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Rare disease genomic testing in the UK and Ireland: promoting timely and equitable access

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ABSTRACT

Purpose and scope The aim of this position statement is to provide recommendations regarding the delivery of genomic testing to patients with rare disease in the UK and Ireland. The statement has been developed to facilitate timely and equitable access to genomic testing with reporting of results within commissioned turnaround times.

Methods of statement development A 1-day workshop was convened by the UK Association for Clinical Genomic Science and attended by key stakeholders within the NHS Genomic Medicine Service, including clinical scientists, clinical geneticists and patient support group representatives. The aim was to identify best practice and innovations for streamlined, geographically consistent services delivering timely results. Attendees and senior responsible officers for genomic testing services in the UK nations and Ireland were invited to contribute.

Results and conclusions We identified eight fundamental requirements and describe these together with key enablers in the form of specific recommendations. These relate to laboratory practice (proportionate variant analysis, bioinformatics pipelines, multidisciplinary team working model and test request monitoring), compliance with national guidance (variant classification, incidental findings, reporting and reanalysis), service development and improvement (multimodal testing and innovation through research, informed by patient experience), service demand, capacity management, workforce (recruitment, retention and development), and education and training for service users. This position statement was developed to provide best practice guidance for the specialist genomics workforce within the UK and Ireland but is relevant to any publicly funded healthcare system seeking to deliver timely rare disease genomic testing in the context of high demand and limited resources.

INTRODUCTION

Ensuring that people affected by rare diseases receive the right diagnosis faster has been identified as the first priority within the UK Rare Diseases Framework.[1–5] Reaching an accurate diagnosis within a clinically relevant timeframe (ie, early enough to inform key clinical decisions that modify outcome) facilitates informed decision-making, improves access to specialist healthcare and treatments, including advanced therapeutic medicinal products, and connects patients and families with shared lived experience. For patients with a treatable genetic condition, in particular children, any delay in diagnosis can result in potentially preventable morbidity and mortality.

Around 80% of rare diseases are thought to have a genetic basis. The value of genomic sequencing in rare disease diagnostics has been demonstrated by many translational research studies, including the flagship 100,000 Genome Project and the Deciphering Developmental Disorders (DDD) study.[6 7] Both the technology and the knowledge base used in genomic test interpretation had to evolve at pace to meet the rapidly changing testing landscape.[7–9] In many countries diagnostic genomic testing for rare disease has transitioned to healthcare system funding.[10 11] Whole genome sequence (WGS) analysis is currently considered the most comprehensive genomic test for patients with rare disease and was implemented within the National Health Service (NHS) in England in 2019 and in Wales in 2020.

In 2020 the UK government publication 'Genome UK: the future of healthcare' set out its high-level strategy for the four nations working together to harness the latest advances in genetic and genomic science, for diagnosis and personalised medicine, prevention and research, with key underpinning enablers.[12] This was followed by a collection of high-level UK-wide shared implementation commitments[13] and implementation plans for each nation.[14–17]

The NHS in England published its first strategy for 'Accelerating Genomic Medicine into the NHS' in 2022 with 36 ambitious commitments across four main pillars of delivery which linked with other key NHS Long Term Plan priorities, including in rare disease and cancer.[18] A national strategy for accelerating genetic and genomic medicine in Ireland was published in 2023.[19]

The NHS in England, Northern Ireland, Scotland and Wales and the Sláintecare programme in Ireland are publicly funded healthcare systems based on clinical need, not the ability to pay. Genomic testing services are centrally commissioned in each nation and delivered either by a network of genomics laboratories (seven Genomic Laboratory Hubs in England and four genetics laboratories in

Scotland) or a single provider laboratory. A central feature of the NHS England Genomic Medicine Service is the National Genomic Test Directory, which sets out the tests and the technological approach for delivery.[20] The genomics laboratories work together collaboratively, with their clinical scientists (trained in bioinformatics, genomics, molecular genetics, cytogenetics or biochemical genetics) and genetic technologists supported by the UK's Association for Clinical Genomic Science (ACGS). The ACGS facilitates the writing and publication of Best Practice Guidelines[21] to aid the delivery of high-quality standardised approaches to diagnostic testing and reporting. External quality assessment is provided by the UK-based Genomics Quality Assessment (GenQA) organisation with participation from >90 countries.[22]

The publicly funded healthcare systems in the UK and Ireland facilitate close multidisciplinary working between laboratories, regional clinical genetics centres and mainstream specialties. There are established clinical pathways, from referral for testing to coordination of complex care across specialties, to provision for family follow-up. The ACGS Best Practice Guidelines for Variant Classification supplement the USA-led work[23 24] by providing guidance that leverages the advantages of close multidisciplinary and interlaboratory working practices within the NHS, particularly in the reporting of variants of uncertain significance (VUS) and incidental findings.

Prominent UK-based charitable organisations that support patients with rare diseases and their families include Genetic Alliance UK and Unique.[25 26] Genetic Alliance UK is a coalition of over 230 charities and support groups with a 30-year track record of working together to improve the lives of people in the UK with genetic, rare and undiagnosed conditions. Unique provides support and information to people affected by rare chromosome and gene disorders and their families. Access to genomic testing has benefited many patients with rare conditions, but there are still challenges with obtaining a timely diagnosis and in finding and accessing relevant information and support, and awareness of rare diseases among healthcare professionals is often low.[27] Continued collaborative working of patient support groups with policy makers, commissioners and service providers will inform further development of genomic medicine services to address these challenges.

Significant progress towards embedding advanced genomic testing within routine healthcare in the UK and Ireland has been made during the 5 years since diagnostic WGS analysis was implemented in the NHS in England. The current focus is to deliver high-quality interpretation and reporting to support comprehensive genomic testing pathways established to accurately diagnose patients with rare diseases in a timely manner according to clinical need. The aim of this position statement is to describe a set of recommendations to support streamlined service delivery.

APPROACH AND METHODS

A 1-day workshop was convened by the UK ACGS[28] to identify best practice and innovations for delivering timely genomic test results to patients with rare diseases across the UK and Ireland (see online supplemental material for details).

TARGET AUDIENCE AND SCOPE

The recommendations within this position statement apply to genomic testing pathways for all monogenic rare and inherited diseases within a national health service setting. They are of particular relevance to diagnostic genome/exome tests (trio, duo or singleton gene agnostic and large panel sequence analysis) where multiple variants are prioritised by a bioinformatics pipeline typically used when the differential genetic diagnosis is wide. Some of the recommendations will be relevant for inclusion in health systems commissioning and planning guidance.

This position statement aims to support greater consistency in the approach to timely genomic testing outcomes for patients with rare diseases throughout the UK and Ireland. It may also serve as a framework to initiate and support similar discussions in other countries,[29] particularly those with national healthcare systems where meeting the demand for equitable access to timely rare disease genomic testing is a challenge.

REQUIREMENTS FOR TIMELY GENOMIC TESTING

Key requirements and enablers are outlined in figure 1. They are described in full in the following sections, with recommendations to support the timely delivery of results within commissioned test turnaround times. The requirements and recommendations are listed in table 1.

Testing service capacity and capability to meet the needs of the population (volume and turnaround times)

The first requirement is to define the scope of the testing service, for example through a National Genomic Test Directory, and the capacity required to meet the needs of the population. An agile but evidence-based approach is required to ensure that genomic testing is costed appropriately. Consideration of test volumes, predicted growth of testing, turnaround times, technologies, laboratory staff costs and workforce skill mix is necessary.

NHS-commissioned genomic testing is delivered by UK Accreditation Service (UKAS)-accredited laboratories working to the ISO 15189 standard. In England, the National Genomic Test Directory (NGTD)[20] outlines the full range of genomic tests that are commissioned for the NHS. A similar approach has been adopted in Scotland,[30] and all of the UK nations participate in the NHS England Test Evaluation Working Group. Test eligibility criteria describe which patients may be considered for each clinical indication, noting that testing should be targeted at patients in whom a genetic cause is likely to underlie their clinical presentation and where a genetic diagnosis will guide management for the proband or family. The NGTD also sets out the technology that should be used.

To efficiently meet the growing genomic testing requirements of the population, genomic test ordering and results viewing will need to be integrated with, and managed through, existing clinical systems facilitating access to the NGTD. To achieve this, it will be necessary to uplift the digital capabilities of the systems used to request and undertake genomic testing to enable the interaction with a centralised interoperable informatic and data infrastructure.

Demand and capacity modelling

Commissioning is the continual process of planning, funding, and setting delivery standards and performance management and assurance of services. Commissioners are responsible for ensuring that sufficient activity has been procured to meet the needs of their population and that providers have sufficient capacity to meet the demand for their services (volume and turnaround times), all delivered within the allocated financial budget. Robust demand and capacity planning is achieved through transparent partnership working of commissioners with providers. Implementation of evolving testing and analysis

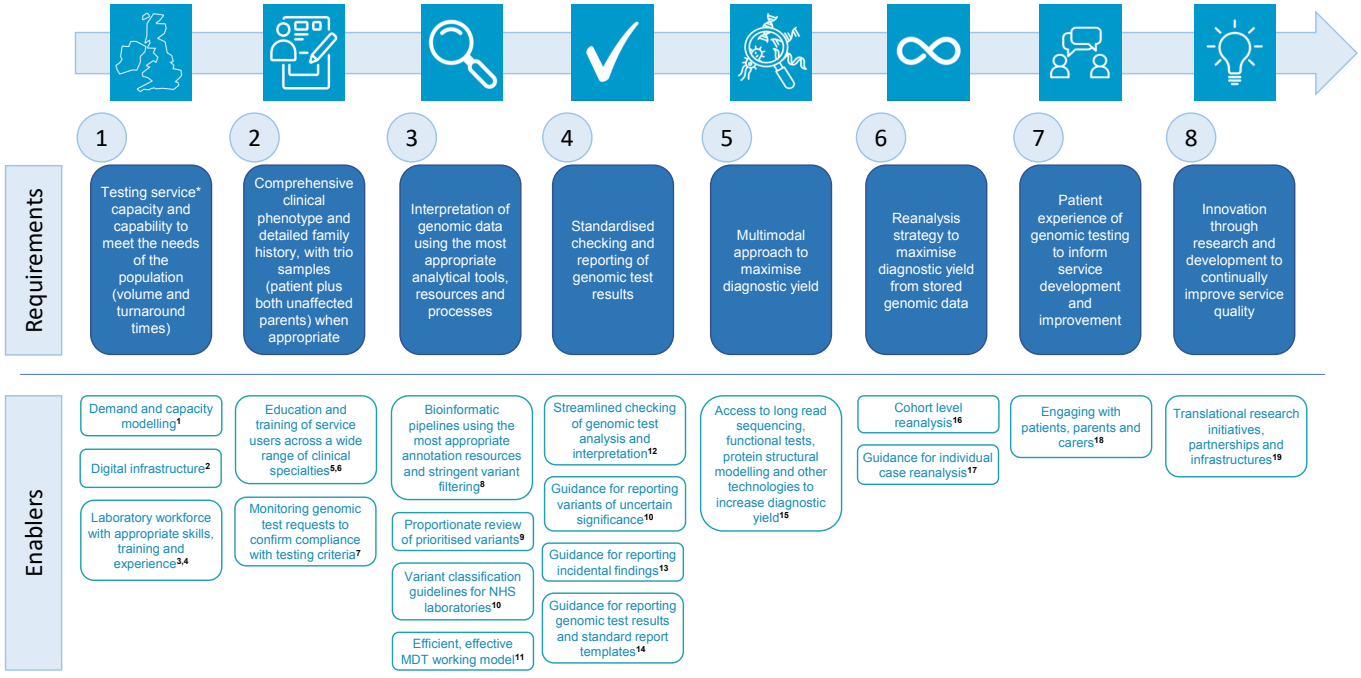

Figure 1 Key requirements and enablers for timely genomic testing. Numerical superscripts refer to the recommendations described in table 1. *Testing service is defined (eg, by a test directory) and delivered in a UKAS-accredited laboratory working to the ISO 15189 standard. MDT, multidisciplinary team.

strategies, emerging technologies and automation is required to meet increasing demand for genomic testing services.

Recommendation 1: National health systems, commissioners and providers of genomic testing services should work together to ensure that service capacity and demand for services reflect the population needs and financial budget.

Digital infrastructure

The implementation of electronic messaging for test ordering, tracking and reporting back to the clinician is critical to ensure that patients and their families can be followed through their testing journey and that accurate information is available for reporting. Establishing methods for capturing consent for data sharing for multiple purposes, including for care and research, is important in the evolution of evidence for the interpretation of complex genomic data in rare disease. This is dependent on the development and adoption of shared data and communication standards, such as those published by the Global Alliance for Genomics and Health.[31]

Recommendation 2: Governments, national health systems, commissioners and providers of genomic testing should work together to develop and adopt shared data and communication standards as a first step to developing a fully interoperable data infrastructure.

Laboratory workforce with appropriate skills, training and experience

Workforce planning to meet current and future service delivery focuses on training, retention and innovative ways of working (eg, see NHS England's Long Term Workforce Plan).[32] NHS genomics laboratories are staffed by personnel with a range of roles to support sample receipt and processing, laboratory testing, data interpretation and issue of results. Scientific leadership is provided by clinical scientists[33] responsible for reporting of genomic tests that require analysis and interpretation of data in the context of the clinical referral. Both timely reporting of genomic test results and continued service development require appropriate numbers of clinical scientists (including bioinformaticians; see online supplemental material), coupled with new ways of working and appropriate utilisation of the genetic technologist workforce.

Recommendation 3: Each genomics laboratory should have a workforce development plan and work with their national health system's bodies responsible for education and training to improve the recruitment and retention of clinical scientists.

Recommendation 4: Workforce development is required to create/expand other roles to support clinical scientists.

Comprehensive clinical phenotype and detailed family history, with trio samples (patient plus both unaffected parents) when appropriate

Comprehensive clinical information should be provided to demonstrate that the patient meets the eligibility criteria and maximise the likelihood of finding a genetic diagnosis. This includes detailed phenotypic data and the results of previous genetic and non-genetic investigations, combined with family history relevant to the reason for testing, to facilitate the interpretation of variants and increase the likelihood of identifying a genetic diagnosis. Including thoughts on the differential diagnosis (either a specific disorder, gene or gene pathway) can enable more focused analysis and inform variant interpretation. Provision of this information via an electronically completed test order form is a prerequisite for timely reporting of genomic tests.

De novo pathogenic variants are a major cause of rare paediatric diseases and neurodevelopmental disorders, accounting for >30% of patients who have received a genetic diagnosis via the

Table 1 Requirements and recommendations for delivering timely rare disease genomic testing in the UK and Ireland healthcare systems

Requirement	Recommendations
1. Testing service capacity and capability to meet the needs of the population (volume and turnaround times)	1. National health systems, commissioners and providers of genomic testing services should work together to ensure that service capacity and demand for services reflect the population needs and financial budget. 2. Governments, national health systems, commissioners and providers of genomic testing should work together to develop and adopt shared data and communication standards as a first step to developing a fully interoperable data infrastructure. 3. Each genomics laboratory should have a workforce development plan and work with their national health system's bodies responsible for education and training to improve the recruitment and retention of clinical scientists*. 4. Workforce development is required to create/expand other roles to support clinical scientists.
2. Comprehensive clinical phenotype and detailed family history, with trio samples (patient plus both unaffected parents) when appropriate	5. Targeted education for service users that addresses key competencies and is evaluated for effectiveness is essential to ensure that genomic testing is offered to those patients who meet eligibility criteria and for whom the test has clinical utility. 6. Test order forms must be completed electronically where available, with full clinical information provided alongside the submission of appropriate family samples whenever possible to maximise the diagnostic yield. 7. Genomics laboratories should establish operational policies to ensure that test requests comply with eligibility criteria, and sufficient clinical information is supplied to deliver equitable access to testing and maximal diagnostic yield.
3. Interpretation of genomic data using the most appropriate analytical tools, resources and processes	8. Bioinformatics pipelines for rare disease variant analysis should include appropriate up-to-date annotation of variants and stringent filtering to remove variants unrelated to the clinical question wherever possible. 9. A pragmatic and proportionate approach to variant interpretation is required in order to achieve a balance between diagnostic sensitivity, timely reporting and service capacity. 10. All NHS laboratories should be compliant with the current ACGS Best Practice Guidelines for Variant Classification within 6 months of ratification. 11. Multidisciplinary input for individual case-based variant interpretation should be separated from case-based education and service update group meetings.
4. Standardised checking and reporting of genomic test results	12. External quality assessments should be developed to evidence the competency of individual clinical scientists to be solely responsible for the analysis, interpretation and reporting of genomic test results without a requirement for additional clinical scientist input. 13. All NHS laboratories should comply with their national guidance on reporting incidental findings. 14. All NHS rare disease clinical reports should comply with the current ACGS best practice guidance for reporting, with standard report templates used wherever possible and within the context of the individual countries' health system requirements.
5. Multimodal approach to maximise diagnostic yield	15. Health systems, commissioners and genomics laboratory providers should work together to ensure there is a standardised and comprehensive funded approach with validated protocols for using the most suitable multimodal testing methodologies to maximise diagnostic yield from genomic testing.
6. Reanalysis strategy to maximise diagnostic yield from stored genomic data	16. A cohort-level reanalysis strategy for NHS patients' WGS data should be developed, supported and funded by health system commissioners, for implementation by service providers and other commissioned partners, with agreed turnaround times for reporting of putative diagnoses identified. 17. Requests for individual case reanalysis should follow national health system guidance; only in defined clinical situations and where there is a high likelihood that reanalysis will yield a genetic diagnosis.
7. Patient experience of genomic testing to inform service development and improvement	18. Existing patient and public voice structures within the Genomic Medicine Service should be harnessed and developed to maximise the impact of patient involvement across the system and provide an evidence-based and robust patient-led service.
8. Innovation through research and development to continually improve service quality	19. Government and health systems should focus attention on national strategic approaches and provide sustainable funding to enable the rapid translation of new technologies and research discoveries into NHS diagnostic practice.

*Clinical scientists include those trained in bioinformatics, genomics, biochemical genetics, molecular genetics or cytogenetics.
ACGS, Association for Clinical Genomic Science; NHS, National Health Service; WGS, whole genome sequence.

DDD study.[7] *Trio genomic testing of an affected child, alongside their clinically unaffected parents (where this is possible), is the most effective way to detect biologically confirmed de novo variants.*

Service users require access to comprehensive, readily accessible point-of-care information regarding genomic testing. Embedding this within the user interface of an electronic test ordering system (see Digital infrastructure section) is optimal. Alternatively, this should be provided via genomics laboratory websites. Education and training is paramount to ensure that service users request the appropriate testing for their patients, providing the necessary clinical information and samples for the testing laboratory (see next section).

Education and training of service users across a wide range of clinical specialties

The NHS England National Genomics Education Programme delivers and advises on learning and development opportunities to help the UK NHS specialist genomics workforce maximise the use of genomics in their practice (see online supplemental material). A range of resources have been developed.[34] In 2022, a nationally agreed, cross-professional competency framework for England was published which outlined the knowledge, skills and behaviours required to facilitate a genomic test.[35] Training for service users includes how to request a genomic test using the appropriate laboratory test order form (see online supplemental material).

Recommendation 5: Targeted education for service users that addresses key competencies and is regularly evaluated for effectiveness is essential to ensure that genomic testing is offered to those patients who meet the eligibility criteria and for whom the test has clinical utility.

Recommendation 6: Test order forms must be completed electronically where available, with full clinical information provided alongside the submission of appropriate family samples whenever possible to maximise the diagnostic yield.

Monitoring genomic test requests to confirm compliance with testing criteria

It is the responsibility of service users to comply with eligibility criteria and provide comprehensive clinical information. Genomics laboratories are responsible for establishing operational policies for checking compliance of test requests to minimise inappropriate testing and the avoidable patient harm that can result from misdiagnosis and uncertain and incidental genetic findings. Inclusion of sufficient clinical information maximises the possibility of finding a genetic diagnosis, increasing the efficiency of analysis and decreasing turnaround times (see online supplemental material).

Recommendation 7: Genomics laboratories should establish operational policies to ensure that test requests comply with eligibility criteria, and sufficient clinical information is supplied to deliver equitable access to testing and maximal diagnostic yield.

Interpretation of genomic data using the most appropriate analytical tools, resources and processes

The requirement for efficient analysis and interpretation may be achieved through a combination of optimal bioinformatics pipelines developed to meet agreed quality standards, access to high-quality analytical tools and appropriate data resources, and a streamlined and proportionate approach to variant interpretation.[7 36] Determining the sequence of a human genome is relatively straightforward, but the interpretation of genome sequence data is highly complex with multiple uncertainties, a growing knowledge base, expanding data sets and evolving analytical approaches. This presents a significant challenge for service delivery, requiring continuous cycles of innovation, assessment and standardisation while meeting increasing demand for testing.

Bioinformatics pipelines using the most appropriate annotation resources and stringent variant filtering

The optimal bioinformatics pipeline maximises both sensitivity and specificity by incorporating the most suitable and contemporary tools for alignment and variant calling with the most appropriate annotation and use of up-to-date resources and stringent filtering to remove variants unrelated to the clinical presentation and/or those with a low prior probability of pathogenicity (see online supplemental material).

Recommendation 8: Bioinformatics pipelines for rare disease variant analysis should include appropriate, up-to-date annotation of variants and stringent filtering to remove variants unrelated to the clinical question wherever possible.

Proportionate review of prioritised variants

Bioinformatics pipeline analysis of genomic data may generate a large number of prioritised rare variants for manual review. The clinical scientist responsible for a patient's data interpretation seeks to identify the (likely) causative variant(s) that might explain their clinical presentation. A proportionate approach is required both to maximise sensitivity and specificity for individual patients and to deliver timely genomic data interpretation for the entire patient population accessing rare disease genomic testing. Many variants prioritised by bioinformatics pipelines are not relevant to the patient's reason for testing and therefore can be rapidly excluded from detailed consideration using simple criteria, as they are incompatible with a classification of actionable VUS or higher (see online supplemental material). Regular systematic cohort reanalysis of patients' WGS data will identify additional genetic diagnoses through the inclusion of new disease gene and mechanism discoveries, expanded data sets and a focus on identifying variants intractable to standard clinical bioinformatics pipelines and analytical approaches.[37]

Recommendation 9: A pragmatic and proportionate approach to variant interpretation is required in order to achieve a balance between diagnostic sensitivity, timely reporting and service capacity.

Variant classification guidelines for NHS laboratories

The ACGS Best Practice Guidelines for Variant Classification[24] have been developed to provide supplementary information relevant to the NHS specialist genomics workforce for use in conjunction with the American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology (AMP) sequence variant guidance,[23] subsequent ClinGen recommendations[38] and standards for CNVs[39] developed by colleagues in the USA.

The ACGS guidance recommends that a summary of the evidence supporting variant classifications is included in clinical reports to expedite family member testing performed by other NHS laboratories. These guidelines also note the responsibility to ensure that data are shared responsibly for improved patient care, using ClinVar as the international data sharing standard for reported rare disease variants.[40]

Recommendation 10: All NHS laboratories should be compliant with the current ACGS Best Practice Guidelines for Variant Classification within 6 months of ratification.

Efficient and effective multidisciplinary team working model

Multidisciplinary team working is a key component of high-quality genomic testing, but the scale of testing required to meet the needs of patients with rare diseases and the increasing number of different disorders (>6000) requires a contemporary format to deliver timely reporting of results with expert input when required (see online supplemental material). The NHS England Genomic Medicine Service model recommends that individual case-based variant interpretation discussions should ideally take place via email (within a defined governance structure). It is recommended that educational case-based learning should be delivered separately in a dedicated meeting format, often virtually across large geographies to facilitate stakeholder participation, with an opportunity for service updates (see figure 2).

Recommendation 11: Multidisciplinary input for individual case-based variant interpretation should be separated from case-based education and service update group meetings.

Standardised checking and reporting of genomic test results

Timely reporting of results from genomic data analysis requires a streamlined approach. Many different laboratory information management systems (LIMS) are employed across the UK and Ireland with varying capabilities to readily generate clinical

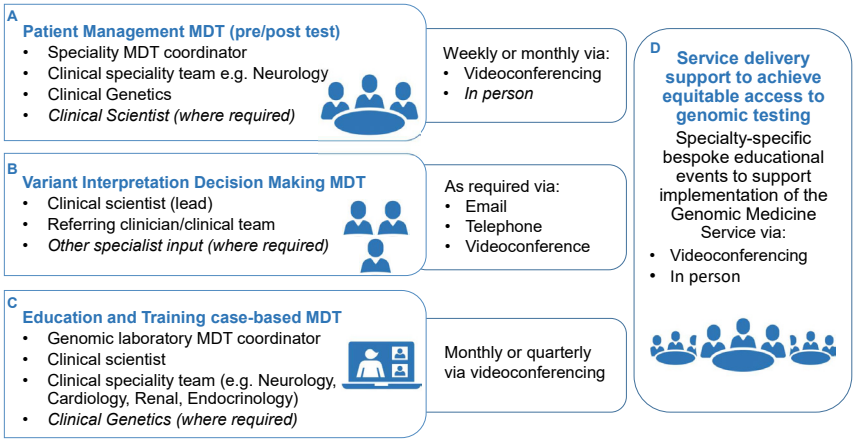

Figure 2 Multidisciplinary team (MDT) working model for rare disease genomic medicine. The different types of MDT meetings and ways of working are separated in order to deliver timely, high-quality genomic test results. (A) Education and training initiatives for service users, together with the availability of up-to-date information about genomic testing, mean that patient management MDTs for pre–post testing discussions relating to individual patients or families should not usually require clinical scientist attendance. It is more efficient for patient testing queries to be emailed to the laboratory, providing an audit trail of information that the laboratory can store electronically ahead of receiving samples for testing. (B) Variant interpretation decision-making MDTs usually include the clinical scientist responsible for analysis and interpretation of the patient's test data and the clinician who requested the test. A clinical geneticist may also be involved when appropriate. The MDT case discussion may take place via telephone or videoconferencing but is typically conducted by email. The use of email is advantageous because it does not delay decisions and hence reporting of results from complex cases through the need to find a meeting time convenient for all participants. It enables expert input (including those working in different time zones) and contributions from multiple clinical specialties, and allows time for the clinical scientist (and other participants) to seek additional information or advice from colleagues in response to the case discussion. The emails will be stored by the laboratory as part of their case records as part of the clinical governance process to document the decision-making process. (C) Education and training case-based MDTs are organised for groups of healthcare professionals (eg, by clinical specialty or for clinical users of a specific genomic testing service) across the geography served by the laboratory (or Genomic Laboratory Hubs). Cases are presented by the clinical teams with the genomic testing results explained by the clinical scientists. Key learning points are included and there are ample opportunities for questions via the chat function or orally. These MDTs also provide an opportunity for service updates. (D) Bespoke specialty events (in person or via videoconferencing) provide opportunities for focused education and additional support for clinical teams using genomic tests for rare disease.

reports by selecting an appropriate report template for incorporation of the stored patient demographics, reason for testing, test methodology and variant details. It would be advantageous to move to genomics LIMS using a standardised template for reporting, including discrete and defined data elements that can be surfaced in clinical systems via electronic messaging for integrated reporting.

Streamlined checking of genomic data analysis and interpretation

Data analysis may be undertaken by healthcare scientists or other staff working under the supervision of registered clinical scientists,[33] who will check their analysis and interpretation before a result is issued. There is no requirement for more than one competent clinical scientist to check WGS or Next Generation Sequencing (NGS) panel test data (or any other type of genetic/genomic test data/analyses). Despite the hypothetical merits of second checking, the research base is limited on its efficacy and the factors that support or hinder the process. It is not common practice in pathology laboratories. A systematic review of effectiveness of two person-checking to reduce medication administration errors found inadequate evidence to support the process.[41] This conclusion is supported by similar studies within aviation, chemical engineering and psychology.[42] An audit of historical data will inform the competency training required to adopt this more streamlined analysis and reporting model. If a clinical scientist seeks additional input for a complex case, this should be recorded for audit purposes. Developing national competency assessments for reporting outcomes, for example through the GenQA GENie assessment tool,[43] will support this approach. An evidence and risk-based approach is essential to make best use of clinical scientist resource (see online supplemental material).

Recommendation 12: External quality assessments should be developed to evidence the competency of individual clinical scientists to be solely responsible for the analysis, interpretation and reporting of genomic test results without a requirement for additional clinical scientist input.

Guidance for reporting VUS

Genomic testing frequently identifies VUS.[44] A recent survey of 19 North American laboratories found VUS reported for 32.6% of multigene panel tests and 22.4% of exome/genome sequence analysis tests.[45] To reduce the risk of misdiagnoses and potential clinical mismanagement due to medical misinterpretation of these variants, the UK guidance from the ACGS recommends that VUS should generally only be considered for reporting where there is a high level of supporting evidence and additional evidence might be obtained to allow reclassification as (likely) pathogenic.[24]

Recommendation 10 (as above): All NHS laboratories should comply with the current ACGS Best Practice Guidelines for Variant Classification within 6 months of ratification.

Guidance for reporting incidental findings

A guidance document for NHS clinicians and genomics laboratories has recently been produced by the British Society for Genetic Medicine.[46] It was developed to support a consistent approach that does not inappropriately harm patients and their families, divert limited resources from the core task of interpreting and reporting the results of the test(s) requested, nor over burden clinical services.

The guidance provides a framework for clinical scientists with case examples and a gene list-driven approach for cancer susceptibility variants. In the absence of a clinical phenotype, pathogenic variants should typically only be reported where there is evidence of high penetrance and available treatment or surveillance that is likely to change clinical outcome.

Recommendation 13: All NHS laboratories should comply with their national guidance on reporting incidental findings.

Guidance for reporting genomic test results and standard report templates

The ACGS has produced best practice guidelines for reporting genetic results,[47] and a set of standard report templates for genomic tests using WGS analysis is available to members.[24] These template reports were designed to increase the consistency, clarity and efficiency of reporting (see online supplemental material).

Recommendation 14: All NHS rare disease clinical reports should comply with current ACGS best practice guidance for reporting, with standard report templates used wherever possible and within the context of the individual countries' health system requirements.

Multimodal approach to maximise diagnostic yield

Short-read WGS technologies enable the detection and analysis of multiple genomic variant types, including copy number, some structural variants and mitochondrial DNA variants. Use of an alternative test methodology may be required to provide sufficient additional evidence to upgrade a VUS to a likely pathogenic classification that will inform a patient's clinical management. The methodology required will depend on the type of variant (eg, cDNA sequencing for splice site variants), gene (eg, biochemical test) or scenario (eg, long-read sequencing to define the phase of two heterozygous variants or interpret a complex structural variant).[48] There are also situations where a different methodology might be beneficial as a second-line test to increase diagnostic yield (eg, *NF1* cDNA sequencing for neurofibromatosis). Timely access to additional technologies accredited for medical laboratory testing is essential for reporting clinically actionable results without further delay. Access to and integration of new technologies/multimodal diagnostic approaches will require collaboration and engagement with academic centres and highly specialised services, dedicated funding and significant capital investment.

Access to long-read sequencing, functional tests, protein structural modelling and other technologies to increase diagnostic yield

Diagnostic yield may be increased through the application and integration of additional multiomic approaches (including RNA/transcriptomic sequencing, proteomics and metabolomics), other genomic technologies (eg, genome-wide methylation analyses or long-read DNA sequencing) and functional tests (including cDNA studies, biochemical tests, immunostaining, flow cytometry and assessment of steady-state protein levels) or protein structural analysis.[49] An exemplar of a group of challenging genetic diseases where a multimodal approach has been successfully introduced is that of rare mitochondrial diseases,[50–53] epitomising the necessary collaboration between academic researchers and diagnostic laboratories to deliver timely results. This work also highlights the requirement for access to biopsy samples and/or cell lines and assay standardisation/validation to enable integration into routine genomic testing pathways.

Recommendation 15: Health systems, commissioners and genomics laboratory providers should work together to ensure there is a standardised and comprehensive funded testing approach with validated protocols for using the most suitable multimodal testing methodologies to maximise diagnostic yield from genomic testing.

Reanalysis strategy to maximise diagnostic yield from stored genomic data

The diagnostic yield from genome-wide sequence or large gene panel analysis will increase as new knowledge about gene–disease associations, pathomechanisms and variants emerges,[7 54 55] and to a far lesser extent when updated bioinformatics pipelines detect more types of (likely) pathogenic variants. Reanalysis is faster and less costly than resequencing a patient's DNA sample. A reanalysis strategy is required both for individual families and at a cohort level where data are analysed for all patients collectively (see online supplemental material). An effective cohort-level reanalysis will support the proportionate approach to genomic data analysis, interpretation and checking.

Cohort-level reanalysis

Cohort-level reanalysis offers many advantages over individual case-based reanalysis. It focuses on the identification of variants with a higher likelihood of being relevant to a patient's clinical question and is a more efficient and equitable approach to reanalysis than a family-based strategy. Cohort-level WGS reanalysis is highly efficient in identifying putative new diagnoses for new gene–disease associations and variants present in multiple patients with similar phenotypes within the diagnostic cohort and/or external databases such as ClinVar. It also mitigates scenarios that are difficult to accommodate in high-throughput pipelines, for example technically challenging loci, imperfect/unusual segregation, unexpected dual diagnoses or mosaicism.

Recommendation 16: A cohort-level reanalysis strategy for NHS patients' WGS data should be developed, supported and funded by health system commissioners, for implementation by service providers and other commissioned partners, with agreed turnaround times for reporting of putative diagnoses identified.

Guidance for individual case/family reanalysis

National guidance for reanalysis of data for individual cases is available for the Genomic Medicine Service in England. Currently reanalysis is only performed when there is:

- A high expectation that reanalysis will yield a diagnosis (eg, significant and relevant changes in gene panel content).
- A new significant change in phenotype or pedigree structure or an urgent clinical trigger (eg, a new pregnancy or a new potential treatment available).

Recommendation 17: Requests for individual case reanalysis should follow national health system guidance; only in defined clinical situations and where there is a high likelihood that reanalysis will yield a genetic diagnosis.

Table 2 Core requirements for patients and families undergoing genomic tests for rare disease

	Requirements for patients and their families
1	People living with rare conditions and their families need high-quality information about how to access genomic testing, what happens at a genomic testing appointment and how long it takes to get results from genomic testing. Depending on what the test is for, there may also be a need for pretest counselling and/or help to understand the limitations of genomic testing, including the chance that no significant finding may be found. It is important to acknowledge that not everyone will receive a diagnosis after undergoing genomic tests. Some people will receive a finding of a variant of uncertain significance (VUS) or be affected by a condition that is so rare that it does not yet have a name. A lack of a definitive diagnosis leaves people and their families with little or no information about how their condition is likely to progress and even whether or not the condition will be life-limiting. It is important to provide support to individuals without a diagnosis or with a VUS result and the opportunity for reanalysis in the future.
2	Once samples have been submitted for testing, patients and their families need to receive their results within the timescale indicated by the clinical team arranging the test. Prompt communication is required regarding any issues that will delay results, for example unsuitable or insufficient samples.
3	A copy of the diagnostic report should be provided on request. This laboratory report should follow an agreed standardised format with an agreed minimal data set. A summary of the findings written in appropriate, accessible language should be included.
4	Patients and their families need to know who will explain what their test results mean and what will happen next and within an appropriate timeframe. This may include referrals to appropriate medical specialties, the provision of high-quality information to help them understand what the diagnosis means, and additional support to come to terms with the diagnosis and understand how it will impact on their day-to-day lives and their future. When test results indicate a condition has been inherited from a parent, people need access to support and accurate information about how it may impact any future pregnancies and other family members. Depending on their response to this information, they may wish to be referred for reproductive choice options, including preimplantation genetic testing and/or prenatal testing. It is important to clearly signpost people living with rare conditions and their families to the part of the NHS from which they will receive ongoing support for their condition. It is also important to signpost them to condition-specific charities and support groups that can provide information and peer-to-peer support for their journey.

The patient-facing elements of these requirements are delivered by clinical genetics services, paediatrics and many other medical specialties. These services are outwith the scope of this position statement, which is focused on laboratory genomic testing.
NHS, National Health Service.

Patient experience of genomic testing to inform service development and improvement

NHS commissioned genomic testing laboratories are accredited to the ISO 15189 2022 standard, which includes a requirement to identify and implement opportunities for improved patient care. Examples might include improving the availability of information about genomic testing for patients and clinical teams, updating bioinformatics pipelines or analytical strategies to increase test diagnostic sensitivity, or streamlining laboratory processes as part of a programme of continual quality improvement. Understanding patients' and families' experiences of genomic testing is essential for effective service development and improvement. The core requirements for patients and families undergoing genomic tests for rare conditions are described in table 2.

Engaging with patients, parents and carers

The complexity of delivering NHS genomics services via a broad range of clinical specialties across large geographies presents a challenge in capturing a wide and diverse set of patient views and experiences. The governance structures of the NHS England Genomic Medicine Service and Genomics England have been designed to include dedicated patient and community participation (see online supplemental material). Using patient and public voice involvement already embedded within the landscape of NHS genomic service delivery provides an ideal opportunity for effective monitoring to inform service development and delivery improvements.

Patient support groups and organisations frequently collect data and information to better understand the needs and experiences of their community,[56 57] sharing the results via their website and with their community. Opportunities for these results and conclusions to be fed back to those developing laboratory services should be encouraged and explored.

Recommendation 18: Existing patient and public voice structures within genomic medicine services should be harnessed and developed to maximise the impact of patient involvement across the system and provide an evidence-based and robust patient-led service.

Innovation through research and development to continually improve service quality

Innovation, through research and development, is paramount to improving all aspects of rare disease diagnosis, including determining new gene–disease associations and pathomechanisms, creating population variant data sets with greater global diversity, improving bioinformatics pipelines, multimodal technologies and variant classification tools, and implementing artificial intelligence algorithms to enhance laboratory informatics. For example, advances in long-read sequencing mean that it is now possible to generate complete human genome sequences with both parental haplotypes phased telomere to telomere within hours.[58]

To increase laboratory efficiency and productivity and reduce turnaround times, a healthcare system engineering approach driven by data and quality improvement is required. Continuing investment and support for research and innovation strengthens the essential ecosystem between NHS laboratories, academia and industry that is necessary to improve rare disease diagnosis and develop novel treatments.

Translational research initiatives, partnerships and infrastructure

The successful transition of exome and genome sequencing to healthcare system implementation has highlighted the value of building virtuous cycles between research and clinical genomics and the need for continued investment in both. As an exemplar, the NHS England's rapid sequencing service for acutely unwell children launched in 2019, and has provided testing to more than 4000 patients to date. Together with similar programmes,[36 59–61] it has demonstrated the value of prompt diagnosis in critically ill children with rare conditions. The continued development of these diagnostic services involves successful collaborations with industry partners, enabling timely implementation and maximising the benefits of technological advances.

Patients and families undergoing WGS testing in England can join the National Genomic Research Library,[62] developed in partnership between NHS England and Genomics England, to enable ongoing research and discovery from approved researchers, academia and industry.

Co-location of diagnostic laboratories and academic partner institutions can foster integration of research and diagnostic approaches within shared spaces, scientist and bioinformatics staff that work across the NHS and academia, leading to increased innovation and adoption of research discoveries, data sets, pipelines and tools into diagnostics. Dedicated genomics and rare disease themes within the National Institute for Health and Care Research (NIHR) Biomedical Research Centres, the Rare and Inherited Disease NHS Genomic Network of Excellence and the LifeArc Translational Centres for Rare Diseases are all contributing to bridge the gap between research and service delivery, facilitating access to clinical trials.[63 64] This needs to be coupled with a greater understanding of, and the need for, clinical trials and real-world evidence generation for new and emerging treatments for rare and inherited diseases.

Recommendation 19: Government and health systems should focus attention on national strategic approaches and provide sustainable funding to enable the rapid translation of new technologies and research discoveries into NHS diagnostic practice.

CONCLUSIONS

Diagnostic genomic tests, including WGS analysis, are embedded at earlier stages within clinical pathways in a rapidly expanding number of clinical presentations for patients with known or suspected rare genetic conditions. These recommendations were developed on the basis of evidence to contribute to best practice within the nationally commissioned health services in the UK and Ireland. Our overarching objective is to facilitate efficient and effective multidisciplinary working in order to provide high-quality diagnostic genomic testing services within a clinically relevant timeframe, in the face of rapidly increasing demand and clinical actionability of results.

The recommendations we outline here (summarised in table 1) may evolve over time as more data and evidence are generated and as new technologies and testing approaches are incorporated into NHS diagnostic testing. This position statement may prove useful to healthcare professionals in other countries working to increase availability and access to timely genomic testing in the care of patients with likely monogenic diseases. Realising the full potential of genomic sequencing to improve health and social care outcomes for patients and families affected by rare diseases requires the medical, clinical scientific, academic, patient organisations and third-party sectors to work in collaboration.

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