# Welcome to the new genomics: an introduction to the NHS Genomic Medicine Service for oral healthcare professionals

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## Key points

- Includes information about the new NHS Genomic Medicine Service.
- Discusses the implications of this service for healthcare.
- Includes information on how this service might impact on dentistry.


## Abstract

Genomic medicine is on the threshold of a significant advance in the United Kingdom (UK) with the introduction of a National Health Service (NHS) Genomic Medicine Service. This world-leading initiative aims to integrate genomic medicine into routine NHS care and has the potential to revolutionise healthcare in the UK, including dentistry. The initial focus will be on increasing diagnostic services for rare diseases and cancer, while also harnessing the use of personalised medicine for therapeutic interventions in multiple disorders. Here, we provide a brief overview of this new service, outlining the historical background that has led to its development and how it will work, as well as discussing some of the wider implications for healthcare within the NHS and highlighting the potential longer-term impact of genomics for oral health.


## Introduction

It is now almost two decades since the draft sequence of the human genome was published,[1,2] and in that time, the discipline of genomics has advanced at a staggering rate.[3] The automated technology that now exists can sequence the entire human genome in a matter of hours, providing an almost limitless information resource that has huge potential significance for personal wellbeing. This so-called next-generation sequencing produces a huge volume of data that can potentially be utilised within healthcare for diagnosis, treatment and research, and ultimately facilitate a more personalised approach to medical care.[4] The United Kingdom (UK) is at the forefront of this technology, and we are on the threshold of a unique large-scale and ambitious transformation project, which has the aim of incorporating genomic medicine into routine care within the National Health Service (NHS). Here, we introduce the new NHS Genomic Medicine Service and highlight some of the implications for healthcare that this innovative project will bring. In addition, we will provide some focus on what the impact might be for clinical dentistry in years to come.

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## Background

The Department of Health established Genomics England as a government-owned limited company focused on delivery of the 100,000 Genomes Project (100kGP) in 2013. This ambitious and large-scale undertaking aimed to complete whole-genome sequencing (WGS) (Box 1) of 100,000 genomes derived from patients with cancer, and families affected by rare disease.[5] The establishment of 13 Genomic Medicine Centres spread

### Box 1 Next generation sequencing

Next generation sequencing technology is increasingly being used in healthcare to provide high throughput data on the genetic code of many individuals. This technology allows vast amounts of DNA to be sequenced very rapidly and is revolutionising genomic medicine. Whole genome sequencing (WGS) provides the genetic code for the entire genome of an individual – all the coding and non-coding regions – while whole exome sequencing (WES) is limited to the exons, the regions of DNA that provide the instructions for making proteins. WGS is more expensive than WES and generates more data, although the diagnostic utility is relatively similar between the two techniques.[19] WES is useful for identifying mutations associated with rare Mendelian disorders where sample sizes of affected individuals are small. As most disease-causing mutations occur in the exons, WES is a useful method of identification; however, genetic variation in the non-coding regions outside the exons can also cause disease and WGS is required to identify pathological changes in these areas of the genome.

across NHS trusts throughout England to deliver 100kGP placed NHS England in the enviable position of having a platform to move forward with an innovative new programme focused on integrating genomic medicine into routine care.[6] Indeed, the annual report of the Chief Medical Officer for England had championed this theme in 2016, highlighting the considerable opportunities for clinical practice that advances in genomic technology could bring and advocating the widespread accelerated uptake of genomic medicine in the NHS as a strategic priority.[7]

The NHS England Board subsequently acted upon these recommendations and set out a strategic approach to establish a national Genomic Medicine Service with mobilisation due to begin in 2018. This service will comprise of five key elements (Box 2) and provide the foundation for genome-based personalised medicine as a key component of routine NHS care provision. An integral part of this service will be a national laboratory network in England to perform genomic testing for patients within their respective geographical areas. This testing is set out by the new National Genomic Test Directory and, currently, will cover rare diseases and cancer clinical indications, with services ranging from single-gene sequencing through to WGS. The genomic tests that are available within the service will be evidence-based and updated annually through consultation with an appointed expert scientific group. It is expected that testing services will rapidly evolve and expand as the service becomes established. The existing 13 Genomic Medicine Centres developed as part of 100kGP will be replaced by seven Genomic Medicine Service Alliances during 2020. Their primary role will be to support the systematic embedding of genomic medicine and ensure that all eligible patients can access these services.

**Box 2 Key elements of the NHS national Genomic Medicine Service**

- National genomic laboratory service delivered through a network of genomic laboratory hubs in England
- National genomic test directory to underpin the genomic laboratory network and enable equity of access to testing
- National WGS provision and supporting bioinformatics infrastructure in partnership with Genomics England
- A clinical genomics service and evolved genomic medicine centre service
- A national coordination and oversight genomics unit within NHS England.

**Box 3 Phase 1 clinical indications for WGS**

- Ultra-rare and atypical monogenic disorders
- Congenital malformation and dysmorphism syndromes – microarray and sequencing
- Intellectual disability – microarray, fragile X and sequencing
- Hypnotic infant with a likely central cause
- Skeletal dysplasia
- Rare syndromic craniosynostosis or isolated multi-suture synostosis
- Neonatal diabetes
- Inborn error of metabolism
- Hereditary ataxia
- Early onset or syndromic epilepsy
- Childhood onset hereditary spastic paraplegia
- Arthrogryposis
- Rare neuromuscular disorders
- Cerebellar anomalies
- Holoprosencephaly (non-chromosomal)
- Hydrocephalus
- Cerebral malformation
- Severe microcephaly
- Childhood onset leukodystrophy
- Cystic renal disease.

## A national Genomic Medicine Service

There is no doubt that the data derived from genomic sequencing have the potential to transform medicine; in particular, allowing more rapid and accurate diagnosis in rare and infectious diseases, and cancer – but importantly, also allowing the development of therapies targeted to the individual (so-called personalised medicine). A number of phase 1 clinical indications have already been established for WGS within the national Genomic Medicine Service (Box 3), with future phases also planned to include more conditions such as thoracic aortic aneurism or dissection, growth failure in early childhood and disorders of sex development. In addition, WGS clinical indications for cancer will initially include sarcoma, acute myeloid leukaemia and paediatric tumours, with specific tests available for over 120 additional cancer clinical indications, including adult solid tumours, neurological and haematological tumours. There will also be a platform for standardised non-WGS testing to include over 300 rare diseases spread over 16 clinical indication groups. An interim service for neonatal and paediatric intensive care units (NICUs/PICUs) will also provide WGS for children with undiagnosed, likely monogenic, disorders and rapid whole-exome sequencing (WES) (Box 1) for fetal anomalies. Collectively, these advanced services will provide a significant new resource for a wide range of patients within the NHS.

Accompanying this is a new model for consent to testing and participation in research called 'patient choice'. Initially just for WGS requests, patients will choose whether, in addition to their whole-genome analysis, they wish their DNA and de-identified data to be used in research studies via the National Genomic Research Library, results from which may benefit themselves or others in the future.

## What are the implications for healthcare?

Genomic information can help to improve healthcare through increased knowledge of the genetic contributions that underpin both health and disease – advancing the science of medicine to help improve medical practice for the whole population.[4] Genomic medicine will provide fundamental impact through improved diagnostic and therapeutic services, and this will be formally embedded into the NHS care pathway.

A definitive diagnosis of disease-causing genetic variants provides the molecular basis of a particular condition and is the gateway for developing appropriate therapies. It can also provide further invaluable information relating to overall management of a condition and, where relevant, recurrence risk and disease-risk determinations for other family members. Genomic medicine is having particular impact in two fields of diagnostic medicine: rare diseases and cancer. The majority of rare diseases affect children, and achieving a molecular diagnosis can be a long, time-consuming process using traditional methods of phenotyping and genetic testing. The advent of WGS affords much greater potential for the rapid discovery of causative genes associated with these rare conditions[8] (Box 4). In addition, within the field of cancer diagnostics, increased discovery of genomic sequence-based diagnostic and predictive markers is positively influencing management for a wide range of inherited and acquired cancers. Individualised cancer treatment is based upon knowing the effect of disease-causing variants at the cellular level and designing therapeutic strategies that specifically target the disrupted molecular pathways.[9]

Another area of huge potential benefit lies within the field of therapeutics and the use of safer, more effective drug therapy informed by knowledge of the genome at both individual and population levels.[10] The genomic basis of a disease provides a foundation for identification of the molecular basis and, therefore, potential targets for drug development and therapeutic targeting. In cancer therapy, pathogenic genetic variants responsible for tumour development and progression can be specifically targeted to improve clinical outcome. The genetic profile of an individual can also influence disease progression, drug dosage requirements and potential adverse drug reactions, and information about these variables can all contribute to the tailoring of therapy to the individual patient.

## Integrating routine genomic services into the NHS

While these developments are all to be welcomed, it is important that genomic medicine is integrated into the NHS according to the quality and standards that apply across all medicine. Moreover, there are significant financial, logistical, ethical and educational considerations associated with a project of this nature. The Academy of Medical Royal Colleges has recently released a statement on behalf of the medical Royal Colleges outlining the principles on which genomic medicine should be implemented in relation to patient care and population health [11]. There should be equity of access to testing and screening, and the implementation of genomic medicine should be based upon sound evidence-based clinical benefit. There is a risk that genomic medicine can lead to over-diagnosis and the treatment of conditions that might never manifest; safety is paramount, and testing should only be undertaken when there is evidence of appropriate sensitivity and specificity. There are multiple potential issues in relation to consent, not only for the patient but also for related family members, and the implications are long-term. WGS generates significant levels of data and there are multiple opportunities for high-quality research, particularly in relation to the biology of disease, mechanisms of drug action and epigenetics. Patient and public engagement will therefore be important, particularly in relation to the opportunities, limitations, complexities and uncertainties of genomic testing for the population. Widespread routine genomic services will require appropriate information technology and informatic systems, and ready access to supporting information for patients and clinicians. Moreover, further innovations in sequencing technology and data analysis will be required to achieve truly comprehensive datasets. A key issue will be the training requirements for medical professionals involved with genomic medicine and this will extend to those involved in bioinformatic analysis. This all needs to be coordinated with ongoing feedback and interaction between key stakeholders.[11]

### Box 4 Diagnosing rare diseases

A rare disease is defined as one that affects less than 1:2,000 individuals, which equates to around 7% of the population or approximately 3 million people in the UK. These conditions have a predominantly genetic basis and are a significant cause of childhood mortality or long-term disability. A rare disease might not be identified *in utero* or manifest itself immediately after birth in an affected individual, and diagnosis can be both challenging and lengthy – sometimes taking many years. Traditional diagnostic methods are complex and involve the investigation of single genes, panels of genes or chromosomes, informed by clinical examination and phenotyping, and often following testing and input from multiple specialists. A prolonged lack of diagnosis can make appropriate management, including therapy and support, difficult to institute. Moreover, families can be left uninformed about the longer-term implications of their particular rare disease and the risks of having further children with the disorder. Rare diseases are often single-gene disorders, but their very rarity makes traditional methods of linkage analysis more difficult to accomplish because acquiring suitable pedigrees is difficult. WES can be used as a method of rapidly sequencing the protein-encoding regions of the genome, and the nationwide Deciphering Developmental Disorders (DDD) project has been highly successful in identifying multiple novel genes associated with rare developmental disorders.[20] The use of next-generation sequencing within the national Genomic Medicine Service is likely to further increase diagnostic yield in rare diseases and make a major contribution to the management of these conditions for both affected individuals and their families.

## Health Education England Genomics Education Programme

The introduction of genomic medicine within the NHS will also require a significant educational commitment for healthcare providers at all levels. Health Education England (HEE) has established a Genomics Education Programme (GEP), with the goal of providing a strategic and coordinated approach to the genomics education and training needs of the current 1.3 million staff within NHS England. In addition, the needs of the prospective workforce are also being addressed through a review of relevant undergraduate and postgraduate curricula, and the introduction of genomics into professional standards of proficiency. The GEP has already developed both formal and informal educational courses, ranging from a full master's degree in genomic medicine through to shorter courses and bite-sized e-learning for those with little or no previous genomics knowledge.[12] The HEE-funded multi-professional master's framework is also helping to build a cadre of genomics champions who can aid the spread and adoption of genomics in their specialties, whereas bite-sized courses will raise awareness of genomics in healthcare and build confidence for further learning. To directly support the

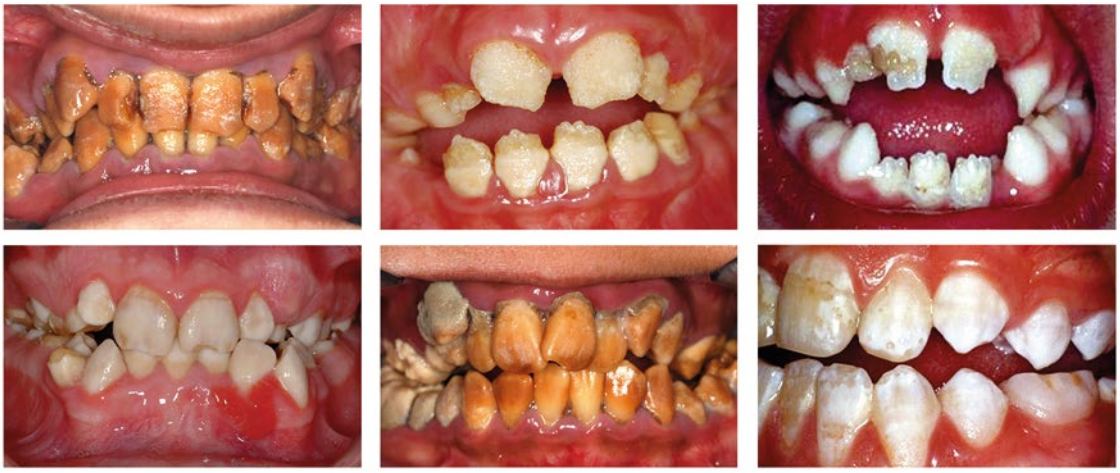

**Fig. 1 Amelogenesis imperfecta is the collective term for a group of inherited conditions characterised by abnormal enamel formation. The upper three panels show examples of hypoplastic amelogenesis imperfecta (note the presence of anterior open bite in some cases) while the lower three panels show hypomineralised forms. Images courtesy of Mike Harrison and Joanna Johnson**

implementation of WGS and mainstreaming of genomics, the GEP is supporting the development of skills through introduction of competency frameworks with supporting clinician guides and resources in areas such as the new patient choice and consenting model, as well as variant interpretation. Further development of targeted resources, toolkits and funded CPD opportunities will supplement and diversify the existing portfolio.

## Genomic medicine and dentistry

Genetic factors are known to play an important role during development of the craniofacial region. A significant number of monogenic conditions are associated with structural defects in the orofacial region and dentition, occurring either in isolation or as part of a defined syndrome.[13] Genomic testing for some of these rare and inherited diseases is already commissioned by the NHS in England as part of the normal diagnostic pathway for affected individuals and they are listed in the National Genomic Test Directory.[14] These include diagnostic analysis for conditions such as ectodermal dysplasia (R163), skeletal dysplasia (R104), nevoid basal cell carcinoma syndrome (R214) and a multigene panel for amelogenesis imperfecta (R340). Amelogenesis imperfecta represents a genetically heterogeneous condition that has traditionally been diagnosed on the basis of clinical phenotype (Fig. 1); however, this is often not consistent with genotype, and in the absence of definitive diagnosis, associations with other health problems can be missed.[15] An accessible method of genetic screening for patients identified with amelogenesis imperfecta represents a significant advance in the overall care pathway for these individuals.

The more widespread use of next-generation sequencing is likely to increase candidate gene discovery in the diagnosis of other rare disorders affecting the craniofacial region and provide insight into their molecular basis.[16] The identification of disease-causing variants forms the starting point for functional studies using animal models to further delineate the molecular aetiology of a particular condition.[17] Genetic testing for specific susceptibility alleles should become available within the national Genomic Medicine Service as they are identified, after appropriate evaluation and peer review. Genetic testing of this type is likely to remain within the domain of specialist clinics in secondary care, working under relevant guidance as to which tests are appropriate for each specific clinical indication. However, the initial identification and appropriate referral of these patients, particularly those with oral and dental phenotypes, will often depend upon general dental practitioners in a primary care environment.

### Complex disease

Genomics is also starting to inform knowledge of oral health and potentially influence the provision of dental care on multiple different levels;[18] however, many disorders affecting the oral cavity are relatively common complex

#### Box 5 Caries and periodontitis: complex diseases

It is well established that both dental caries and periodontal disease represent complex diseases with a significant multi-loci genetic component, which influences both disease susceptibility and progression in different individuals.[21,22,23,24] There are also increasing reports of variants associated with aggressive forms of periodontitis in different populations,[25,26,27] and as these acquire a firmer evidence base, they are likely to form the basis of appropriate screening strategies that will help to identify susceptible individuals and inform effective prevention, disease management and prognosis. In addition, the use of next-generation sequencing and complex bioinformatic analyses are increasingly demonstrating the importance of the oral microbiome in both oral disease and general health.[28] It is likely that characterisation of the oral microbiome may also form an important component of the diagnostic and prognostic status of an individual, and the dental surgery is the most logical environment to facilitate routine screening for patients. Collectively, population-based genomics has demonstrated multiple composite traits associated with oral diseases, which is leading to revised classifications and is likely to underpin future approaches to precision medicine for these conditions.[29,30] There is no reason why these technologies should not form part of routine dental care in the future, as they become more established and as public perceptions of what dental care can deliver potentially change. Indeed, genetic markers associated with dental caries and periodontal disease may soon be added to analyses offered by direct-to-consumer genetic testing companies, impacting primary dental services and the expectations of patients.

**Table 1 Genes associated with monogenic and complex disorders affecting the craniofacial region**

| Monogenic syndrome | Complex disorder | Gene |
|---|---|---|
| Van der Woude syndrome [113900][31] | Orofacial clefting[32]<br>Tooth agenesis[33] | IRF6<br>IRF6 |
| Witkop syndrome [189500][34] | Orofacial clefting[35]<br>Tooth agenesis[36] | MSX1 |
| Odonto-onycho-dermal dysplasia [257980][37] | Tooth agenesis[38] | WNT10A |

diseases (Box 5). Complex diseases are caused by a combination of genetic and environmental factors, and do not follow normal patterns of Mendelian inheritance. Identifying the genetic variants that contribute to complex disorders requires the comparison of affected and unaffected individuals at the population level. These genome-wide association studies (GWASs) rapidly scan markers across the genome to find genetic variations associated with a particular disease. Once new associations are identified, these can inform strategies for improved detection, treatment and prevention of the disease. Although GWASs are not part of the national Genomic Medicine Service – which is primarily focused on rare diseases, genomic-therapeutic interactions and cancer – knowledge of rare single-gene disorders can inform the genetics of complex disease. A number of alleles known to cause rare monogenic disorders affecting the craniofacial region have also been identified in association with more common complex disorders, such as orofacial clefting and tooth agenesis (Table 1).

## Conclusions

The new Genomic Medicine Service is rapidly becoming established within the NHS in England, improving diagnosis for many patients with rare diseases and cancer, and paving the way for greater personalised treatment and management of these disorders. Genomics is relevant to many areas of clinical and academic dentistry, and its application is expected to grow over the next decade. Dental healthcare professionals should be aware of this forthcoming service and its associated infrastructure. This bold initiative will come with multiple challenges but is to be welcomed and heralds the start of an exciting new era for NHS healthcare, not only in medicine and surgery, but also dentistry.

*Conflict of interest*

*MTC and AS represent the Faculty of Dental Surgery at the Royal College of Surgeons of England and the Genomics Education Programme at Health Education England, respectively on the Academy of Medical Royal Colleges Genomic Clinical Champions Group. The remit of this group is to oversee the work related to championing and supporting the NHS in embedding the use of genomic medicine into clinical practice. This will help to ensure that the NHS is prepared to harness the full potential of genomics across all clinical specialities. The main role of the group is to ensure the work meets its objectives, and to provide guidance and advice on current and future work.*

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