreserved ova to generate embryos for transfer into recipient females results in lower pregnancy rates compared to *in vivo* derived embryos.

⁴ Hall (2013) Defra Project Report *GC0146: Development of co-ordinated in situ and ex situ UK Farm Animal Genetic Resources conservation strategy and implementation guidance*.

When storing cryopreserved semen and embryos (or ova) in a biobank, it is important to make sure that they represent a wide genetic pool from across the breed in order to maintain genetic diversity.

Current *ex situ* stores from 'breeds at risk' appear to largely consist of frozen semen. This means that regeneration of the breed in the event of a major loss of *in situ* populations would be impossible without the introduction of crossbreeding to a female of another breed followed by backcrossing to the preserved breed. While this approach may be appropriate when all else fails, it is important to realise that it will inevitably result in the introduction of genetic material from the 'alternative' breed used in the initial crossbreeding process. Conservation organisations therefore need to give careful thought to the cryopreservation of embryos as well as semen to guard against this eventuality, especially now that the costs associated with generating and storing these has decreased.

It is also important to recognise that *ex situ* stores of semen laid down for other purposes (*e.g.* as part of the National Scrapie Plan for sheep) have significant limitations for breed conservation purposes and should not be considered an appropriate substitute for carefully planned biobanks of genetic material.

While some may think that biobanking semen and embryos is relevant only to rare breeds, this is not necessarily the case. History has clearly shown that the relative importance of breeds to mainstream agriculture can change in a very short time period, and that once important native breeds can quickly become 'native breeds at risk'. Therefore, all breed societies should be encouraged to biobank genetic material for conservation purposes to guard against this eventuality. This strategy is especially important for some of the numerically smaller mainstream breeds, especially those with limited geographical distribution which are very vulnerable to the consequences of some unforeseen disease event leading to the loss of important genotypes.

'Small' breed societies responsible for both farm animal and equine species should work closely with conservation organisations to seek the most cost-effective solution for biobanking to guard against such eventualities.

Cloning

Cloning involves the removal of the nucleus from a somatic cell (the cell from any body tissue that is not a germ cell) of an animal, transferring it into an enucleated egg of a donor animal of the same species and then generating an embryo for transfer into a surrogate mother. Embryos derived through this process have a much lower success rate than those derived through conventional embryo transfer. It may also result in significant welfare issues for a proportion of the resulting offspring⁽⁵⁾.

The main focus of commercial cloning in livestock breeding to date has been to multiply up high genetic merit animals. This has been used in North and South America to create 'copies' of high genetic merit dairy bulls, with their semen then being made available for conventional breeding purposes.

There has been considerable public resistance to cloning using somatic cell nuclear transfer in the UK, at least for mainstream breeds supplying food for human consumption. However, the use of cloning

⁵ FANGR Report on Cloning; available at <https://www.gov.uk/government/publications/farm-animal-genetic-resources-fangr-statement-on-cloning-farm-animals>

does offer a means to regenerate animals from cryopreserved somatic cells. Such an approach could be very useful for regenerating 'breeds at risk' that have been lost through some unforeseen catastrophic event (e.g. major disease culling) or to overcome 'bottlenecks' within a breeding programme. This approach would enable animals that are unable to breed naturally (e.g. castrate males, aged animals) to generate progeny into the breeding programme.

The use of cloning for the preservation of 'breeds at risk' does not seem to have the same public resistance as cloning in mainstream breeds. However, while cloning does retain the nuclear DNA of such animals, a small proportion of the total DNA of an animal, the mitochondrial DNA, comes from the donor egg. Therefore, a clone is not a complete copy of the animal providing the somatic cell. Consequently, whenever possible, cryopreservation of embryos remains preferable for biobanking because these retain all DNA, nuclear and mitochondrial, of the breed in question, and therefore will generate a 'true' copy of the original donor breed.

In the past, cloning was a necessary step to facilitate genome editing (see later section). However, recent advances with the genome editing approach mean that cloning is no longer required for this technique.

Avian primordial germ cells

The preservation of poultry breeds or lines poses particular challenges especially with respect to biobanking. This is due to the different structure of their ovum compared with mammals together with the poor fertility of frozen poultry semen. Cloning using somatic cell nuclear transfer is also not an option because embryo transfer is also not possible in avian species.

Recent developments made in the UK with the chicken have indicated that the isolation and freezing of primordial germ cells (PGCs) may provide an alternative approach for biobanking poultry material. PGCs are specialised stem cells that can be isolated from Day 3 embryos and which, depending on the sex of the individual embryo, will eventually differentiate into sperm or ova. Following isolation, these PGCs can be cultured and cryopreserved, and after thawing be transferred back into a Day 3 'recipient' chick embryo to develop and differentiate into gametes (ova or sperm) alongside the recipient bird's own PGCs. Some of the resulting gametes will therefore be derived from the donor breed and could permit the regeneration of the breed from which the cryopreserved cultured PGCs were initially taken. Furthermore, as described in a later section, the recovery of cryopreserved PGC's would be greatly aided by the use of genome edited sterile birds, particularly if the generation of sterile males follows the success already achieved in generating genetically sterile female chickens. Such developments offer exciting possibilities for the conservation of poultry breeds.

Current research has focussed largely on the chicken, and it will be necessary to establish whether, and under what conditions, this approach can be applied to all poultry species. While the technology may have special relevance for the preservation of poultry 'breeds at risk', it may also have an important role within poultry breeding companies to maintain important parental lines of mainstream poultry breeds used in commercial poultry production without the need to keep large populations of live birds.

4. Modelling social genetic effects

Conventional selection approaches focus primarily on estimating the effects of an animal's genetics on its own physical performance as accurately as possible, by using records for the characteristic of interest on the animal, its contemporaries and relatives. Whilst it was generally accepted that an animal's social behaviour can also affect the performance of contemporaries managed with them, both through negative effects such as aggression, bullying, tail biting or feather pecking, and also through positive effects, such effects were historically not being taken account of in breeding programmes. As interest in developing strategies to improving the welfare of animals has grown, the primary focus has been in changes to management practices and through environmental enrichment. However, interest in selecting for improved behaviours and social interactions has also grown, particularly as restrictions on management practices such as tail docking and beak trimming has increased.

Variation in the behaviour of animals is known to be partly accounted for by differences in genetics. However, collecting useful records to facilitate genetic selection has been very difficult, often requiring hours of human observation to generate even small amounts of data. Nevertheless, some successes have already been achieved, such as improving temperament in beef cattle, to help reduce aggression and injury to farmers and the animals when handled. As more advancements in Agri-tech are made (see earlier section), the scope to collect more useful records through automated observation methods and advanced data analytics is likely to increase.

Where effective recording has been achieved, it has tended to focus on reducing negative behaviours. Recording behaviours that can have a positive effect on the welfare and performance of contemporaries is more difficult.

The genetic effects of an individual on the phenotypes of its social partners, such as its pen mates, are known as social genetic effects. An approach that could potentially allow selection for positive social behaviours more generally, without the need to record social interactions separately, is to estimate social genetic effects from the data on individual performance, and to incorporate them in selection programmes⁽⁶⁾. The approach is largely based around the use of more advanced statistical models, but to be successful it also requires data to be collected in a more structured manner to allow good estimates of the social genetic effects. While initially proposed a number of years ago, most of the successful work to date has been done on research populations managed in small mixed family groups. However, the approach is now being integrated into some commercial pig and poultry breeding systems.

5. Use of Animal Genomics: Genomic selection and related techniques

DNA markers

DNA is copied (replicated) every time a cell divides. Very occasionally errors occur during this replication process. This random event gives rise to a naturally occurring mutation (often referred to

⁶ For more information, see e.g., Ellen *et al.*, (2014) *Frontiers in Genetics*, 11 November; available at <https://doi.org/10.3389/fgene.2014.00377>

as a polymorphism). If the polymorphism occurs within the genes of the cells that give rise to eggs or sperm, this can alter the appearance and/or the biological function of the offspring. These naturally occurring mutations can affect different lengths of DNA – from a single nucleotide up to a number of sequential ones.

Most DNA mutations are ‘silent’ and have no obvious effect on an animal’s appearance or performance. However, some mutations do influence the function or appearance of an animal. This often occurs when the mutation arises within a gene (*i.e.* a sequence encoding a protein) or within the regulatory region that determines expression of a gene. Collectively, these accumulated mutations account for much of the variation we observe in different characteristics between animals within breed populations, and differences between breeds.

Historically, selection and breed creation were done without knowledge of which DNA mutations were being selected for or against. However, recent advances in genomic tools now provide additional insight and enable us to better manage the process.

Originally, the main focus was on developing individual genomic tests for either known diseases or traits of commercial interest, and a number of commercially available DNA marker tests have now been developed ⁽⁷⁾.

Early markers were based on detecting differences in the DNA sequence that consisted of multiple adjacent nucleotides in known parts of the genome that had been found to be closely associated with the trait or characteristic of interest. As genomic technologies have advanced, the number of genomic markers available has increased, and the number of nucleotides included within each marker has tended to reduce. Many tests used today focus on using single nucleotide polymorphisms (SNP’s) that are known to be linked to, or directly responsible for, some or all of the genetic variation in traits of interest.

Only a few markers are available that are known to include polymorphisms that directly account for all or a high proportion of the genetic variation in any single trait of interest. However, where they do exist, they can be used as a basis for selection in a single step approach (*e.g.* see the section on inherited diseases).

Most inherited characteristics are regulated by a combination of gene products rather than by that of a single gene. These are known as complex traits. These traits require a number of markers in different genes to be assessed. Even then, the markers may still not fully account for the total genetic variation present in that trait. As a result, genomic markers are generally considered most useful as an indicative tool to increase the accuracy of breeding value estimates for specific traits of interest for an individual animal. These are generated using conventional statistical approaches within breed improvement programmes (an approach that is commonly referred to as ‘marker assisted selection’). They can be particularly useful to help increase accuracy of selection:

- when measurements of the trait of interest are directly available on the animal itself, but where the proportion of variation accounted for by differences in genetics is low;

⁷ For examples see ‘Genetic markers in beef and sheep breeding programmes: Unravelling the practicalities of DNA technologies’; available at <https://meatpromotion.wales/en/industry-resources/sheep-management>

- where measurements of traits are only available on relatives (*e.g.* milk production for dairy bulls) and/or are difficult to measure (*e.g.* meat eating quality or resistance to specific diseases).

The general principle of all DNA marker tests is to detect polymorphisms that are known to be linked to, or directly responsible for, some or all of the genetic variation in the traits of interest. However, since mutations in germ cells occur randomly in an individual animal of a specific breed and are then passed down to its progeny, it is important to recognise that the phenotypic effects of individual mutations may be breed-specific, and also that other between-breed genetic differences may influence its expression. There are a number of known examples where this is indeed the case; for example, the same mutations in the myostatin gene that cause the highly muscled appearance of Belgian Blue cattle can also be found within the Highland cattle breed but are not expressed. Furthermore, there are also examples (*e.g.* fecundity genes in sheep) where both breed-specific mutations within the same gene as well as breed-specific mutations in different genes can result in similar phenotypic effects. Therefore, for breed improvement purposes, it cannot be assumed that the effect of selection using specific DNA marker tests will be universal across all breeds.

As further advances in genomic technologies have been made, and more detailed genome maps for various livestock species have been developed (including gene and SNP locations as well as information on the biological functions of different parts of genomes) it has allowed:

- more detailed consideration to be given to most, if not all, of the DNA that individual animals carry;
- a gradual increase in the number of markers that can be considered simultaneously;
- consideration to be given to even more complex attributes of genomes that are increasingly known to affect a range of physical attributes. These include:
 - the number of exact repeat copies of genes or genome sections (commonly referred to as Copy Number Variation [CNV] – which are known to affect a number of characteristics of interest in various livestock species ⁽⁸⁾;
 - modification of how gene sequences are expressed in an animal's body (referred to as epigenetics), sometimes as a result of which parent the gene was inherited from (imprinting);
 - common genomic deletions in a population that may have resulted in deleterious effects, such as the death of some early stage embryos.

With respect to epigenetics there is now good evidence in laboratory species that the environment in which an animal is kept and/or the diet that it is fed not only alters the expression of specific genes within the animal itself but that this altered regulation is heritable and passed down to its progeny. Similar effects are likely to also occur in farm species, but, as yet, genetic evaluations in farm livestock do not take account of them.

⁸ *e.g.* see Bhanuprakash *et al.*, *Vet World*. 2018 11(4): 535–541; available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5960796/>

Over the last decade, the cost of applying genomic technologies has dramatically reduced. Consequently, a range of genomic tools have been developed for use in most livestock species. For example, the cost of sequencing a whole genome is typically around £1,000 or less. In addition, high, medium and low density SNP chips (each typically with around 600-750k, 50k and 10-20k SNP's, respectively) are now commercially available for cattle, chickens, sheep, pigs and horses, and medium and low density chips are also available for goats. The availability of these tools and the ability to develop bespoke genomic chips offer a range of options for how the technology can be used.

As advanced analytic approaches have also been developed, it is now possible to use the large amount of data generated to increase the effectiveness of modern breeding programmes that are aimed at genetic improvement and/or conservation. Potential benefits would also be expected to increase as costs reduce and further advances are made with genomic tools and analytical approaches. The latter will include the development of system biology methods to model how variations in gene products modify expression of other genes and the consequence that this has on the phenotype of the animal.

Genomic selection

New genomic marker technologies using SNP chips enable quick and detailed simultaneous analysis of a large number of SNP's that are evenly spread across the whole genome of individual animals. This combined with developments in statistical analyses has given rise to an approach called "genomic selection".

Unlike specific gene DNA marker tests (see above), genomic selection relies on a statistical approach that associates traits of interest with all SNP's using a comparatively large 'training population' (minimum 1500-2000 genetically linked animals and considerably larger in the case of dairy cattle). Essentially, this involves initially 'training' the statistical model to estimate the effect of each specific SNP on the trait of interest. Subsequently, the combined effect of all the SNP's an individual animal carries is calculated and used, alone or in combination with individual animal performance, as the basis for selecting the most desirable breeding animals.

With use of appropriate 'training populations' and trait measurement, this technique provides opportunities to select for 'difficult to measure traits' such as robustness and disease resistance far more precisely than with conventional breeding, as well as being used to improve the accuracy of selection for more conventional traits, particularly in young animals. However, it should be noted that genomic selection does not remove the need for performance recording. This is because there is a need to regularly update the statistical association between traits of interest and SNP's.

Currently, genomic selection is generally being adopted where large performance-recorded populations of a breed exist and the commercial advantage through accelerating the rate of genetic improvement can justify the increased costs of implementation, as is the case in some mainstream breeds of cattle, pigs, and poultry. This is because the costs of generating the required information using 'training populations' are currently prohibitive except for species and populations that are fully or partly controlled by multinational companies and where returns in sales of breeding stock/semen can justify the increased costs.

Genomic selection is already having an impact in Holstein dairy cattle where it can dramatically increase rates of genetic progress by allowing more accurate selection of young animals with high genetic merit for progeny testing (males) or to select replacement heifers or bull mothers (females).

This is in contrast with the traditional approach where bulls may have needed to be around 6 years old before their genetic merit results were available based on the production of their daughters. By July 2016, over 50% of all dairy cow inseminations in the UK were from bulls that had been evaluated genomically.

The high costs of establishing 'training populations' and the high numbers of genetically-linked performance-recorded animals required means that genomic selection is beyond the reach of numerically small breeds, including many mainstream breeds of sheep and beef cattle, and especially 'breeds at risk'. Even with further developments in genome sequencing, it is unlikely that the costs will reduce sufficiently to overcome this limitation. In an attempt to circumvent this issue consideration is being given to whether 'multi-breed training populations' could provide a cost-effective route for their application in at least some of these breeds. However, early indications with cattle are not particularly encouraging.

As with all breeding technologies, care must be taken to ensure that genomic selection does not narrow the genetic base and reduce effective population size. Within that context, it is important to realise that an added advantage of using genomic markers is that they can unequivocally define parentage, and therefore may be more accurate than pedigree recording (see later section).

Imputation

The use of genomic techniques is resulting in a large amount of data being generated for animal populations. These are likely to increase even further as sequencing costs continue to reduce and knowledge of the function of different parts of the genome increases. More advanced statistical models and computing strategies will be required to allow effective use of such data. The wide range of genomic tools now available also allows consideration to be given to developing novel advanced statistical approaches that allow a high level of benefit to be achieved without the need to fully sequence the genomes of all the animals in the populations, using a process called imputation, and adopting a tiered approach when using the genomic tools available. For example, within a dairy cattle population, whole genome sequencing can be used to analyse DNA from widely-used grand sires, high density chips used on his sons, and medium or low density chips used on their daughters. By combining pedigree information with genotype imputation, it is possible to infer the higher density genome sequence or SNP information (essentially filling-in the gaps) for animals lower down in the breeding pyramid, thus further increasing the accuracy of the PTA's that can be generated.

Genomic tools for managing inherited diseases and relatedness

In addition to their effectiveness in commercial breeding programmes, genomic tools also have an important role in managing inherited recessive diseases that can arise through the emergence of disruptive mutations (*e.g.* microphthalmia in sheep, spider lamb syndrome, neuropathic hydrocephalus in calves, Tay Sachs disease in sheep), and as such, have relevance for all breeds. Such inherited diseases can exist within both mainstream breeds and 'breeds at risk' and it is crucial to be able to distinguish between heterozygous carriers and homozygous non-carriers within a breeding population.

Stand-alone DNA marker tests that identify carriers (animals that show none of the disease symptoms) can help breeders manage their breeding programmes to (i) avoid the production of ‘double copy’ individuals with the condition and (ii) eventually remove all carrier animals from the breeding population. The Ridgene Manual ⁽⁹⁾ provides detailed guidance for breeders and breeding groups on the steps needed to identify inherited diseases within their own populations and to develop a suitable genetic test, with expert help, to help manage it. The first key steps to successful management of emerging inherited diseases is to record and collect DNA from any animals that show physical or performance abnormalities, and to develop a culture of willingness to record such events within breeding groups. When abnormalities are not recorded, this can lead to an increase of carriers within a population or breed, particularly in populations where a small number of sires have a large influence.

As well as being used for selection purposes, SNP analysis is also widely used to define breeds and their relatedness. It can therefore play an important role in both breed and breed-product authentication. It also offers a means to more accurately (compared to analysis of pedigree alone) assess the relatedness of individuals within a given population, as well as the level of genetic diversity within a breed and species. This approach requires SNP profiles to be compared between individuals within a breeding population. Such an approach could be especially important for the conservation of ‘breeds at risk’ by providing breeders with a technology to monitor and maintain genetic diversity within them and in biobanks.

Genome editing

As discussed previously, mutations in DNA naturally occur within all livestock populations. While most mutations have no obvious effects on the appearance or performance of animals, some do, particularly when they occur within DNA sequences for genes or within regions that regulate the expression of a gene. It is the accumulation of these naturally ‘functional’ mutations through their subsequent selection by breeders that has given rise to the differences in appearance and performance that we observe today, not only between breeds but also between animals within a given breed.

Novel molecular biology tools are now available that allow fine scale editing of individual genes within the genome(s) in a cell, embryo or ovum to bring about a desired genetic change. They can be used to make modifications of varying sizes but can be as small as changing a single nucleotide base within a specific gene. This alteration would be indistinguishable from a naturally occurring DNA polymorphism.

The technology is generating considerable interest within human medicine because of its potential for treating or eliminating inherited disease in an individual caused by a naturally occurring disruptive mutation in a functionally-significant gene.

One example of how the technology is being applied is through editing the genome of stem cells to correct the disruptive mutation responsible for some inherited diseases. Stem cells exist in various tissues within the body and are required for normal cell replacement and tissue repair. They are basic

⁹ The Ridgene Manual is available at <https://connect.innovateuk.org/documents/3285671/31025255/RIDGENE%20Manual>

cells at an early stage of development that, through natural processes within the body, can be programmed to differentiate into specific cell types. Ethical approval has already been granted for human clinical trials to treat a number of diseases. The process involves harvesting stem cells from a patient's bone marrow, gene editing them in the laboratory to correct the disruptive mutation, and then putting them back into the patient. Specific examples include treatment for β -thalassemia (an inability to produce haemoglobin in red blood cells), sickle cell anaemia (a problem with producing normal red blood cells), and haemophilia B (an inability to produce coagulation factor IX used to stem bleeding following tissue damage).

In addition to gene editing within stem cells, other applications under investigation include extracting other types of cells from a patient's body which are then replaced after gene editing in the laboratory (*e.g.* as a possible mechanism for increasing resistance to HIV). An alternative approach involves *in situ* editing cells within the patient's body (*e.g.* as a possible treatment for muscular dystrophy).

In all of these cases, while it is hoped that the treatment will result in a permanent cure or long-term treatment for the disease within the patient in question, it will not correct the disruptive mutation (where present) within their germ cells (eggs or sperm). Therefore, the treatment will not prevent the condition potentially being passed on to their offspring (this would require gene editing of embryos with its additional ethical concerns).

However, many of the scientific developments needed to improve the technologies are very similar, regardless of which approach is used and whether the application is for human health or for use in farm animals.

Genome editing technology could offer real benefits for animal breeding, particularly where inherited diseases arise in 'breeds at risk' and where the effective population size is already at dangerously low levels. As selective breeding is already commonly used in animals, editing of embryos to provide a more permanent solution to the elimination of inherited diseases can also more easily be considered.

While, at least in theory, genome editing of embryos may potentially offer the means to generate new variation within a given breed that could be used to accelerate the rate of genetic improvement for mainstream traits that influence animal performance (*e.g.* growth rate, carcass quality, milk yield *etc.*), the level of industry interest is likely to be extremely low or non-existent as good progress can already be achieved using far more cost-effective approaches such as traditional performance recording and/or genomic selection (see earlier sections).

However, gene editing of livestock embryos may be an attractive option to introduce variation known to confer resistance to specific diseases where current breed populations have little or no natural resistance. This has already been successfully used by two research groups (one in America and the other in the UK) using different methods to experimentally produce pigs that are resistant to the porcine reproductive and respiratory syndrome virus (PRRSv)⁽¹⁰⁾. PRRSv is currently endemic in many counties around the world, causing substantial piglet mortality, significant welfare concerns and a high

¹⁰ Whitworth *et al.*, (2015) *Nature Biotechnology*, 34 (1), 20-22; available at <https://www.nature.com/articles/nbt.3434>, and Burkard *et al.*, (2017) *PLOS Pathogens*, 13(2); available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5322883/>

economic cost. Prior to these gene editing reports, there were very limited prevention and treatment options available. The estimated economic cost of the disease to the USA and EU industries is more than \$2.5 billion/year.

Another example under investigation is the introduction into domestic pigs of natural resistance to African Swine Fever virus (ASFv). This devastating disease has already entered eastern Europe and is progressing in a westerly direction. The virus causes haemorrhagic fever with high mortality rates and is a major animal welfare issue because there is no effective vaccine or treatment. Comparison of gene sequencing data from African wild pigs (that are naturally resilient to the disease) and current domestic pigs (which are not) has shown that there are three single nucleotide base differences within one key gene which are believed to be the basis for the differences observed involved in mounting an effective immune response. Changing just these three nucleotide bases in the relevant gene of domestic pigs to the 'wild type' using gene editing of embryos has now been achieved through a collaborative project led by a UK-based research group. Disease challenge studies are now underway under tightly controlled experimental conditions to test the effectiveness of this approach ⁽¹¹⁾.

Genome editing has also been used to produce naturally polled cattle in two horned breeds without the need for initial crossbreeding to introduce the polled variant of the gene. This delivers improvements in animal welfare because it removes the need for surgical disbudding of young calves ⁽¹²⁾. In contrast to the PRRSv and ASFv examples above, the polled cattle were produced through editing a larger number of bases. However, this still involved mimicking a genome variation that occurs naturally in polled breeds.

Other examples of genome edits with the potential to confer animal welfare benefits that have recently reported early stage successes in the USA include: (i) male pigs that do not require surgical castration (as is currently common practice in some countries but not in the UK), to avoid hormone tainting of their meat (Boar taint) as they mature; and (ii) improved heat tolerance in cattle and pigs. Given the early stage success, each of these examples outlined above have gained commercial interest for potential use in different parts of the world.

One of the biggest challenges associated with gene editing is the identification of appropriate genes/genomic sites to edit. The successful examples described above have been achieved by editing genes that have either been identified by prior academic research (*e.g.* PRRSv resistance), or via genome comparison between related breeds/species that exhibit different versions of the characteristics of interest (*e.g.* ASFv resistance).

These approaches are time consuming and expensive, but they are likely to continue to play the primary roles in identifying suitable candidate regions for genome editing. However, as more progress is made with the development of stem cells that can be induced to develop into cells of different body tissue types (induced pluripotent stem cells; iPSC) for various livestock species, the development of large libraries of genome edited iPSCs that are differentiated into the tissue of interest could provide

¹¹ Lilloco *et al.*, (2016) Scientific Reports, vol. 6, no. 21645; available at <https://www.nature.com/articles/srep21645>

¹² Carlson *et al.*, (2016) Nature Biotechnology, 5, 479-481; available at <https://www.nature.com/articles/nbt.3560>

a high throughput, relatively low cost lab-based method for early stage detection of edits that may be of interest, before testing the effects of these edits to live animals. Use of such an approach has been under development and discussion for human genetic conditions for some time ⁽¹³⁾. For farmed animals such an approach would likely be most useful for identifying edits that could confer resistance of animals to new or emerging diseases, and could offer a means to reduce potential risks to the welfare of edited animals as well as reduce development costs.

As indicated in an earlier section, there are a number of examples of inherited diseases in farm animals caused by single gene recessive disruptive mutations. Where such inherited diseases occur in mainstream breeds it is possible to use specific DNA marker tests to identify heterozygous carriers of the mutation and remove them from the breeding population. However, when such problems occur in 'breeds at risk' and where the effective population size is already very small, removing carrier animals may not be a viable option because it would lead to the loss of important genetic material from the population, leading to even greater levels of undesirable inbreeding. Instead, gene editing could be used to correct the disruptive mutation in embryos that are the progeny of such carrier animals.

Currently this technology is very expensive, and there is an urgent need to generate more examples within farm animals to provide unequivocal proof of its potential. Once these exist, genome editing could be highly relevant for both conservation and improvement of animal health and welfare.

Other applications of genome editing

As well as direct effects on an animal's own health and welfare, genome editing is also being used to successfully generate animals with other characteristics that could have a direct effect on managing farm animal genetic resources, such as genetically sterile hosts. Researchers in the UK have successfully produced hens that do not have the ability to develop their own gonads but are perfectly healthy in all other respects ⁽¹⁴⁾. The research team have further demonstrated that when thawed cryopreserved female primordial germ cells (see earlier section) from a rare breed are inserted at a specific early stage into the development of an edited embryo, the resulting hens develop gonads and are able to successfully lay eggs. When the hens are then inseminated with semen from males of the same rare donor breed, the progeny produced carry only genetic material from the rare cryopreserved breed ⁽¹⁵⁾. These sterile birds could therefore play an important role in both the conservation of rare breeds and in the biosecurity of high value commercial genetic lines as they provide an effective means for their recovery using cryopreserved primordial germ cells.

Research is also on-going to produce gene edited genetically sterile male chickens, and good progress has already been made. If successful, this may allow substantially higher rates of successful recovery

¹³ e.g. Marx (2015), Nature Methods, vol. 12, no.2, Feb; available at <https://www.nature.com/articles/nmeth.3263.pdf?origin=ppub>

¹⁴ <https://www.ed.ac.uk/roslin/news-events/archive/2017/egg-free-surrogate-chickens-produced>

¹⁵ Woodcock *et al.*, (2019) Proceedings of the National Academy of Sciences, 116 (42) 20930-20937; available at <https://www.pnas.org/content/116/42/20930>

from stored genetic material to be achieved for chickens. This could also be important for breed conservation given that that fertility rates from cryopreserved and thawed poultry semen is currently very low.

Genetically sterile male pigs have also been successfully produced using a gene editing approach. However, unlike the sterile hens, gonad development in the boars is less affected, with the testes developing normally, but the pigs do not have the ability to produce sperm as they lack their own spermatogonial stem cells (SSCs). By transferring SSCs from a donor male into the edited males, the edited boars develop the ability to produce sperm for a period of time and can mate naturally. In so doing, they transfer genetics to their progeny that has been derived solely from the donor males. This approach would potentially enable large numbers of progeny from high genetic merit boars to be produced through natural mating. Such an approach could offer substantial benefits in terms of improved biosecurity as well as increase rates of genetic improvement within breeding populations. This could be extremely valuable, especially in situations where artificial insemination has proved difficult.

Biomedical models

The use of genome editing has also been used in livestock species (primarily pigs but also sheep and other species) to generate large animal biomedical models (animals that carry and exhibit human genetic diseases). These offer a means to greatly accelerate the rate of discovery and validation for new drugs and therapeutics for use in human medicine. Many of the models generated to date have been made using mini pigs, which are not commonly used in commercial meat production, but some models have been developed in more commercially relevant breeds of pigs⁽¹⁶⁾ and sheep⁽¹⁷⁾.

The generation of livestock-based biomedical models may not seem to be directly relevant to maintain farm animal genetic resources. However, many of the scientific advances required to improve the underlying technology can be used by both applications. Consequently, methods that are developed to improve human health may also benefit farm animal production and conservation.

Gene Drive

For the vast majority of genome edits that may be considered, a structured breeding programme would subsequently be required in order to increase the prevalence of the edited genes throughout a population. Such an approach offers a high level of control. However, it can be slow, particularly in species where generation intervals are high.

One approach that has been proposed to overcome such a challenge is a concept known as Gene Drive. As well as introducing the genome edit of interest, the process also involves editing into the genome an additional associated section often referred to as a CRISPR portion of the gene drive. If an animal then inherits a gene drive from one parent and a non-edited genome from the other parent

¹⁶ e.g. Yang and Wu (2018) *Frontiers in Genetics*, vol. 9, article 360; available at <https://www.frontiersin.org/articles/10.3389/fgene.2018.00360/full>

¹⁷ e.g. a juvenile form of Battens disease; see Eaton *et al.*, (2019) *Scientific Reports*, vol. 9, no. 9891; available at <https://www.nature.com/articles/s41598-019-45859-9>

during early embryo development the CRISPR portion cuts the non-edited section of genome and the cut strand is then repaired using the gene drive as the template. This results in an animal with two edited genome copies ⁽¹⁸⁾.

To date, use of the Gene Drive concept has mostly been discussed as a putative method for population control – for example to introduce sterility into mosquito and rodent populations ⁽¹⁹⁾. In contrast, the potential benefits of using this approach in livestock populations is less clear, particularly given that the introduction of the additional CRISPR portion in the edited animals will likely add more complexity to the question over the need for a suitable regulatory framework for generating such animals (and if so, in what form), and more questions regarding how such animals could then potentially be used in breeding programmes or wider supply chains. Within countries such as Australia, where discussions on the requirement for a suitable regulatory framework for use of genome editing in animal populations is more advanced, separate consideration is already being given to the use of Gene Drive technology – the consensus being that stricter regulation should be applied ⁽²⁰⁾.

6. Other uses of Genomics

Assessing the Microbiome

Animal species and humans have a large number of non-pathogenic bacterial species within their gastrointestinal tract. These bacterial communities are known as microbiomes. They primarily form after birth and are dynamic over time in terms of the relative prominence of different bacterial species.

Recent developments in genomics and metagenomics (analysing genomic samples of mixed populations *e.g.* of bacteria) have made it possible to better characterise these communities and study how they change over time within an individual, and also vary between animals and breeds. There is now evidence that differences in composition of the gut microbiome can influence the animal's health. It could also play a role in how efficiently animals digest different foodstuffs and hence the level of GHG emissions from ruminant species.

This is a relatively new field, and much is unknown about how the gut microbiome develops and is maintained over time. It is also unclear how much influence the animal may have over those processes. However, there is growing evidence to suggest that the genetics of the host animal may play a key role in the composition of the gut bacterial composition ⁽²¹⁾.

¹⁸ Gonen *et al.* (2017) *Genetics Selection Evolution*, 49, article 3; available at <https://www.researchgate.net/publication/312477065>

¹⁹ Scudellari (2019) *Nature*, July 9; available at <https://www.nature.com/articles/d41586-019-02087-5>

²⁰ Mallapaty (2019) *Nature*, 23 April; available at <https://www.nature.com/articles/d41586-019-01282-8>

²¹ *e.g.* see Roehe *et al.*, (2016) *PLOS Genetics*, 12(2); available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4758630/> and Fan *et al.*, (2020) *The ISME Journal*, 14: 302–317; available at <https://www.nature.com/articles/s41396-019-0529-2>

Given the wide range of environments, management systems and feed conditions under which the UK's livestock breeds are preferentially kept, the presence of genetic differences that influence the establishment and maintenance of bacterial colonies that are better suited to their traditional environments would be no surprise. Establishing that these differences exist, and better understanding the interactions with different feeds, management systems and environments would be vital steps so that this information can be harnessed to improve the animal's health and reduce emissions, particularly through tailoring breed and animal use to best suit the conditions in which they are intended to be kept.

Public acceptance and regulation

Public opinion will be key in determining whether many of these new and developing technologies are accepted and under what circumstances they can be adopted. Communication with the general public must be handled with great care and openness. The benefits of the technologies must be emphasised throughout.

As might be expected, there are differences in opinion on how any new technology should be regulated amongst different interested groups within the UK, and this should be kept in mind when discussing potential uses of all novel technologies. Furthermore, we need to be entirely open with the public to avoid a repeat of the backlash that occurred with GMO crop plants. In that case, no-one was prepared to discuss potential benefits of the technology nor seek public opinion and support for it. This failure in communication no doubt played a key role in the widespread rejection of GMO technology.

There has been considerable public resistance to cloning using somatic cell nuclear transfer in the UK, at least for mainstream breeds supplying food for human consumption. This has not been a major issue as there are many other techniques that are widely used for breed improvement purposes. In contrast, cloning may prove to be crucial to save 'breeds at risk' from extinction (especially for those breeds where no cryopreserved embryos exist). In these situations, this technique could be used to regenerate such breeds or overcome 'bottlenecks' within a breeding programme as it would enable animals that are unable to breed naturally (*e.g.* castrate males, aged animals) to generate progeny into the breeding programme. The implications of cloning for conservation purposes are therefore very different from its use in mainstream agricultural breeds, and a justifiable case needs to be made to garner public support.

In the case of gene editing, discussion with the general public should be aligned with the development of an appropriate regulatory framework for its industrial use. When used to edit only a small number of nucleotide bases, it will be essential to emphasise that the technology is simply mimicking the variation, a naturally occurring polymorphism, albeit in a targeted manner. Unlike transgenic GM technology, the use of gene editing does **not** involve the introduction of 'foreign' genes from another species.

In communicating the use and benefits of the technology it will also be important to emphasise that the main use of the technology will most likely be to improve the natural resistance of livestock to a range of different diseases. Therefore, gene editing will help deliver improved animal health and welfare. This in turn, should reduce the need for antimicrobials to treat infectious disease in farm

animals which will decrease the potential development of antibiotic resistance, a matter of increasing concern for human health.

Gene editing is a technology that is not limited to animals; it is being used to modify specific genes within a range of plant species from one naturally occurring allelic form to another and, as indicated above, is also being experimentally used for human medicine through approaches such as gene edited cell therapy. In both cases, the regulatory framework under which the technology can be used is in development across the world.

For use in agriculture, very different approaches are being advocated and adopted across different countries:

- Brazil and Argentina have both adopted a non-regulatory approach to the technology for use in both plants and animals provided no 'foreign' genes have been introduced;
- in Canada the approach adopted is more focused on outcomes rather than use of the technology itself, and regulation would not be applied provided no novel traits were produced;
- in Australia, the use of DNA cutting techniques at a specific target site to facilitate a gene edit will not be regulated for plants or animals as long as the tools allow the host cell to repair the break naturally. Any animals produced using the Gene Drive technique would likely be subject to regulation as introduction of the CRISPR part of the gene drive into the genome would be viewed as an introduction of foreign DNA;
- the US Department of Agriculture announced in 2019 that it did not intend to regulate gene edited crops with mutations that could have occurred in nature. Application of the technology in animals is overseen by the Food and Drug Administration (FDA) which adopts a risk based approach to regulation. Whilst the details of the regulatory framework in relation to the technology itself is still under debate, it is thought that any edits viewed as posing a low risk (to the animal or people eating any resulting food products) would not need to apply for authorisation.

Within the European Union, the view to date is that genome edited crops and animals should be subject to the same stringent regulations as other GMOs. This opinion will place EU agriculture at a significant disadvantage. However, such small edits are virtually impossible to detect, represent naturally occurring mutations that already exist within the given species and involve no transfer of 'foreign' genes from another species. It is therefore not clear how such a ruling could ever be monitored or enforced. Furthermore, the gene editing may result in significant animal welfare benefit and therefore a more balanced approach seems justified.

Following the UK's recent withdrawal from the European Union, it is unclear how the technology will be adopted across the agricultural industry post the transition period, and an appropriate regulatory framework will need to be developed. In developing the framework, it will be important to recognise the range of applications that the technology could potentially be used for, including correction of inherited diseases in breeds at risk, development of sterile hosts as well as editing of animals destined to be used in main stream production.

Opportunities to further reduce disease and environmental impacts through breeding

As discussed previously, genetic improvement of livestock has already been shown to be an effective method for both improving resistance to infectious diseases (and thus reliance on antimicrobials) and reducing GHG emissions per unit product from production systems. Such positive impacts can be expected to increase as more developments are made.

The biggest challenge to achieving this is the availability of useful records on sufficient numbers of animals to allow genetic improvement to be made. As developments in Agri-tech continue, more and more tools to help overcome this challenge are expected to become available, driven mainly but not exclusively by the development of tools to improve the management of animals and supply chains (see earlier section). For sectors where supply chains are typically more fragmented, such as beef cattle and sheep, a long-term vision and implementation for data collection and use across the UK industry will be needed. Approaches adopted in other countries may help provide ideas for developing a suitable plan. For example, a highly integrated recording system for cattle has been developed in Ireland as part of the Irish Cattle Breeders Federation (ICBF). The ICBF system is based primarily around data collection for use in breeding, but whether that approach for on-going development is suitable for all sectors, countries and industry starting points is not yet clear. The ICBF system has already delivered additional benefits to improving animal health by allowing use to be made of disease data collected in abattoirs, with EBV's for resistance to liver fluke infection having been launched in 2019. As mentioned previously, more detailed on-farm recording of other health incidences has also been used to generate PTA's for dairy cattle in the USA, and investigating the approach used may offer additional ideas.

Developments in genomic technologies can also offer tools that can be used to improve the accuracy of selection within existing breeding programmes, particularly where collecting suitable records can only be done on a sub-set of animals due to being hard or expensive to measure (*e.g.* recording feed intake in beef cattle or monitoring disease status). For example, research in New Zealand, Australia and across Europe have identified SNP's that are associated with parasite resistance in sheep, but the proportion of variation accounted for tends to be small, and the effects are often breed specific. Research in New Zealand has also identified SNP's for resistance to facial eczema (not relevant to the UK).

While potentially of some value for marker assisted selection, harnessing significant benefits through use of genomic selection is still heavily reliant on the ability to collect sufficient quantity of good quality records. In Australia and New Zealand significant efforts and resources have been put into the establishment of intensively recorded populations of sheep, beef and dairy cattle (called information nucleuses in Australia [SIN, BIN and DIN], respectively) so as to maximise the potential benefits that can be gained by using genomic tools.

Although of value for improving a range of animal characteristics of interest, improving resistance to diseases relies on the disease of interest being endemic in the targeted populations, and this presents significant limitations to the progress that can be made for more than a handful of diseases. Provided the appropriate infrastructure and agreements are developed and further advances in Agri-tech are made, the amount of good quality data collected on farms and in other part of the supply chains (*e.g.* abattoirs) that can be linked together should dramatically increase. The availability of such data could

offer the ability to identify data dense industry populations in real-time (*e.g.* when specific sporadic diseases arise) that can then be recorded in more detail and animals genotyped heavily to generate good genomic tools in a highly cost effective manner that can then be used more widely through the industry without the need to establish information nucleuses.

As discussed in earlier sections, gene editing also offers the potential to be an important tool in the fight against a range of diseases in animals. However, to date, this technique has only been applied to a small number of cases.

When considered all together, there is little doubt that genetic selection and genomic tools can play a key role in reducing environmental impact of livestock production and in improving the resistance of animals to a variety of diseases, thereby helping to improve welfare and reduce the need to use antibiotics. However, there are a number of key challenges that need to be recognised when considering how best to apply the tools and approaches available, not least of which is that selective breeding, even where beneficial, can take a number of years in livestock populations to generate any significant increase in the level of resistance.

Consequently, genetic selection and genomic tools should be used alongside other key approaches, such as improved management practices, improved feed and appropriate use of vaccines and health treatments. In addition to genetic selection, we would therefore recommend that producers, should also:

- maximise use of highly cost-effective vaccines available to protect their livestock from a range of different diseases;
- maximise biosecurity.

Both will have a major impact on reducing antibiotic usage. Furthermore, as with human diseases, it is imperative to recognise that vaccination simply primes the animal's immune system to allow it to resist the disease challenge; it does not remove the disease-causing bacterium from the farm environment once present. Continued vaccination is therefore essential to maintain immunity from disease within the population once present on the farm.

Conclusions

There is a wide range of technologies that have relevance in the management of farm animal genetic resources, both through genetic improvement of breeds or lines and for conservation. Not all technologies have relevance in all situations, but the information provided in this paper has highlighted where each may have a role to play. As such this review provides background information and guidelines to all interested parties on the appropriate choice of technologies and their benefits so that they can be actively applied.

While many of the technologies are at a stage where they can be used by industry now, some require further development. The status of each technology is summarised in Appendix 1. Similarly, the structure of some industry sectors may allow adoption to be done more easily, while others, such as the beef and sheep sectors, may require help and guidance on how best to develop the supporting infrastructure so that benefits from appropriate use of the technologies available can be accrued more easily, allowing the sectors to thrive.

Below are a number of recommendations that would allow the UK industry to capture more benefits from using the technologies that have been covered in this paper.

Recommendations

General

- Industry (all mainstream sectors and conservation groups) should become familiar with the tools available and how they could be used to enhance breeding schemes and aid conservation. They should also recognise that developments are on-going and new opportunities to capture benefits will continue to arise.
- Livestock breeds do not generally recognise national boundaries within the UK, even though agriculture is a devolved responsibility. To maximise the potential benefits that genetic improvement can provide it is therefore essential that Devolved Administrations always work collaboratively with the UK Government to ensure an integrated approach to all aspects of animal breeding and genetics.
- Government and industry should recognise that many of the tools available can deliver benefits for conservation, genetic improvement and animal health and welfare, as well as also offering wider environmental benefits such as: enhancing the efficiency of animal feed and nitrogen use; help to optimise land use demands by requiring less animal feed to produce a given quantity of human food; and can concurrently reduce impacts on water and air quality associated with animal excreta. On-going developments and enhancements can deliver benefits for all these applications.
- Public funding bodies (Government, Research Councils, and Innovation support bodies) should ensure that funding support continues to be available for on-going development of existing technologies and the development of relevant new technologies.
- The UK should establish clear signposting for where relevant commercial services and expertise can be found for each technology and approach.
- Breed Societies should consider using DNA testing to support verification of parentage (either routine or random testing).
- Breeding groups and Societies should establish clear recording policies, protocols and appropriate infrastructure for recording and DNA sampling where physiological and performance abnormalities occur, so as to manage emerging inherited diseases.
- An industry led vision and roadmap for future data collection, integration and use should be developed for each livestock sector that covers developments in industry and in public bodies. In developing the vision and roadmap, consideration should be given to applications beyond just genetic improvement, and to developments that have already been successfully made in other countries, and their suitability for adoption in the UK.
- UK-wide standards for the recording of specific novel characteristics should be developed to ensure comparability between measurement taken using different detection methods.

Beef and sheep sectors

- In contrast to the situation in pigs, poultry and dairy cattle where genetic improvement within the commercial production sectors is well established, the penetration of genetic improvement in commercial beef and sheep production is generally very poor.
- For the beef and sheep sectors Government should consider use of public support mechanisms to stimulate increased uptake of on-farm software and transfer of data from farms and other sector stakeholders to generate industry wide benefits.
- In developing an industry wide vision and roadmap for future data collection, integration and use, special consideration should also be given to the role that UK wide data hubs could potentially play in facilitating data sharing, along with the development of clear rules on how various data sources could be used, so as to build confidence, trust and thus effectiveness of the system.
- Government should provide on-going or new support for industry-led coordinated initiatives such as the beef feed efficiency programme, that can deliver innovation in areas that individual breeders cannot consider due to lack of scale or costs.
- Government should consider use of public support mechanisms to stimulate use of animal genomic testing for performance characteristics within the industry to increase the level of benefits that can be captured. In doing so, special emphasis should be given to animals that have been recorded as part of coordinated programmes or can provide data of relevance to specific diseases.
- Government and Industry should consider developing a coordinated UK-wide approach to purchasing of standard genomic tools (e.g. SNP chips) to help lower costs.
- Particularly where EBV's for new characteristics are developed, industry should consider using standardised approaches for expressing and explaining the new EBV's so as to help stimulate greater understanding and uptake across the industry and breeds, and to minimise confusion.
- Government should recognise genetic improvement of livestock as a tool that can play a key part (along-side other tools) in improving animal health, welfare and reduce environmental impact and use of antibiotics in production systems, and include it as an option in the development of policy.

Conservation

- Conservation groups and breed societies should prioritise biobanking semen (sexed if possible) and embryos.
- For poultry, breeding groups and Societies should consider cryopreservation of PGC's. The technology is already available for chickens, but further development will be needed for other poultry species.
- Conservation groups and breed societies should use genomic tools to support the management of appropriate biodiversity within biobank stores, but public funding will likely be required to help cover the costs.
- Government should consider and garner public support for changes to the current ban on cloning, but only for use as a last resort for recovering endangered populations of rare breeds.

Genome editing

- Government needs to have clear and open dialogue with the general public about genome editing technologies and how they could potentially be used to benefit animal populations, particularly through increasing resistance to endemic or emerging diseases. The aim should be to promote an informed and balanced consideration of how the technology could be used, and to mitigate any confusion that may arise through the promotion of misinformation by lobby groups intent on stopping the adoption of any new technologies.
- Government needs to develop a clear UK position regarding a regulatory framework for the use of genome editing technology. This needs to emphasise that the technology is quite different from GMOs and that regulation needs to recognise this. In doing so consideration should be given to its use in a wide range of potential applications, *e.g.* animals and sterile hosts.
- Government and other funding agencies need to fund exemplar projects to demonstrate how the technology could be used to reverse the effect of inherited diseases in small populations.

Appendix 1. Summary Table

Technology area	Potential Applications	Current status	Livestock Species suitability	Applications (Conservation (C), Genetic Improvement (GI))
Opportunities through Agri-tech				
<i>Improved detection methods</i>	Means to collect data on novel characteristics and improve level of detail and volume for traits already being selected – thus improving selection accuracy	Many already available, but development is on-going and accelerating, being driven by demand for monitoring to aid management of animals	All	C and GI
<i>Data sharing and integration</i>	Substantial benefits could be captured through combining data already being collected by industry and/or public bodies For beef and sheep – could also have a big impact on increasing uptake of improved genetics	Some success already achieved, but substantially more could be captured through development of appropriate infrastructure and data sharing approaches. Appropriate development of data hubs could have a big effect in some species (e.g. beef and sheep)	All	C and GI
Reproductive technologies				
<i>Semen Freezing</i>	Method to preserve male genetics	Existing methods good for most species, but pregnancy rates using	All	C and GI

		frozen-thawed semen varies between species		
<i>Artificial Insemination</i>	Method to inseminate females with harvested fresh or frozen semen	Possible in all species using fresh semen, but high pregnancy rates using frozen semen currently only possible in cattle, or in sheep using a laparoscopic insemination technique	Fresh semen – All Frozen semen – Cattle, Sheep	C and GI
<i>Semen Sexing</i>	Method to improve efficiency of breeding and production systems, by increase rates of genetic improvement, and improve welfare	Substantial improvements achieved in recent years for cattle, with fertility rates being close to those with unsexed semen More research needed to improve efficiency in other species	Cattle	C and GI
<i>MOET</i>	Method to increase number of progeny per female and number of fertile embryos for cryopreservation	Primarily used on species with small progeny numbers. Available as a commercial service for cattle and sheep.	Cattle and Sheep	C and GI
<i>In-Vitro Fertilization</i>	Method to increase number of ova collected from females, and to reduce amount of semen required (compared to MOET)	Commercial services available for cattle, with reasonable success rates being achieved	Cattle	C and GI

		More research needed to improve efficiency in other species		
<i>Embryo Freezing</i>	Method for cryopreservation of embryos for long-terms storage or transport	Commercially available for use in pigs and ruminants Needs more development for routine use for equine species	Pigs, cattle, sheep and goats	C and GI
Biobanking and related cryopreservation technologies				
<i>Cryopreservation of semen, ova and embryos</i>	Methods for long-term storage of genetic material	Commercial services available for most species, but differences exist in pregnancy rates when frozen semen used (see above) Storage of sexed semen and embryos recommended if possible	Semen – All Embryos and ova – Cattle, sheep goats and pigs	C and GI
<i>Cloning</i>	Method for animal recovery from cryopreserved somatic cells	Technology advanced, but not widely offered as a commercial service Could be useful to recover highly endangered or lost breeds	All	C

	Method to replicate high value animals	Possible and used in some counties, but its use is currently banned in the EU because of high levels of public resistance	All	NA
<i>Avian Primordial Germ Cells</i>	Method to cryopreserve female poultry genetics and improve efficiency of long-term storage of male genetics	Possible in chickens through recent advances. More research needed to improve approaches for other poultry species	Poultry (Chickens)	C and GI
Modelling social genetic effects	Method of selecting animals based on their own performance and their effect on the performance and behaviour of their contemporaries	Models already available and the approach is now being integrated into some industry systems	Pigs and poultry	GI
Use of Animal Genomics				
<u><i>Genomic selection and related techniques</i></u>				
<i>DNA Markers</i>	Method for improving accuracy of selection for existing and difficult to measure traits	Range of standard genomic tools now commercially available for all species, and some DNA markers being used. More work needed to identify useful associations for most traits. Most useful for difficult to measure characteristics and in small populations where genomic selection cannot be easily adopted.	All	C and GI

<i>Genomic Selection</i>	Method for improving accuracy of selection for existing and difficult to measure traits	Range of standard genomic tools now commercially available for all species	All, but more likely used in large commercial cattle, pig and poultry populations >2k	GI
<i>Imputation</i>	Method that allows more cost effective use of genomic tools in genome selection assisted breeding programmes	Approaches and software already being used commercially, but continue to be improved	All, but more likely used in large commercial cattle, pig and poultry populations	GI
<i>Genomic tools for managing inherited diseases and relatedness</i>	Methods to detect and manage inherited disease and to accurately assess genomic relatedness and parentage	Number of genetic tests already commercially available. Manual to guide industry development of test for inherited diseases (with expert help) available.	All	C and GI
<u><i>Genome editing</i></u>				
<i>General</i>	Method for making small genome changes to confer genetic advantages (<i>e.g.</i> for increasing disease resistance) or to correct inherited diseases in small populations	Technology advanced, with a number of edits of commercial interest currently being tested	All	C and GI

		<p>Identification of suitable new editing targets is challenging</p> <p>Regulatory landscape evolving and varies between countries</p> <p>Limited exemplars for use to correct inherited diseases</p>		
Induced Pluripotent Stem Cell libraries	Possible means for high throughput evaluation of possible genome editing targets – which could offer dramatic reductions in identification costs for new targets	Development of successful methods for culturing iPSC's for most animal species still at research and development stage	All	GI
<i>Biomedical models</i>	Methods for developing animal models of human diseases	Some models available, but research on-going	Pigs, sheep	NA
<i>Gene Drive</i>	Method for accelerating frequency of genome edits in populations	Potential uses in livestock breeding likely to be limited or non-existent	None	NA
Other uses of Genomics				
<i>Assessing the Microbiome</i>	Method for assessing impact of an animal's genetics on gut microbes. Potential method for improving animal health and reduce environmental impact.	Good early signs but still at research stage	All	C and GI

Appendix 2.

Summary of typical breeding pyramid structures, genetic improvement drivers and data flow within the largest UK livestock sectors

Poultry (*including, broilers, layers, turkeys and ducks*)

Breeding structure

Production of breeding animals is under the control of multinational breeding companies and small-scale private breeders. Genetics derived from multinational companies account for a very high proportion of the birds used in commercial production. Small private breeders tend to produce pedigree poultry, and some of these breeds may be used for niche commercial production systems.

A breeding pyramid is used to describe the flow of genetic improvement, from the elite highly selected (nucleus) genetic stock at the top of the pyramid through to the commercial level at the bottom. For most poultry species germplasm flows down the pyramid where it is multiplied and crossed to form commercial (3 and 4-way) hybrid production birds. Multiplication and crossing to produce birds for different levels in the typical pyramid tend to be done on units owned by the multinational companies or under contract on partner farms.

Genetic improvement and data flows

Almost exclusively, multinational breeding companies drive genetic improvement of commercial poultry, and each company run their own genetic evaluations in house.

Genetic evaluations for elite flocks generally includes only data generated from purebred pedigree birds held in high biosecurity units at the top of the breeding pyramid within the breeding companies. In general, pedigree is maintained on all birds via trap nesting or genotype information. Data from siblings of the breeding animals are important in generating breeding values for traits such as carcass and performance in sub-optimal environmental conditions.

Data is also collected and available from out-with the elite flocks and used in different ways. Within some layer breeding programmes progeny test data on lay performance from multiplier levels is included in the genetic evaluations. These data are generated from birds held in groups as sire families. Management and performance data are collected at the multiplier and commercial producer level, but the flow of data back to breeding companies is limited and tends to be used only to understand the general performance of the birds disseminated to each level. Commercial level data is considered important to understand the commercial acceptance of birds and used to optimise the selection decisions within the breeding programme to ensure that consumer and producer demands are met.

Pigs

Structure

Production of breeding animals is under the control of multinational breeding companies or small-scale private breeders.

The majority of commercial genetic improvement is driven through the multinational companies in breeding pyramids consisting of nucleus, multiplication and commercial herds. At the multiplication and commercial levels crossbreeding is done to capture added value from hybrid vigour/heterosis.

Recording of individual identities is done at nucleus and multiplier level, and of breeding animals at the commercial level by means of electronic or simple ear-tags. Younger production animals at the commercial level are most commonly identified using the herds or holding identification only. All slaughter animals are identified by 'slap-marking', with use of individual identities common.

Management (including health) data are collected at all pyramid levels. Most commercial production units use on-farms software to record and manage the herd, and various different systems of on-farm software are available and being used.

Recording movements of pigs with AHDB pork[†] (England and Wales), ScotEID (Scotland) or DEARA (Northern Ireland) is compulsory.

Commercial carcasses are weighed and graded in abattoirs and most information is sent back to producers electronically on individual animals.

Genetic improvement and data flow

Genetic improvement within the multinational companies is focused in the purebred nucleus herds through intensive within-breed/genetic line selection within high biosecurity units, and each company run their own genetic evaluations in-house. Increasingly, data collected at other levels in the pyramid are being incorporated into genetic evaluations to increase the accuracy of selection for improved commercial performance. Use of data from the multiplier level to increase the accuracy of selection in the nucleus is already common, and there is a growing trend to also use data from commercial herds.

Cattle (Dairy)

Structure

Breeding animals are largely produced by commercial pure-bred breeders, who run the herds as commercial milk producing units. Elite populations are run separately or managed along-side non-elite cows. Most commercial herds contain predominantly pure-bred animals but use of crossbreds is increasing in popularity.

Individual recording and tagging of all animals (pure and crossbred) is compulsory, along with registration on BCMS[†] and APHIS (Northern Ireland) for traceability, so they can be issued with a passport. Pedigree recording is undertaken through Breed Societies.

[†] It is planned that the data recording and collation in Great Britain will be done in the near future through three new country specific multi-species (cattle, sheep and pigs) traceability systems, namely, Livestock Improvement Programme (LIP, England), EIDCymru (Wales) and ScotEID (Scotland).

On-farm software is used by many breeders and commercial producers, with most choosing to record through one of three milk recording agencies (NMR, CIS or Dale Farm).

Testing and recording of bTB infection status is also conducted by APHA in England, Wales and Scotland. Data on periodic BVD testing and status is also recorded through ScotEID in Scotland as part of a mandatory BVD eradication scheme.

Genetic improvement and data flow

National genetic evaluations are run by EGENES on behalf of AHDB. All three milk recording agencies regularly transfer data to EGENES for use in national UK genetic evaluations for dairy cattle. As well as routine national evaluations, the data are also used to support the UK's participation in international genetic evaluations for some breeds. Genetic evaluations are also run by EGENES for linear type (structural) traits using data that has been collected through classifications conducted by Holstein UK staff, and for bTB resistance using data collated through BCMS and APHA.

Multinational companies tend to have a strong influence and role in collection and sales of semen, particularly for elite bulls. Breeding of bulls for semen collection and sales tends to be done through their own herds or under contracted arrangements with elite pedigree breeders.

The proportion of commercial producers using semen from elite bulls on at least a proportion of their herd is very high (~90%).

Cattle (Beef)

Structure

Production of breeding animals is largely driven by small scale commercial pure-bred breeders, which run their herds separately or alongside other commercial herds on farms. Some commercial herds are purebred, but many are hybrids, using cross-bred females (commonly first generation crossbreds, often beef x dairy) and a purebred beef bull so as to take advantage of hybrid vigour.

Individual tagging and recording of all animals (pure and crossbred) is compulsory, along with registration on BCMS for traceability, so they can be issued with a passport. Pedigree recording is done through Breed Societies.

On-farm software is already used by some breeders and commercial producers, and the level of demand and number of providers is increasing.

Some commercial slaughter animals are finished on the farm of birth, but many are sold as stores to separate cattle finisher units. Slaughter animals are sold through live auctions or directly to abattoirs.

Carcass weight and grade (conformation and fatness) is recorded in abattoirs and is used as a basis for payment to producers if the animals have been sold directly to the abattoir by the producer/finisher. Carcass grade is not used as a basis for payment where abattoirs buy animals through live auctions. Some animal health data are also collected at abattoirs.

Testing and recording of bTB infection status is also conducted by APHA in England, Wales and Scotland. Data on periodic BVD testing and status is also recorded through ScotEID in Scotland as part of a mandatory BVD eradication scheme.

Genetic improvement and data flow

Genetic improvement is largely based on data collected on purebred animals by recording breeders. The proportion of breeders that record varies between breeds. Some data from crossbred commercial animals has started being used in genetic evaluations, but so far is limited to a small number of traits (*e.g.* carcass traits and feed intake recording) or specific projects (*e.g.* Beef Efficiency Scheme in Scotland).

Data collection and collation and support for genetic evaluation results is driven and managed by the relevant Breed Society, or Signet in collaboration with the Breed Society. Genetic evaluations are conducted by one of two genetic evaluation providers: (i) EGENES (UK based) or (ii) BREEDPLAN (Australia based; 7 UK breeds). Standard methods for the presentation of EBV's for a given characteristic tend to be used where EBV's are generated by the same provider but can differ across providers.

Some multinational companies are involved in semen collection and sales, but their influence on genetic improvement within the industry at present is limited although their involvement in gathering their own data is increasing.

For the majority of breeds, the proportion of pedigree breeders that performance record is low.

Sheep

Structure

Production of breeding animals is largely driven by driven by small scale pedigree breeders, with pedigree flocks often run alongside other commercial flocks on farms.

Some commercial flocks are purebred (*e.g.* hill flocks), but older hill breed ewes are crossed with Longwool breed rams in the uplands to provide (Longwool x Hill) females for most lowland flocks where they are mated to purebred terminal sire rams. This system of crossbreeding exploits hybrid vigour at both the upland and lowland flock levels.

Individual tagging of all animals is compulsory for traceability purposes. However, tags used for the majority of commercial animals tend to only have flock or holding number information, although some farms do record individual identities using EIDs.

For pedigree breeders, individual animal identification and parentage is common for terminal sire and longwool breeds but is less so for hill breeds. The recording of pedigree tends to be done through Breed Societies.

Recording sheep movements with ARAMS[†] (England) EIDCymru (Wales), ScotEID (Scotland) or DEARA (Northern Ireland) is compulsory.

On-farm software is used by some pedigree breeders and commercial producers, but it is not a high proportion.

Some commercial slaughter animals are finished on the farm of birth, but many are sold as stores to separate finisher units. Slaughter animals are sold through live auctions or directly to abattoirs.

Carcass grade and weight is collected at the abattoir and used as a basis for payment to producers if animals have been sold directly to the abattoir. Carcass grade is not used as a basis for payment where abattoirs buy animals through live auctions. Some animal health data is also collected at abattoirs.

Genetic improvement and data flow

Genetic improvement is largely based on data collected on purebred animals by recording breeders. Some progeny data from crossbred commercial animals has started being used in genetic evaluations, but these examples are limited to individual R&D projects (*e.g.* RamCompare funded by the Levy Boards).

Data collection and collation is driven by the Breed Societies or Signet in collaboration with the respective breed society. Genetic evaluations are conducted by EGENES on behalf of Signet, in collaboration with the relevant Breed Society or on behalf of the Breed Society directly (*e.g.* Texels).

The proportion of breeders that performance-record varies between breeds and is generally very low in the hill and longwool breeds. Even in the terminal sire breeds, where recording is more popular, the proportion of rams sold that are performance recorded is less than 25%.

Horses

Structure

Breeding tends to be done within relatively small (numerically compared to other species) studs, which are pedigree recorded through Defra approved breed societies.

'Commercial' level animals (*e.g.* racing, sports or recreational use/pets) can be pure-bred or hybrids and the animals tend to be managed in small, often mixed breed groups.

With the exception of feral and semi feral herds, all animals are individually identified and issued with passports and are recorded on the Central Equine Database which is operated by Equine Register.

Management information for veterinary treatments and medicines administered is recorded on the databases of individual veterinary practices. Results of affiliated competitions that the horses have been entered into *e.g.* racing, multi-eventing competitions is held on sport governing body databases.

[†] It is planned that the data recording and collation in Great Britain will be done in the near future through three new country specific multi-species (cattle, sheep and pigs) traceability systems, namely, Livestock Improvement Programme (LIP, England), EIDCymru (Wales) and ScotEID (Scotland).

Some sport horse breed societies carry out phenotypic evaluations and British Breeding assesses some 400-500 potential sport horses from the ages of foals to three years each year, recording linear traits for those horses on their own database.

Genetic improvement and data flow

Genetic evaluations are rarely conducted for horses in the UK currently, and breeding values are not generally used to aid breeding decisions.

As data on sport horses accumulates, this may provide a source of data that could be used for starting point for genetic evaluations in the future.

Appendix 3. List of Abbreviations Used

AHDB	Agriculture and Horticulture Development Board
AI	Artificial Insemination
APHIS	Animal and Plant Health Information System
APHA	Animal and Plant Health Agency
ARAMS	Animal Reporting and Movement Service
ASFv	African Swine Fever virus
BCMS	British Cattle Movement Service
BIN	Beef Information Nucleus
bTB	Bovine Tuberculosis
BVD	Bovine Viral Diarrhoea
CIS	Cattle Information Service
CNV	Copy Number Variation
Defra	Department for Environment Food and Rural Affairs
DIN	Dairy Information Nucleus
DNA	Deoxyribonucleic acid
EBV	Estimated Breeding Value
EGENES	Edinburgh Genetic Evaluation Services
EID	Electronic Identification
FAnGR	Farm Animal Genetic Resources
GHG	Green House Gas
GMO	Genetic Modified Organisms
HCC	Hybu Cig Cymru
ICAR	International Committee for Animal Recording
ICBF	Irish Cattle Breeders Federation
IPSC	Induced Pluripotent Stem Cell
IVF	In Vitro Fertilisation
MOET	Multiple Ovulation and Embryo Transfer
NMR	National Milk Records
PGCs	Primordial Germ Cells
PRRSv	Porcine Reproductive and Respiratory Syndrome Virus
PTA	Predicted Transmitting Ability
SIN	Sheep Information Nucleus
SNP	Single Nucleotide Polymorphism
SSC	Spermatogonial Stem Cell
VIA	Video Image Analysis