

Introduction

1. The Wellcome Sanger Institute uses genomics to advance the understanding of human and pathogen biology to improve human health. We use science at scale to tackle the most challenging global health research questions.
2. The Wellcome Sanger Institute is based on the Wellcome Genome Campus: a world-leading hub for genomes and biodata research. The campus is also home to EMBL-EBI, Connecting Science, Sanger Institute spin-out companies, start-up companies and Genomics England.

Summary

3. The widespread sharing of datasets is crucial to realising the full potential of genomic data.
4. If increasing numbers of consumers seek genomic testing, there will be added pressure on an already stretched healthcare system.
5. Genomic data and polygenic risk scores are extremely complex to interpret and, as such, a highly skilled workforce is required to deduce health implications and risks from them.
6. There must be clarity on the usage, storage and sharing of genomic data for the public. To maximise the full impact of genomics, data must be representative, accessible and interoperable.

Recommendations

7. The NHS should require NHS-commissioned commercial genomic test companies to use standard file formats and accessible databases.
8. The Government should evaluate the integration of polygenic risk scores into existing screening tests by investing in genetic epidemiology, public health and clinical pathway development to ensure that there is good evidence of clinical utility and a clear pathway for managing results.
9. The Government should fund and resource genetic services (clinical geneticists, genetic counsellors and clinical scientists) to help those in receipt of genomic test results that have major implications for their own health and that of family members.
10. The NHS should make clear to those accessing commercial genomic testing through the NHS how their data can be used and by whom, how the data is stored, to what extent the data will be used to inform healthcare decisions for themselves and others and clarify whether the data could be analysed by artificial intelligence.
11. The Government should initiate a health economic study to assess the value and effectiveness of polygenic risk scores and to inform risk thresholds.
12. The Government should appoint an independent regulatory body to oversee genomic testing in the UK and set standards and codes of conduct for the industry and practice of the sector. This should include which tests are suitable for direct to consumer access and which should only be accessed through a registered health professional. The parameters of quality and performance should be published to enable effective comparison between different providers.

Provision of accurate and unambiguous health results

13. Genomic data holds tremendous value for understanding human biology and disease, but an individual genome only has meaning when compared with many other genomes. The larger the pool of comparison genomes the more accurate the insight. Therefore, the ability for researchers and healthcare professionals to compare large genomic datasets is as important as the ability to generate a dataset. Sharing datasets is crucial for maximising the impact of genomic research, innovation and translation into the NHS.
14. It is important to recognise that genomic testing covers a broad range of applications including prenatal screening, assessing polygenic risk scores, studying ancestry or identifying genetic variants that influence pharmacogenetics or underpin rare genetic disorders and late onset disorders. The implications of different types of genomic test must be considered separately rather than as a collective.

Diagnosing rare diseases: iterative reanalyses

15. In the Deciphering Developmental Disorders (DDD) study, the Wellcome Sanger Institute is working in partnership with NHS clinical genetics services throughout the UK to diagnose children with rare genetic disorders. By whole exome sequencing 13,600 children with severe undiagnosed developmental disorders and their parents (33,500 exomes in total) and sharing this data with researchers and healthcare professionals, the DDD project has provided 4,500 diagnoses for previously undiagnosed children. By sharing key findings in >150 publications and via the DECIPHER web platform¹, the DDD project is facilitating diagnosis for children with rare genetic disorders globally. The project is ongoing to diagnose the remaining cases.
16. The accuracy of determining disease-causing variants and diagnosing genetic conditions improves as datasets enrich and as good dialogue between clinicians and genomic scientists is developed. For the DDD project, the initial diagnosis rate was around 27%, but after three years, with continued clinical engagement and real-time updating of newly published research findings both from within the DDD study and by external teams, reanalysis of the same data increased the diagnosis rate to 40%. As we continue to understand more about the human genome and the interplay of genes in disease, diagnosis rates, certainly for rare diseases, will continue to improve.

Predicting a disease: the difficulty of understanding polygenic risk score

17. Genetic tests designed to predict the likelihood of an individual developing a health condition use polygenic risk scores to quantify the cumulative effect of many genomic variants, which individually contribute to an individual's susceptibility to disease. The analysis and interpretation of polygenic risk scores is extremely complex and, as with most predictors of risk, are poorly understood by lay individuals. Estimates of the relative risk between a polygenic risk score and a disease have to be extremely high for the polygenic risk score to merit consideration as a standalone screening test.
18. Although polygenic risk scores hold promise in assessing an individual's risk of disease, we are still far from being able to use the tool with certainty and confidence. The choice of which genetic variant to test and the subsequent polygenic risk scores derive from databases comprised of predominantly European genomes. This underrepresentation and lack of genetic diversity not only limits the ability of ethnic minorities and those of non-European heritage to benefit from healthcare advances but puts them at a greater risk of misdiagnosis.

¹ <https://decipher.sanger.ac.uk/>

19. A health economic study should be performed to assess the effectiveness and value of polygenic risk scores and other genetic tests for consumers and the NHS. This study should inform the definition of statistical thresholds for identifying individuals with high-risk disease likelihoods.

Benefits of commercially available genomic testing for consumers

20. Commercial companies offer a broader range of genomic tests for consumers than the NHS currently offers, because evidence of clinical utility is required before genomic tests are introduced into the NHS. Commercial tests vary greatly in quality and cost and the results are variable among different companies, with little regulation or guidance available for consumers to distinguish between quality healthcare products and pseudoscientific claims.
21. In our view, increasing numbers of consumers will seek genomic testing to alleviate health concerns, take ownership of their health or to satisfy simple curiosity. With appropriate support from healthcare professionals, positive test results could drive lifestyle changes, reproductive decisions or encourage individuals to seek medical advice for early diagnosis or preventative treatments. For many diseases, early diagnosis undoubtedly improves health outcomes, but for others it simply extends the interval between diagnosis and disease end-points. Early entry into the healthcare system based on predictive test results could risk the unnecessary over-testing and/or over-treatment of apparently high-risk individuals unless such an approach has been carefully evaluated and shown to meet standard criteria for screening as advocated by the UK Screening Committee.

Impact on the NHS of increasing availability of commercial genomic testing

22. Genomics is driving a push for disease prevention, early diagnosis and individual responsibility for health. Commercial genomic testing could offer a promising outlook and greater health outcomes for each of these themes by proactively encouraging earlier screening and diagnostic testing before the onset of disease symptoms, but this needs to be based on sound evidence, hence strong investment in research is needed to build this evidence base. In particular, pharmacogenetic testing has the potential to reduce poor drug treatment outcomes, such as ineffective treatment and adverse drug reactions, saving the NHS time, money and medical resources while improving patient outcomes.
23. However, without adequate preparation and planning, in conjunction with clinicians and public health physicians, direct to consumer genomic testing presents several serious challenges that could outweigh any positive effect:
 - Increasing numbers of individuals entering the NHS pre-disease onset will cause capacity issues within an already strained healthcare system. Without clear advice from commercial genomic testing companies, the number of individuals wishing to discuss their genome test results with healthcare practitioners could overwhelm local GP surgeries, who lack the capacity or training to adequately manage these individuals.
 - The data generated by next generation sequencing and polygenic risk scores is complex and requires skilled individuals to analyse and infer the extent of health risks. In many cases, knowledge of disease penetrance is unknown and this data needs to be in place before such testing is offered in order to avoid over-diagnosis. Polygenic risk scores can easily be misinterpreted if used in isolation and without integration with other risk factors for disease

and subsequent health risks can be over- or under-estimated. Risk score statistics can also be portrayed in different ways and these can cause confusion or be misleading.

- A resourced and skilled NHS workforce with expertise in genomics and interpreting genomic test results is crucial for the successful implementation of genomics into healthcare. This particularly includes primary care providers who could become the front line for patients wishing to discuss genetic test results. Accurate analysis of sequence data and genomic test results is complex, but crucial for ensuring that individuals are given the best available advice for diagnosis, treatment or lifestyle changes. NHS Genomic Medicine Services are already beginning to fill this void, but further resource to strengthen the core clinical and scientific expertise is required to prepare for future demand and educate the wider NHS workforce in the appropriate use of genomics.

Data usage, security and sharing

24. To fully realise the potential for genomic medicine, patients and the public must be kept well informed of how their health and genomic data will be used. Loss of public trust would be a major barrier to implementing genomics in healthcare.
25. There is a lack of clarity on how commercial genomic testing companies, within and outside the NHS, could use individuals' genomic data. We are concerned that consumers do not understand how their data could be used and by whom, which medical decisions could be made according to their genomic test results and where their data might be stored. There is also a lack of clarity on how consumers' data can be used by third parties (e.g. other companies, police and security services, immigration departments, insurance companies).
26. Aggregated genomic data derived from commercial genomic tests should be made anonymous and freely available to scientific researchers within a secure data environment in order to further research and improve health outcomes, particularly where those databases have been derived from NHS patients. Genomic data should adhere to international data standards, use standard file formats, and be interoperable with different data systems according to the FAIR principles of data sharing.²
27. Commercial genomic testing companies should be discouraged from developing proprietary file formats or store data in proprietary archives that would otherwise hinder or prohibit researchers, healthcare professionals or other organisations from accessing the data to help aid further research or inform healthcare decisions. Where genomic testing companies are commissioned within the NHS, data should be made available in interoperable formats.

Impact on the NHS of offering genomic testing to healthy individuals

28. The UK is a world leader in genomic research and translating genomics into healthcare. By offering genomic tests to healthy individuals who are willing to pay and share their data, the NHS will continue to be at the forefront of integrating genomics into healthcare and drive the joining up of genomic data with health records to improve health outcomes. This proposal enables the creation of a huge aggregated genomic dataset, which would be an invaluable resource for understanding health and developing novel genomic medicine applications at little or no cost to the NHS.

² <https://www.nature.com/articles/sdata201618>

29. However, there is a risk that offering genomic tests to healthy individuals who are willing to pay and share their data could lead to the creation of a large genomic dataset that represents self-selected wealthy individuals rather than the diverse socioeconomic groups and ethnic backgrounds within our society, further excluding groups who are already underrepresented in many genomic databases. Any implementation of genomic testing within the NHS must not fuel social inequality and proactive steps should be taken to counteract that.
30. Offering paid-for genomic tests to willing healthy individuals does not align with the core NHS principle of being free at the point of care. The NHS risks losing trust from the public if they perceive the healthcare system as commercialised or socially divided.
31. As the genomic era progresses, there will be increased frontline pressure on the NHS to handle an increasing volume of patients entering the healthcare system to discuss or allay concerns arising from genomic testing, requiring additional screening, treatment or confirmatory diagnosis (e.g. blood tests, scans). This increased volume risks adding further pressure to an already under-resourced and strained healthcare system.

Concluding remarks

32. The UK is a world leader in genomics research and its implementation into healthcare. Simultaneously, the public is becoming increasingly interested in their genetic make-up and ancestry. Greater public interest in direct-to-consumer genomic testing offers the potential for improved health outcomes for individuals, but risks adding frontline pressure onto existing healthcare systems and exacerbating existing social inequality.
33. Large aggregated genomic datasets are crucial to further understand the role of genomics in disease and health. To realise the full potential of such resources, the data should be representative of our diverse population and be made freely available and as accessible as possible for researchers and healthcare professionals.