# 1 What is clinical genetics and genomic medicine?

## What is clinical genetics?

Clinical Genetics involves the identification of individuals with, or at risk of, single gene inherited traits that could impact their health, alongside that of their relatives. Clinical geneticists are clinical doctors who diagnose and manage families with genetic disorders.

Their role encompasses coordinating the overall care of patients with rare disorders, diagnostics/genetic testing, and counselling regarding risk assessment (for example, with future pregnancies and for other potentially affected family members).

Geneticists work closely with their laboratory-based colleagues and genetic counsellors to perform and interpret the wealth of evolving molecular diagnostic tests in the clinical context.

Examples of conditions managed by clinical geneticists include:

- Chromosomal abnormalities
- Congenital (birth) defects with an underlying genetic basis
- Single gene disorders (for example, cystic fibrosis, muscular dystrophy, and Huntington's disease)
- Familial cancer and cancer-risk syndromes (for example, inherited breast or colorectal cancers; neurofibromatosis)
- Other inherited conditions that cause morbidity/mortality (for example, cardiac conditions at risk of causing sudden cardiac death)
- Developmental delay or learning difficulties in children (with other associated features suggestive of an underlying genetic aetiology)

## How does clinical genetic testing help clinical care?

Clinical genetics is underpinned by making a correct clinical and molecular diagnosis. Rare diseases with Mendelian (single disease) traits affect 1 in 17 of the population, and 1/2 of the population are likely to develop cancer at some point in their lifetime caused by acquired pathogenic variants deregulating cell growth, differentiation, and cell death.

A highly suggestive medical diagnosis can be made by bringing together a series of symptoms and signs within either an individual patient, or by combining information from several relatives. For example, this could include linking bilateral vestibular schwannomas and a meningioma in a patient under 40 years of age with a diagnosis of neurofibromatosis type 2, or considering a pituitary adenoma with concurrent hyperparathyroidism in a proband with a story of her mother having had kidney stones and a pancreatic tumour being highly suggestive of Multiple Endocrine Neoplasia type 1. Genetic testing can then be used to either confirm this medical diagnosis or assist with family planning in the future. As testing costs fall and genetic and genomic testing becomes more readily accessible, molecular tests are increasingly being used to either make or further inform the suspected medical diagnosis. Improving the ability of clinicians to make a correct diagnosis leads to a better understanding of the natural history of the condition, thereby providing scope for potential interventions to reduce the burden of disease at an earlier stage.

Having the correct molecular diagnosis allows us to compare the patient to others in the medical literature to determine the inheritance pattern of the condition. When extensive case series have been studied, the penetrance of the condition can also be estimated. Note that this is not always assessed from probands (the first affected patient in the family that presents clinically), as sometimes these patients, by definition, tend to be more severely affected to be offered a test and hence may produce biased results when calculating future risk for relatives.

## Pedigrees

Identifying familial risk is carried out by drawing a family tree (pedigree), which shows who is present in the family and their basic demographics in a pictorial form. Men are generally placed on the left and depicted as squares and women as circles. The consultant (the person seeking medical advice) has an arrow pointing towards the symbol and the symbol is shaded to represent if a patient is affected.

Apart from ascertaining who is at risk, the pedigree might indicate an inheritance pattern. As clinical geneticists work with family files, care must be taken in showing individuals the data collected from other relatives (such as including medical and molecular information on pedigrees) if consent has not been obtained to share.

## Variant interpretation and the role of the clinical geneticist

Variant interpretation is an increasingly important component of a clinical geneticist's role, particularly as genetic testing and genomic sequencing becomes more widespread and it becomes clear that we all have multiple subtle variants that may impact on risk. This requires significant resource due to the sheer size of the human genome. Molecular biology expertise and framing within a clinical context is crucial in being able to explain risk effectively to patients, and this is an area where general physicians often struggle.

Classically, clinical geneticists have been highly effective in bringing together cohorts of patients for either research, governance, or shared experience. This has helped our understanding of the natural history of disorders and improved our ability to improve outcomes through large clinical research networks and patient support groups. Improved digital connectivity is making this more straightforward and effective.

Developing and championing a molecular culture within the wider NHS and public health is a key leadership role for geneticists. There are several competing acute medical and social care strains on our economy, and genetics has a potential role in improving some of this burden through targeted screening and prevention strategies, personalised medicine, and links to digital health. This involves education and training around molecular biology, innovation, and being early adopters of initiatives such as gene panels, genomic testing, and precision medicine. As artificial intelligence leads to improved integrated molecular, clinical, and social data sets, our ability to predict, prevent, and treat disease will improve. Clinical genetics therefore has a major role in Public Health, assisting with variant data collection and integrating this with health outcomes, as we generate an equation for life and well-being.



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## What is the impact of genetics on insurance and migration?

These are common areas of concern for patients undergoing diagnostic or predictive testing. Health insurance coverage can be a significant concern, particularly in countries with primarily private medical cover-based systems. Patients are therefore advised to investigate any specific policy exclusions, especially if planning to live or spend considerable periods of time overseas. Fortunately in the United Kingdom, this issue does not impact receipt of NHS care.

Unselected population-based genetic testing in the private sector for well individuals can create funding and capacity challenges, for example, when it comes to confirming any significant findings in a NHS accredited laboratory, which is required to act on any findings and arrange either screening or preventative measures.

Insurance companies in the United Kingdom are currently able to ask about family history or on-going investigations and screening. They can also currently ask about large amounts of cover for patients at risk of Huntington's (an autosomal dominant inherited condition with high penetrance), but not regarding other conditions. This is regularly reviewed with government oversight. The results from the 100 000-genome project are also exempt (but not any downstreamed medical investigations). It is currently unclear as to whether this advice is likely to change. Given the potential for genetics to target screening and healthcare to those most likely to benefit, it is hoped that policies would seek to maintain the current position with insurance companies to not impact the benefits of appropriate genetic screening on patient care.

## What is genomic medicine?

There is no single agreed term that encompasses Genomic Medicine, but it can be broadly classified into three areas: personalised medicine, holistic and integrated care modelling, and integrated data science for the wider population. Each of these complement Clinical Genetics and whole genome sequencing to improve future health and disease modelling.

- In personalised medicine, additional nucleic acid-derived data from the closer analysis of a broader spectrum of genes, intronic coding regions, or single nucleotide polymorphisms are used in conjunction with tumour or microbial genetics and circulating biomarkers to try and personalise care. This includes tumour-specific therapies, pharmacokinetics, detection of potential antimicrobial resistance, and identification and monitoring of infectious agent outbreaks.
- In integrated and holistic care modelling, the aim is to work with patients and patient stakeholder groups to develop and design equitable access to patient-centred healthcare, building on patient involvement and empowerment to make informed decisions about their screening, management, and treatment in partnership with their doctors. This may involve the use of electronic care plans with access to additional support and red flag escalation alert systems for potential predictable complications and educational resources for clinicians and patients.
- The use of patient-centred and controlled electronic records provides opportunities to link health records to outcomes for artificial intelligence-based solutions. These models will be simple to start with, but in time, uploading data (such as our postcode, wearable technology-derived data, social media entries, supermarket store card and online purchase history, mental health questionnaires, alongside pathology, radiology, and genomic results) could provide a more accurate assessment of our health and well-being.

Genomic medicine involves integrating the results of nucleic acid-derived testing from blood and other biologically derived tissues with clinical and potentially social data. This aims to help predict future health outcomes more accurately via either the development of personalised treatments (intervention type and preferred dose of therapeutic agent if required) or through the design of more individualised and cost-effective screening programmes. These aim to treat disease for what it is rather than what it looks like, by planning screening based on calculated risk and not age, alongside smart prescribing to treat the right patient with the right drug at the right dose, first time, every time.

## What does genomic medicine encompass?

Genomic medicine includes six areas beyond the analysis of the coding sequences of genes responsible for Mendelian traits (i.e. classical human genetics):

1 The role of single nucleotide polymorphisms (SNPs) in non-coding regions and epigenetic traits. Large genome wide association studies (GWAS) have identified many variants that are commonly found in the general population that are associated with risk. It is sometimes unclear if these have a cumulative effect when coupled with other variants or how they alter risk (through either altering gene expression from a distance), particularly when common in a population and inherited in close proximity (linked) to a true disease-causing variant that is yet to be identified (variant in linkage disequilibrium with the disease-causing variant).

2 Pharmacogenetics involves predicting the way that drugs are metabolised (and therefore the risk of side effects or lack of effectiveness) by identifying key variants in genes coding the relevant enzymes involved in their breakdown.

3 Testing other microorganisms can be helpful in identifying pathogens and predicting antibiotic or antiviral treatment resistance, as well as providing information about bacteria in the gut flora (microbiome) that is important for digestion. This could, for example, help possibly link food intake with the risk of obesity.

4 Testing other tissues for somatic mutations in either DNA or RNA can be particularly useful to identify circulating free DNA (cfDNA) released from tumours and predict either response to treatment or likelihood of relapse.

5 The use of other data sets, such as electronic patient records with linked radiology and pathology results, biometric data from smart handheld devices (e.g. fitbits) and background social data such as occupation, educational background, post code, supermarket store card/online purchases, and even social media interests, has the potential to be integrated with genomic results. Linking these large applied data sets to long-term health outcomes with machine learning algorithms will provide the opportunity to generate better predictors for disease and health and social well-being, thereby improving future health predictions.

6 Studying how gene expression can be altered by non-sequence variant changes, such as epigenetic changes in methylation patterns of promoters or DNA folding around modified histones, reducing planned transcription.

In a way, Clinical Genetics helps explain where – from an evolutionary perspective – we have come from and may possibly describe why we become unwell. Genomic Medicine tries to understand the more complex aspects of disease within an individual's broader genetic and environmental landscape, to make better future predictions about specific interventions.