JCGM - *Investing in excellence to provide essential core expertise to the NHS Genomic Medicine Services: Role of the Clinical Geneticist*

Summary

- *Genomics is being integrated into all patient pathways across all healthcare specialities. The specialist genomic workforce within the Genomic Medicine Services (GMSs), the Clinical Geneticists, Genetic Counsellors and Clinical Scientists, will need to* ***support and educate colleagues*** *in the safe application of genomics for patient benefit whilst continuing to be* ***responsible for the diagnosis and management of patients with rare and ultra-rare disease****.*
- *Greater genomic awareness of healthcare practitioners (HCPs) in other medical and surgical specialties has resulted in an unprecedented* ***increase in referral rates*** *to GMSs, as well as an* ***increased demand for genomic multi-disciplinary meetings and clinic.***
- ***Offering whole genome sequencing to all seriously ill children as part of their care will generate a large workload*** *for Clinical laboratory teams and Clinical Geneticists as these data are complex and difficult to interpret.*
- ***Championing the safe implementation of genomic medicine requires investment in the clinical expertise that is core to this mission.***

I Background:

Genomic technologies are transforming healthcare with the ability to provide many more patients with accurate diagnoses in shorter time periods and with ever-reducing sequencing costs. Increasingly genomic data are being integrated into all areas of healthcare to inform the diagnosis and management of disease. Genomic medicine has been recognised as a UK priority and is one of the pillars of the NHS Long Term Plan. A key tenet of a future NHS genomics service is that genomic testing is available to all patients who would benefit from a genetic diagnosis. Non-genetics mainstream specialists are therefore being encouraged to order genomic tests in a subset of their patients as outlined in the National Test Directory. However, many mainstream specialists report that they feel uncomfortable with translating the meaning of genomic data for their patients, and will require support and education from specialist Genomic Medicine colleagues.

Why accurate diagnosis of rare disease matters.

In the longer term, there will be a continuing need for specialist clinical genetic expertise for patients with rare or ultra-rare disease. In particular to serve those patients whose molecular genetic diagnosis will be used to:

(i) direct expensive, molecularly targeted therapy,
(ii) enable pre-implantation or prenatal diagnosis
(iii) will serve as the basis for invasive/irreversible interventions eg. prophylactic risk-reducing surgery.

Investment in expert clinical diagnostic assessment to ensure that the variant identified in the laboratory is the major cause of disease in an individual is essential. Diagnostic error with this care based on the wrong variant is costly in human and financial terms resulting in bad medicine and poor and indefensible outcomes. Expert clinical input often needs direct engagement with patients and whilst expertise can sometimes be contributed in a multidisciplinary meeting (MDT) oftentimes face to face clinical assessment is required for 'reverse phenotyping' to determine whether a patient's features fit with a candidate molecular diagnosis or to direct re-analysis of data to find diagnoses not identified through routine analysis.

The surgical specialties have pioneered the principle that safe medical practice is achieved by practitioners who have sufficient throughput to ensure high quality practice, and practice in a safe environment providing peer review to challenge decisions and correct omissions. Delegating rare disease diagnosis to clinicians with very limited experience runs counter to this principle: 'dabbling' will result in poor practice that is no longer tolerated in any other branch of medicine. This problem will not be solved by education as that does not generate the expertise or throughput necessary to maintain high standards of practice.

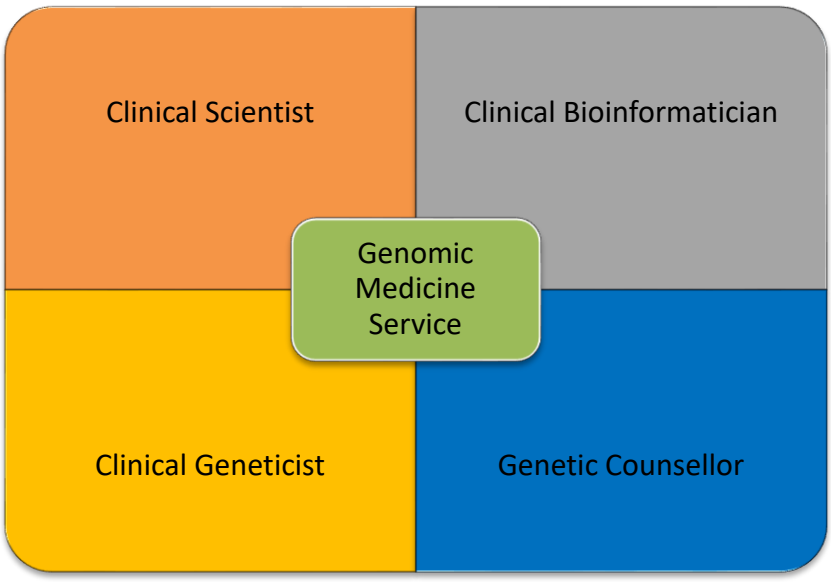
Genomic Medicine is an immature and rapidly evolving field. Clinical Geneticists and Genetic Counsellors will work in partnership to innovate by evaluating new tests, technologies and modes of service delivery and to provide care and advice for those patients whose genetic diagnosis remains elusive after genomic testing (currently >60% of patients with suspected genetic disease). Genetic Counsellors are not trained in diagnostic medicine and cannot fulfil this element of the role.

II The Genomic Medicine Services (GMS)

The UK Genomic Medicine Services were established 40 years ago and have evolved to offer excellent cost-effective clinical care, including diagnostic and predictive genetic testing, to individuals and families with, or at risk from, genetic disease. They are admired internationally for their pioneering work in genomic science and for the high quality of patient care delivered by integrated teams of Clinical Geneticists, Genetic Counsellors and Clinical Scientists & Clinical Bioinformaticians. They offer evidence-based clinical evaluation, laboratory assays, analysis of variants, counselling of individuals and care of extended families.

The GMS specialist workforce consists of the quartet of Clinical Geneticist, Genetic Counsellor, Clinical Scientist & Clinical Bioinformaticians. Each of these roles is distinct and complementary: the Clinical Geneticist is a specialist physician primarily responsible for the medical evaluation of the undiagnosed patient, organising diagnostic testing, clinically interpreting the results and devising a tailored management plan; the Genetic Counsellor is primarily responsible for predictive genomic testing coupled with advanced counselling skills and a responsibility for care of the family; the Clinical Scientist is responsible for molecular assays and generation of genomic reports and the Clinical Bioinformatician is responsible for processing, filtering and archiving the vast quantities of data generated by genomic testing (figure 1).

Figure 1 Key professional groups in an integrated genomic medicine service



This highly skilled genomics workforce will be essential to the safe implementation of genomic medicine over the coming years. They will provide support, often through the MDT or Genomic Laboratory Hub structure, to their healthcare colleagues as more genomic testing is requested without the initial involvement of a genetics specialist. In addition, they will provide a 'from the coalface' educational role in preparing the healthcare workforce to deal safely and accurately with genomic data. Health Education England is tasked with providing resources and teaching to support the upskilling of healthcare professionals; however, the **existing genetics workforce will provide a pivotal complement to this as a highly specialised resource who can advise and support colleagues as they deal with real-world cases**.

In order to provide this support effectively, it is essential that we **invest in the core genomics workforce**, increasing numbers of trained Clinical Geneticists, Genetic Counsellors and Clinical Scientists and Bioinformaticians. In this paper, we outline the current and future roles of one of the four integral professions that will drive high quality Genomic Medicine for NHS patients, the Clinical Geneticist.

III Clinical Geneticists now and in the future

The Consultant Clinical Geneticist is a specialist physician. The Clinical Genetics training programme is four years and trainees enter at ST3 level (4-5 years post clinical qualification), either from paediatrics or adult medicine (and in future from a broader range of specialties). Many Clinical Genetics trainees elect to undertake additional research as a component of a higher degree (PhD or MD). Clinical Geneticists in the UK are fully trained in adult, paediatric, cancer and prenatal genetics, although some choose to sub-specialise in their consultant role. Many are world-leading academic or clinical specialists whose knowledge and expertise is sought by the worldwide genetics community.

Clinical Geneticists work with a team of Genetic Counsellors and Clinical Scientists and Bioinformaticians to provide an integrated care pathway for patients and families with genetic diagnoses. Traditionally, Clinical Geneticists are responsible for the clinical diagnosis of rare adult and paediatric disease, the targeting of genetic testing, feedback of results and discussion of syndrome specific management/surveillance.

<u>Evolving roles and responsibilities</u>

- ***Responsible Genomic Medicine* - As genomic data are increasingly integrated into patient pathways, Clinical Geneticists will see many more patients where testing has been initiated by other specialists.** They will use their clinical judgement to evaluate whether a genomic variant(s) provides a robust clinical genomic diagnosis to explain the patient's clinical features. Their clinical expertise in rare and ultra-rare disease is essential in order to determine whether a novel genomic variant represents a full diagnosis or only partially explains the clinical presentation or is irrelevant to the clinical features seen in the patient. These **clinical judgements cannot be made safely if the requesting clinician has very limited or no prior experience of the disorder** identified by genomic testing, hence **engagement with a Clinical Geneticist is an essential part of a safe Genomic Medicine service** for such patients.

- ***Diagnostic assurance* -** As genomic testing becomes an integral component of the diagnostic pathway in mainstream medicine, more diagnoses will be made which are unexpected, rare and have reproductive implications at earlier time points in the patient diagnostic journey. The diagnosis of a severe genetic disorder has a high personal cost to families and a high cost to the health-service in longterm management. **Ensuring that the genetic diagnosis is accurate is essential both to provide correct individualised management for the patient and to avoid ill-founded predictive testing and misleading prenatal diagnosis.**

- ***Training & Education*** **-** Clinical Geneticists will spend more time providing **training and mentoring for non-genetics colleagues**, in formal and informal settings including specialty-specific multidisciplinary team (MDT) meetings and joint genetic-mainstream specialty clinics. It is essential that the Clinical Geneticist supports colleagues at MDT meetings to ensure optimal stratification of patients to genomic testing and robust interpretation of genomic variation in the context of phenotype. Whilst genomic literacy builds amongst the workforce, these MDT meetings are additionally likely to afford a valuable educational opportunity.

- ***Rare Disease*** **-** Clinical Geneticists will continue to see patients with **rare and ultra-rare disease and those with severe burden of disease who remain undiagnosed after the completion of clinically directed testing**. These patients will be considered for additional diagnostic or research testing, and parents of an affected child will be provided with the opportunity to discuss their reproductive risks in the absence of a secure genetic diagnosis.

- ***Molecularly targeted therapy*** **-** Clinical Geneticists will play a role in **genotype-directed therapies**. Referrals to Clinical Genetics for genomic testing are already rising as new therapeutic trials and proven therapies are becoming individualised, using genomic data as biomarkers. This will affect diverse patient groups who previously felt that the harms of predictive genetic diagnostic testing outweighed the benefits, as well as clinicians who previously did not incorporate genetic testing into the diagnostic pathway. [Referrals to the Huntington's Disease (HD) Genetics clinic in Cambridge have increased very substantially since the commencement of Phase 3 trials of a new HD treatment; as treatments become available, more patients will seek predictive testing for previously untreatable disorders.]

- ***Translation & Innovation*** **-** Clinical Geneticists will continue to be at the leading edge of **incorporating emerging genomic and other -omic based technologies** for diagnostic and therapeutic benefit. Currently, state-of-the-art genomic sequencing provides a causative explanation for only around 50% of children and adults with severe developmental disorders (DDD reference); there is only a limited understanding of the factors which determine the severity of genomic disease, and manipulation of genetic mechanisms to ameliorate disease impact are still in their infancy. **Clinical Geneticists will drive the integration of these new technologies into healthcare, using their highly specialised skill set to translate research findings into improvements in clinical diagnosis and patient management**.