Genomics offers increasing potential to inform and improve the prediction, prevention, diagnosis and management of disease, and it is reasonable to expect that the volume, complexity and scope of genomic testing will therefore increase significantly over the coming years, both in the NHS and the commercial sector.

The main risks to individuals from commercial direct-to-consumer (DTC) genomic tests arise where they are less clinically valid or useful as implied or believed, through lack of follow-up care, and from the inherent uncertainties arising from extensive human genomic analysis.

Commercial DTC genomic testing is likely to place a growing burden on the NHS through patients requiring information or intervention, and may exacerbate health inequalities.

Clear parameters for acceptable engagement of commercial genomics tests and services with health services and publicly funded biomedical research should be developed, including guidance and support for health professionals to respond appropriately to commercial DTC genomic test results.

Appropriate and proportionate regulation of commercial genomics offerings, especially DTC tests, will be increasingly needed.
We believe that NHS genomic testing is the gold standard for delivery and interpretation of all forms of genomic testing for serious diseases.

**Scope of commercial genomics**

Commercial genomic testing offerings have developed rapidly in recent years, and range from analysis of a modest number of genetic variants associated with health, fitness or wellness through to whole genome sequencing and extensive clinical evaluation of variants detected. Many offer direct-to-consumer (DTC) testing, sometimes in association with non-health applications such as ancestry testing, whilst others may be offered in a private clinical setting, potentially alongside other medical services. Some are provided as part of fertility services, such as pre-conception or embryonic screening for the presence of, predisposition to or carrier status for inherited forms of disease.

We believe that NHS genomic testing is the gold standard for delivery and interpretation of all forms of genomic testing for serious diseases. Commercial offerings nevertheless have a place in health promotion and disease prevention for citizens, the main barriers being variation in quality and utility, and the difficulty for consumers in assessing standards and uses.

This submission is primarily concerned with DTC testing, and assumes that this excludes testing for genetic variants that confer high risk of serious diseases, which should be confined to health service settings.

The wider commercial genomics sector has been a critical driver in the technological developments that underpin current NHS genomics laboratory capabilities, and will no doubt continue to pioneer widely beneficial advances in sequencing and analysis. Similarly, commercial development of products and services for use within the NHS may potentially support valuable new services, improved access and clinical outcomes, provided that such tests and services are confirmed by NHS laboratories as offering sufficient analytical and clinical validity and utility.

**Benefits of consumer genomic testing**

The potential health benefits of DTC genomics to purchasers include strengthening of interest in optimising their own health; and identifying specific genetic variants with a genuine and significant impact on disease risk that indicate medical intervention to protect the health of the individual or family members. These are significant benefits, and the capacity to obtain testing privately in terms of ease of access is likely to attract increasing numbers, especially given current trends towards increasing genomic literacy across the general population, and encouraging personal responsibility for (and personalised approaches to) health.
There is little evidence that genetic information alone motivates people to change lifestyle behaviours, though it may motivate other forms of potentially risk-reducing actions such as consulting health professionals or undergoing screening. More research is needed to determine this, and whether such actions reduce long-term risks (or increase others, such as over-diagnosis).

In specialised contexts such as fertility treatment, commercial genomics may offer additional benefits such as opportunities for screening of eggs or sperm pre-conception, or post-fertilisation, cell or embryo screening to maximise the chances of conception by in vitro fertilisation and minimise the chances that successful pregnancies will be affected by certain inherited diseases.

Some forms of commercial testing also offer opportunities for purchasers to share their genetic information, whether by connecting them with individuals with similar genetic features, or to contribute to forms of genomic research, such as the Parkinson’s disease research undertaken using genotype data from 23andMe clients in the US, including thousands of patients and their families.

Risks of consumer genomic testing

Commercial genomics may pose risks for purchasers, for two main reasons. The first is that the tests may not be as clinically valid or useful as implied or believed; even if a test reliably identifies genetic variants that have been shown in scientific literature to display significant association with a disease or disease risk, this does not necessarily mean that it is clinically valid or useful. Harms may arise when a test provider states or implies that a specific test result has certain health implications without robust supporting evidence, or when a consumer believes this to be the case (whether or not the provider has indicated it).

Harms may range from transient psychological impacts such as short-term anxiety or concern, through to influencing harmful decisions or behaviours addressing perceived health risks. An extreme example might be a woman who incorrectly believes herself to be at very high risk of breast cancer on the basis of commercial testing, and seeks prophylactic bilateral mastectomy. In the UK, the risks of serious harm are limited, since the woman would not be able to access an NHS mastectomy without confirmation of this risk and other clinical factors by health professionals. However, false negative findings resulting in false reassurance for consumers who might believe themselves at very low risk of disease also poses dangers – a recent study found that 23andMe testing failed to identify nearly 90% of BRCA mutation carriers, because it tests for only three variants. Both cases might be mitigated by greater transparency about the variants that are (and are not) included.
Although most potential harms based on misleading or misunderstood information will be considerably less drastic, consumers may nevertheless waste money, experience psychological distress, or undertake inappropriate health behaviours or actions. For example, they might believe themselves in need of specific dietary restrictions or nutritional products; or exempt from standard health advice about avoiding smoking and maintaining healthy weight and activity levels.

Finally, many forms of genomic testing carry some risk of uncovering unexpected information, such as misattributed paternity or the presence of unanticipated inherited disease, which may cause distress.

The second main type of risk arises from the inherent uncertainty of extensive human genomic analysis; whilst great progress is being made towards successful clinical interpretation of genomic variation, much remains to be established. Genomic analyses identify many variants of unknown or uncertain significance. Even experts with access to high quality clinical and genomic information may not be able to reliably impute or exclude variants from clinical significance. Over time, growing evidence may assign significance to these (as benign or pathogenic), but it may also change previously held views about the clinical significance of other variants. Communication of such uncertainty is challenging, and even if achieved, the uncertainty itself may be harmful to the individuals concerned.

In the context of testing for serious forms of inherited disease, health professional practice is to provide specialised support by clinical geneticists and genetic counsellors able to offer expert explanation of the risks of and findings from testing, and to support individuals and families through decision-making. Failure to do similarly in the commercial sector, if such tests of serious import are offered, would be to potentially cause significant harm.

Testing outside the clinical context and in healthy individuals necessarily poses a greater interpretative challenge. Even where serious inherited diseases are excluded, there are still plenty of potential risks arising from uncertainty. Correctly identifying genetic variants for which a robust and clinically significant association with disease has been clearly established may not necessarily result in disease in any individual, and for more common, complex diseases (subject to multiple genetic and environmental influences) the picture is even less clear.

Even identification of possession of two copies of the APOE4 genetic variant, which is reliably associated with a 3-5 fold increased lifetime risk of Alzheimer’s disease, could create many questions and concerns for the individual concerned. A number of current commercial tests identify variants considerably less robustly associated with diseases and with specific risks for those diseases, and in some cases also for a very wide range of lesser known diseases, posing plenty of potential for uncertainty and confusion.
Impact of commercial genomic testing on the NHS

If all commercial genomic testing results were reliable, robust and effectively communicated to purchasers, they would nevertheless create some degree of burden on the NHS, as most patients receiving clinically actionable information would probably approach NHS providers to seek interventions. Whilst a minority might have access to private health service provision, this could not be expected of all, especially since the cost of genomic testing is now relatively low.

Given the opportunities for uncertainty over the clinical implications of commercial DTC testing results, it is likely that the actual burden on the NHS will be higher and will increase as testing becomes more widespread. Primary care practitioners will bear the greatest burden of patients seeking clarification, confirmation or action on the basis of commercial test results.

Even if all health professionals were optimally trained in genomics, fully aware of the most appropriate actions for a given situation (whether to reassure, investigate or refer), and had sufficient time available, they would still be hampered by a lack of knowledge about just how accurate, scientifically and clinically valid test results might be. They might therefore be unable to provide comprehensive information for patients as sought, and be obliged to either send them away unsatisfied, or to refer them to more specialist colleagues. These specialists would probably be obliged to retest through the NHS if sufficiently concerned by the results presented.

Whilst increasing numbers of health professionals will gain knowledge and skills in genomics to support patient journeys (including understanding test results and communicating risk effectively), this is likely to take some time. Unless or until patients are able to present commercial test results of robust quality and clinical relevance to genomics-literate NHS professionals who have clear guidance and pathways for appropriate action, the impact of commercial genomics on the NHS may be negative.

Even in this future scenario, questions may still remain about how appropriate it is for individuals who have purchased genomic testing and received reliable, clinically actionable information to receive care within the NHS for it, since it potentially exacerbates health inequalities by allowing enhanced NHS access for those who can afford to purchase commercial testing.

There is also a question of recording. The health benefits of genomic testing are arguably maximised (for the individual, and for others through information sharing and research) when genomic data is integrated with
One important concern is how easily consumers are able to assess the reliability and medical relevance of testing services. In the future there may be increasing need to consider whether, how and under which circumstances it would be appropriate to record information derived from commercial genomic testing in a patient’s records. The development of shared or agreed standards for clinical grade testing and data recording would, if possible, make this considerably more feasible than at present and might be beneficial, if it saved costs of confirmatory NHS testing. It would however necessitate considerable confidence in the commercial test provider.

**Regulation**

Genetic and genomic tests are currently regulated in a light touch fashion under the EU In Vitro Diagnostic Medical Devices Directive. This Directive will be replaced in 2022 when the In Vitro Diagnostic (IVD) Medical Devices Regulation (IVDR) comes into force in the UK, in line with EU law; this is likely to continue for at least some years following any departure of the UK from the EU. Human genetic tests will then be regulated as in vitro diagnostic medical devices and be subject to performance evaluation, requiring manufacturers to provide sufficient scientific evidence, analytical and clinical performance information, provided that tests are intended for medical purposes. Lifestyle tests are likely to be regulated differently.

Under the new regulatory regime, algorithms and software used for medical purposes may also count as medical devices, providing another potential means of oversight.

As with any commercial offering, genomic testing services are also subject to advertising standards regulations which require amongst other things that objective claims are backed up by evidence, and that advertisers do not discourage essential treatment for conditions for which medical supervision should be sought.

One important concern is how easily consumers are able to assess the reliability and medical relevance of testing services; at present it is difficult to distinguish between offerings. Some may be robust and useful, offered according to suitable ethical and legal frameworks (clear consent processes; privacy and data usage policies; proportionate counselling), whereas others may be virtually useless, and it can be hard for customers to distinguish between them. It is particularly difficult to discern the clinical quality, validity and utility of testing; a test may accurately identify the presence of given genetic variants, and those variants may have shown association with a given disease in peer-reviewed scientific literature, but this does not by any means guarantee that the presence of a disease-linked variant determined by the test offers any meaningful information.
Potential mitigation of risks from commercial genomics

Risks to the individual can be minimised by regulation that would ensure consumer protection in the form of adequate pre- and post-counselling, consent processes, and adherence to legal and ethical frameworks. Ideally, it would oblige providers to make clear the reliability of testing in terms of test performance, scientific and clinical validity, and clinical meaning and utility. The challenge here is to require clear and simple information for a potentially highly complex type of test, and so a proportionate approach is particularly relevant, reserving the most stringent requirements for testing with the potential to deliver clinically significant information. In the same way, a simple approach to signposting genetic risk information would be of value, for instance indicating low, moderate or high risk and the suggested actions associated with each.

The introduction of the IVDR in 2022 will go some way to ensure that sufficient pre- and post-test counselling is offered to purchasers of DTC tests. Article 4 of the IVDR sets out the information that an individual being tested should receive, which includes the nature, significance and implications of the genetic test. It also provides that there should be appropriate access to counselling for genetic tests that provide information on genetic predisposition for medical conditions considered untreatable. Nothing prevents Member States from adopting more specific or protective provisions, and indeed many countries in Europe have already criminalised or banned DTC tests. Given that consumers access test kits via the internet and access results by email or via a secure site, questions arise about how enforceable such restrictions will be, and whether there will be medical tourism.

The Human Genetics Commission proposed a Common Framework of Principles for DTC genetic testing services, incorporating a clear set of principles and their proportionate application to different types of test, and puts the onus on the clinical genetics professional to ensure that appropriate counselling and materials are provided. These principles remain valid when considering what further regulation should apply to DTC testing.

Clear policies and guidance for NHS professionals on when and how commercially obtained testing results should be considered (and how to handle situations when they should not be) could help minimise the burden on NHS services considerably; such decisions require considerable thought and effective communication to the public. Developing some sort of NHS standards to which commercial providers might aspire (similar to encouraging the commercial development of health apps for the NHS Apps library) might allow health professionals to respond to test findings, or even integrate results into NHS patient records. Any plans to develop commercial NHS genomic test services would necessarily have a significant impact on such considerations.
Conclusions

Genomics offers increasing potential to inform and improve the prediction, prevention, diagnosis and management of disease. Personalised genomic testing may help to refine risk estimation for common diseases (especially cancers) and inform personalised preventive interventions. Genomic testing may also allow contribution to forms of biomedical research, by determining access to repurposed drug treatments or clinical trials, or consenting to data analysis for research.

The volume, complexity and scope of genomic testing will probably increase significantly over the coming years, in both the NHS and commercial sector. Expansion of the National Genomic Medicine Service, genomics education of health professionals, and approaches to support testing and interpretation such as the development of new specialised health professionals could help the NHS deal with the impacts of expanding commercial testing. However, clarity will also be needed with respect to the boundaries between clinical care and research, and publicly funded health services and commercial services, especially as citizens and patients begin exercising greater control over their own health management and data.

Policy-makers will need to consider acceptable parameters for engagement of commercial genomic testing with health services and publicly funded biomedical research, as well as issues of appropriate and proportionate regulation, to minimise risks to individuals and the NHS.

Our response to the inquiry is confined to health applications of commercial genomics. Other recent consultation responses and reports on genomics and health are freely available from our website. We are happy to comment in greater depth or to provide oral evidence.