Supplemental material

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

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APPROACH AND METHODS

Workshop

A one-day workshop was convened by the UK Association for Clinical Genomic Science (ACGS) to discuss the challenges that delay diagnosis of rare diseases in the UK and Ireland, and address ways to improve the current position. The aim was to identify best practice and innovations for streamlined, geographically consistent services. A broad group of participants from key stakeholders within NHS Genomic Medicine services across the UK and Ireland was convened. These included Clinical Scientists (trained in Bioinformatics, Genomics, Molecular Genetics or Cytogenetics) representing each of the NHS Genomics Laboratories, Clinical Geneticists from Regional Clinical Genetics Centres throughout the UK and Ireland, and representatives from the Association for Clinical Genomic Science, Genomics England, Genomics Quality Assessment (GenQA), NHS England, the Royal College of Pathologists, Academia, Genetics Alliance UK and Unique.

The meeting included presentations from Unique and Genetic Alliance UK, focussing on key issues for patients and families relating to genomic testing and outcomes in rare and inherited disease; test waiting times, reporting of variants of uncertain significance and the uncertainty that is posed by variable penetrance and expressivity. The aim of these was to help participants understand what families with rare diseases need from the genomic laboratory services. A series of presentations, facilitated small group discussions and anonymous polls followed, focussing on key elements of genomic medicine service delivery and consistency in practice:

►How can the specialist medical genetics workforce support the laboratories to ensure appropriate referrals for genomic testing with high quality clinical data?

►Proportionate review of variant data to deliver genomic tests at scale: quality standards for bioinformatics pipelines, variant analysis and efficient reporting of genomic test results

► Multidisciplinary Team (MDT) meetings: a streamlined approach to reduce test turnaround times, ensure clinical governance of decision making and deliver focussed education

►Reporting incidental findings

►Variant classification and reclassification

►Storage and reanalysis of genomic data within an accredited diagnostic setting

The participants were also asked to provide feedback and contribute ideas both verbally and via an on-line survey tool, before and after the workshop. The aim was to consider all component steps within the medical, laboratory and administrative pathways to seek solutions to improve reporting times and reduce test turnaround times.

The final session of the workshop was entitled “Future direction, challenges and closer working partnerships” with presentations from representatives delivering genomic testing services in Northern Ireland, Scotland, Wales and Ireland.

Post workshop

The Position Statement was drafted by a small working group before being circulated to all participants for their input. This Position Statement, and the guidance documents referenced therein, describe the standard approach to delivering timely testing for rare and inherited genomic

disease in UK & Ireland laboratories. For the purposes of any future litigation claims arising as a consequence of missing a genetic diagnosis or a misdiagnosis, this Position Statement describes agreed standards in order to provide reassurance to Clinical Scientists regarding the expected scope of analysis and interpretation.

REQUIREMENT 1: TESTING SERVICE CAPACITY AND CAPABILITY TO MEET THE NEEDS OF THE POPULATION (VOLUME AND TURNAROUND TIMES)

Laboratory workforce with appropriate skills, training and experience

The NHS Genomics Laboratory workforce typically includes Clinical Scientists (trained in bioinformatics genomics, genomics, molecular genetics, cytogenetics or biochemical genetics), Healthcare Scientists (often working towards HCPC registration as a Clinical Scientist), Genetic Technologists (responsible for the "wet lab" genomic testing, high throughput genotyping services, and with an increasing role in analysis/ reporting of NGS/WGS tests), Laboratory Support staff (receiving and processing samples) and administrative staff who support the pathway from sample arrival to report issue. There are also staff with roles in quality management, training or business/laboratory management.

A shortage of Clinical Scientists across the UK and Ireland has arisen because of multiple factors leading to significant numbers of vacant posts within the genomic laboratories. These include higher service demand due to increased test numbers, a wider testing portfolio and higher complexity of analysis following the implementation of next generation sequencing. With a significant number of recent and imminent retirements, and greater recruitment and retention challenges as more scientists leave for other employment opportunities (for example in the growing UK private genomics industry), more trained scientists are needed through both supernumerary and in-service posts. Clinical Scientists have taken on new leadership and educational roles within the NHS that have further reduced the numbers available for data analysis and reporting.

The genomic laboratory's workforce strategy should signal the level of demand for both Clinical Scientists and Genetic Technologists and include effective ways to train both groups of staff. Strategies for increasing training opportunities (in-service and STP) and recruiting scientists from other career pathways (for example scientists from both academia and industry) should be considered. Utilisation of the Genomics Training Academy(1) will support this by providing greater capacity and new virtual approaches to training. This work has been initiated within the Genomic Laboratory Hubs in England by reviewing their workforce profiles and developing workforce strategies. It is paramount that the existing genomics workforce is supported and valued, with initiatives put in place to maximise retention. Health and well-being support should be available in every NHS Healthcare Trust.

Genetic Technologists are a highly specialist and skilled workforce. A national review of this workforce has been undertaken to consider the introduction of formal registration, training and enhanced career pathways. Implementation of this model will support the retention of Genetic Technologists and allow a broader skill mix for their role, thereby increasing analysis and reporting capacity within the service.

Many laboratories have created additional roles to release Clinical Scientists in order that they can focus on tasks that cannot be done by other staff. Examples include Development Scientists or Implementation Officers to manage the development/validation/verification of new services, Service Delivery Managers with Operational Management responsibilities, Quality Support Officers, Scientific Support Officers to facilitate sample assignment to the correct testing pathway and other roles to support data management. University students on placement can also provide additional support which yields shared benefit for both the student and genomics team.

Expanded administrative services and support from Genomics Informaticians will also liberate time for Clinical Scientists to concentrate on tasks that require their HCPC registration. Greater use of integration and automation experts can facilitate consolidation of key processes, bringing

efficiencies to workflows and to service delivery, and releasing capacity for both Genetic Technologists and Clinical Scientists. Improved informatics solutions could deliver significant efficiency savings at every stage of the genomic testing pathway.

Apprenticeships can benefit the genomics service in many of these workforce areas, including administration, informatics, digital analysts and Genetic Technologists. They provide a defined path for training and help to stabilise the workforce.

Medical leadership roles in genomics laboratories (for example Medical Director and Rare Disease Clinical Lead) have been created (or expanded) to include strategic development, delivery and clinical engagement. They support Clinical Scientists both pre-analysis (liaison with clinical teams regarding referrals for testing and gatekeeping of requests for testing) and post-analysis of variant review (discussions about complex cases and incidental findings). Genomic Associates, Genomic Coordinators and Genomic Practitioners have been appointed in some areas to assist clinical teams and laboratories with service user education, triaging of referrals, follow-up of family member samples and obtaining additional clinical information.

The introduction of new roles and expansion of existing roles is helping Clinical Scientists and Genetic Technologists to focus more on specific tasks that require their level of skills and experience. Further workforce development is required to maximise the deployment of these approaches across the UK and Ireland alongside consideration of an appropriate competency framework, and achieve commissioned turnaround times for all patients undergoing genomic testing.

REQUIREMENT 2: COMPREHENSIVE CLINICAL PHENOTYPE AND DETAILED FAMILY HISTORY, WITH TRIO SAMPLES (PATIENT PLUS BOTH UNAFFECTED PARENTS) WHEN APPROPRIATE

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

Over the past decade the number of genes with phenotype associated pathogenic variants has increased from ~3000 to over 5000 and genetic testing has transitioned from single gene or small gene panel (<50 genes) tests to genome-wide sequence analysis or large panel tests (some >1000 genes). The National Genomic Test Directory(2) specifies which genomic tests are commissioned by the NHS in England, the technology by which they are available, and the patients who will be eligible to access a test.

Determining the sequence of a human genome is relatively straightforward, but the interpretation of genome sequence data is complex due to significant knowledge gaps and uncertainties. These include incomplete knowledge regarding genes associated with disease, disease-causing variants not detected by current bioinformatic pipelines and variants with insufficient information to classify as (likely) pathogenic. For these reasons, for many patients with a monogenic rare disease even the most comprehensive current genomic analysis will not identify a genetic diagnosis. Accordingly, it is not possible to use this type of genomic test as an exclusion test.

Education for service users is essential in order that clinical teams are informed of the appropriate genomic testing options that might identify a genetic diagnosis that will be useful for clinical management. Eligibility criteria for genomic testing are available for the National Genomic Test Directory in England(2) and Scotland to facilitate clinically appropriate, equitable testing that informs management decisions. It is important that service users, patients and families have realistic expectations of what the genomic laboratory service can (and cannot) deliver. This should consider

both resources and balancing benefits of a potential diagnosis with risk of uncertain results and incidental findings where the likelihood of a diagnosis is low.

The NHS England Genomics Education Programme(3) delivers and advises on learning and development opportunities to help the UK NHS specialist genomics workforce to maximise the use of genomics in their practice. An example is the e-learning course “Genomics in the NHS: A Clinician's Guide to Genomic Testing for Rare Disease”(4). Genomic Medicine Service Alliances, mapping to GLH geographies, have been established in England to provide educational infrastructure and embed testing pathways across all clinical specialties. In Wales, to embed genomics throughout the healthcare sector, the Genomics Partnership Wales programme has developed e-learning modules with Health Education and Improvement Wales to increase staff understanding and improve patient care. Key delivery partners in this work for Wales are Health Education England and its Genomic Education Programme.

Education focussing on genomic testing (“right patient, right test, right time”) necessitates good communication of the limitations of genomic technologies and testing strategies, chances of uncertainty versus a diagnostic result, in addition to outlining the potential benefits and the reasons for requesting samples from both biological parents when appropriate. For example, there is little value in undertaking testing for the same disorder in patients/families who historically had standard of care testing and where assessment of the current testing available is that there is limited, if any, additional diagnostic value. Raising patient/family expectations of a result can delay important life decisions such as plans to extend their family.

Education for service users should include how genomic tests fit into clinical pathways, identifying which patients meet eligibility criteria and for whom a test offers clinical utility, which type of testing is most suitable, the scope and limitations of a test on the basis of the technology being used, when genomic testing is and is not appropriate in the patient’s clinical pathway, the limitations of genomic technologies and testing strategies, the likelihood of uncertainty versus a diagnostic result, and interpretation and communication of genomic test results.

Education is required at every stage; early on during training and at a specialist level where appropriate. It is essential that the format and delivery of this education addresses the key learning needs of clinical teams as well as promoting the utility of genomic testing. Education strategies should include regular evaluation, feedback and continuous quality improvement to ensure that they meet the needs of the Genomic Medicine Services in the UK and Ireland

A key component of training for service users includes the process for requesting a genomic test. Electronic test ordering systems are not widely available for rare disease genomic testing within the NHS in the UK or Ireland. Investment is required for the development and maintenance of the infrastructure required to enable fully integrated informatic solutions that will increase laboratory and clinical workforce efficiencies, reduce duplicated tests and reduce clinical risk. On-line test order forms could be designed to capture the data required to demonstrate patient eligibility for testing, as well as eliminating the possibility of transcription errors and avoiding delays to testing that result from incomplete test request forms submitted to laboratories. In the absence of an electronic ordering system test order forms should be designed for electronic completion, for example using an editable PDF. Handwritten test order forms are not acceptable due to the high risk of error.

The primary identifier for all patient records and request forms should be the 10-digit unique number allocated at birth or when a patient first accesses healthcare. In England and Wales, this is

the NHS number; in Scotland, the Community Health Index (CHI) number; and in Northern Ireland, the Health and Care (H&C) number.

Completion of the test order form requires a clear indication of the genomic test or tests being requested, using agreed standardised test codes. Standardised test codes are listed in the NHS England National Genomic Test Directory (2) which could be adopted across the UK.

Questions about genomic testing are welcomed by laboratories via e-mail. For some genomic tests, for example rapid genome sequencing for acutely unwell babies and children, or rapid prenatal exome sequencing, pre-test case eligibility is routinely discussed (via e-mail) with the provider laboratory. Clarifying queries or checking eligibility in advance of obtaining samples from patients is preferable to avoid raising false expectations for patients and families.

Monitoring genomic test requests to confirm compliance with testing criteria

In a publicly funded healthcare system with limited resources it is imperative that access to services is managed according to clinical need. For genomic testing in England this is facilitated by eligibility criteria specific to each clinical indication listed within the National Genomic Test Directory(2).

It is the responsibility of service users to comply with eligibility criteria and provide comprehensive clinical information. Review of test requests by laboratories provides an opportunity to check compliance with this requirement in order to reduce inappropriate testing, misdiagnosis and the avoidable patient harm that can result from uncertain and incidental genetic findings. Confirming that sufficient clinical information has been provided also maximises the possibility of finding a genetic diagnosis and increases efficiency of analysis and reduces turnaround times.

The level of monitoring test requests has been variable across laboratories, in part according to historical test portfolios. Support from medical colleagues, either those in leadership roles associated with laboratories or Clinical Genetics services, is essential to educate service users as to the value of gatekeeping for genomic testing. Inappropriate testing can result in patient harm in addition to diverting resources from eligible patients. Pre-test liaison between service users and laboratories should be encouraged for those situations in which there is uncertainty or unfamiliarity regarding testing options and Clinical Scientists should be empowered to refuse requests for inappropriate and/or ineligible testing. Laboratory staff have expert knowledge of genomic testing services and may be able to provide advice regarding better alternative tests. The diagnostic yield and clinical utility of results from the first four years of NHS GMS testing will inform the 2024 review of the Test Directory in England. However, further evidence-based refinement of the eligibility criteria should be combined with efficient and implementable strategies for managing test requests in order for such changes to be effective.

REQUIREMENT 3: INTERPRETATION OF GENOMIC DATA USING THE MOST APPROPRIATE ANALYTICAL TOOLS, RESOURCES AND PROCESSES

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

The migration of clinical diagnostic genomic testing to large gene panel and genome-wide sequencing has made bioinformatics pipelines increasingly critical. The challenge is to present the information required for the analyst to efficiently review variants potentially causative of the clinical presentation that is the reason for testing whilst maximising both sensitivity and specificity. The

approach must involve the provision of appropriate, up-to-date annotation of prioritised variants and a stringent filtering approach to remove variants with a low prior probability of pathogenicity.

Bioinformatic pipelines require continual development to maximise clinical utility by incorporating new knowledge (e.g. new gene-disease associations), new tools for variant calling and annotation, updated resources (e.g. larger variant datasets with greater representation across genetic ancestry groups) and feedback from users.

Bioinformatics pipelines generate a list of variants described using genomic coordinates of the most up to date genome build (currently GRCh38). Clinical reporting also requires HGVS nomenclature where appropriate (e.g. particularly for SNVs and other small variants) annotated against an appropriate reference transcript (in the NHS this includes the MANE Select transcript and any MANE Plus Clinical transcripts).

Diagnostic pipelines use a number of resources to annotate and/or filter variants out of the final list. To ensure maximal diagnostic sensitivity, and that the analysis process is as efficient and effective as possible, a core set of resources providing the evidence streams required to facilitate the classification of variants should be used (see **Supplemental Table 1**). It is advantageous that the most up to date versions of resources are incorporated as soon as possible after they are made available and are validated for the clinical purpose for which they are being used. It is recognised therefore, that the frequency of updates may vary across different resources. For example, clinical laboratories may integrate ClinVar updates every month, as the source is updated weekly and testing is relatively straightforward. A more complex annotation source such as gnomAD will require more extensive testing but which also has a potential high impact on variant classification, should be integrated as quickly as testing allows. This information should be brought into the output wherever possible or links out provided. Aligned data should be available for visualisation by scientists (e.g. prioritised variants accessible in IGV) to aid variant quality checks and interpretation.

There are clear benefits to the ACGS working with the commissioners and GenQA to define the bioinformatics standards for NHS providers of diagnostic genomic services, including pipeline quality standards, best practice for tools and approaches, validation data sets, data-sharing and operational management. The ACGS Best Practice Guidelines for Bioinformatics(5) are updated periodically and provide more information on best-practices for tools and approaches.

It is important for service users to understand that not only will different bioinformatic pipelines generate different lists of variants for review, but the same pipeline run on a different day may also do so, because of the continual updating of resources that are accessed by the pipeline.

Proportionate review of prioritised variants

Large gene panel and genome-wide sequencing generates large numbers of rare variants prioritised by bioinformatic pipelines for manual analysis. The aim of the Clinical Scientist responsible for the analysis is to identify the (likely) causative variant(s) that can explain the patient's clinical presentation relevant to their test request. In a healthcare setting with high demand and finite resources a proportionate approach is required to deliver timely genomic testing for the entire patient population accessing rare disease genomic testing. Systematic cohort reanalysis of patients' WGS data will identify additional genetic diagnoses through new research and expanded data sets.

Many of the variants prioritised by bioinformatic pipelines can be excluded from potential clinical relevance to the patient's reason for testing using simple criteria as they are incompatible with a classification higher than a variant of uncertain significance (VUS) using the ACMG/ACGS variant classification guidelines(6, 7). These criteria (described in detail within Appendix 1 of the NHS

England Genomic Medicine Service Guidelines for Rare Disease Genomic testing, Interpretation and Reporting) are:

- Patient phenotype clearly incompatible with gene
- Frequency in the Genome Aggregation Database (gnomAD) is clearly too high for the disorder
- Detected in an unaffected adult where the disorder is fully penetrant and manifests in childhood
- Variant type inconsistent with disease mechanism
- Variant for which there is little evidence to favour pathogenicity other than rarity

In circumstances where one or more of those criteria apply, a full variant classification is not required and the variant(s) can be excluded from further analysis. A single heterozygous variant in an autosomal recessive gene is not reported unless there is additional testing that the laboratory would recommend that is likely to help confirm the diagnosis in the proband(7). It is essential to record the reason for excluding a prioritised variant as an auditable part of the analytical record. Only the minimum information necessary to support the decision is required. Laboratories are expected to store their variant classification data in a format that provides a knowledge base (e.g. to aid classification of recurrent variants and to enable variant reclassification as recommended by the British Society for Genomic Medicine)(8).

A proportionate approach is also recommended for review of the remaining variants after a (likely) pathogenic variant (or variant pair) that may fully explain the patient's clinical presentation is identified. It is possible that rare variants affecting more than one gene are contributing to the clinical presentation. For example, in a case series of 7374 patients who underwent exome sequence analysis more than one genetic diagnosis was reported in ~5% of patients(9). These included patients with distinct genetic disorders (affecting different organ systems) and a smaller proportion with genetic disorders that included overlapping clinical features. Once a genetic diagnosis that can fully explain the patient's reason for testing has been identified, an in-depth assessment of the remaining prioritised variants is not required since the likelihood of finding an additional genetic diagnosis is small.

Quality assurance for WGS and NGS gene panel analysis may be evidenced through the laboratory audit schedule (review of a subset of cases), individual scientist competency assessments and participation in laboratory external quality assurance schemes and individual competency modules (via GenQA).

Efficient, effective MDT working model

The traditional format for a genetics MDT meeting with Clinical Scientists and service users was a "live" case list with discussion of variants identified through testing to reach a decision on interpretation and reporting. Formal presentations describing the patient's clinical presentation, testing undertaken, variant(s) of interest and evidence for/against pathogenicity were prepared in advance and reporting of results was placed on hold until the appropriate personnel were able to attend. This MDT meeting format provided valuable case-based learning opportunities and updates on changes to service delivery, but was time intensive, often lacked appropriate governance structures for decision making and delayed the return of results to patients.

A different model for case-based variant discussion was implemented for the national rapid genome sequencing service in England for acutely unwell children where the target reporting time is 10-14 days. A preliminary result email is sent to the requesting clinical team that describes the variant(s) identified, together with a brief summary of the evidence in favour of pathogenicity and appropriate

references. The email provides the opportunity for efficient and timely MDT discussion regarding evidence that relates to the patient phenotype (i.e. PS2, PM6 and PP4 as discussed in the ACGS Variant Classification Best Practice Guidelines) and enables participation of international experts in complex cases. In addition to facilitating rapid discussion to expedite issue of the formal report, the emails provide an audit trail for the laboratory records. For highly complex cases it can be helpful to agree on the report text with the clinical team via e-mail. A program of educational MDT meetings held via MS-Teams three times per year supports this service. Each meeting includes a service update, clinical cases selected for their learning points and presented jointly by the patient's clinician with the laboratory team, and a Q&A session.

This model (see **Figure 2**) for genomic MDT meetings is reflected in the NHS England Genomics Unit Interpretation and Reporting Guidance and has been adopted for other genomic tests/specialties in some parts of the UK. It has resulted in more efficient recording of MDT outcomes, faster reporting times due to increased time for scientists to focus on analysis, clearer governance structures and increased access to more focussed educational opportunities.

REQUIREMENT 4: STANDARDISED CHECKING AND REPORTING OF GENOMIC TEST RESULTS

Streamlined checking of genomic data analysis and interpretation

Clinical Scientists are responsible for genomic test results that require analysis and interpretation of data in the context of the clinical referral. Standards of proficiency for Clinical Scientists(10) state the need to manage their own workload and resources safely and effectively (standard 1.2), to identify the limits of their practice and when to seek advice (standard 1.1) and to practise as an autonomous professional, exercising their own professional judgement (standard 4). The UKAS accreditation standard ISO15189:2022 details the requirements for laboratories to specify, manage and document the competence of their personnel (see UKAS ISO15189:2022 Section 6.2.2) and to maintain processes for identifying risks of harm to patients (see UKAS ISO15189:2022 Section 5.6). The Laboratory Director is responsible for risk management to all aspects of the laboratory operations so that risks to patient care and opportunities to improve are systematically identified and addressed (see UKAS ISO15189:2022 Section 5.2.2).

Risk management processes include various types of checking in genomics laboratories, either introduced when a new process is established or in response to an incident to reduce the likelihood of a re-occurrence. An example is tube transfer checks during DNA extraction, historically undertaken by a second member of staff witnessing the transfer of a sample between tubes but largely replaced with end-to-end barcode checking.

Genomic data analysis is often undertaken by Healthcare Scientists, other staff or Clinical Scientists working towards the laboratory's required level of competence. Their analysis and interpretation will always be checked by a Clinical Scientist who has met the laboratory's competency requirements and been authorised by the Laboratory Director (or their delegated deputy/deputies) to perform that activity before a result is issued.

We note that there is no requirement in any ACGS or other UK Best Practice Guidance for more than one competent Clinical Scientist to check WGS or NGS panel test data (or any other type of genetic/genomic test data/analyses).

Analysis and interpretation of WGS and large NGS panel test data is a relatively new type of investigation. In comparison to historic tests that focussed on a single gene or relatively small gene panel, many genomic tests are very broad in their scope. For example, a WGS analysis may investigate several thousands of genes and rare disorders. In some genomic laboratories a "second

check" is included to increase the level of confidence in issuing the correct result i.e. to avoid a misdiagnosis, a missed genetic diagnosis or reporting an incorrect variant classification. Including such additional checks for new processes is good practice, but the data should be reviewed regularly to see if the checks are adding value and to inform training. A risk and evidence-based approach to data checking is required to maximise efficiency of the Clinical Scientist workforce.

The practice of having a second competent Clinical Scientist check every case may be perceived as a useful way to reduce the risk of error. However, double-checking processes have a number of limitations in practice(11), including the disadvantage of diffusing responsibility so that neither person is full responsible. Within genomics laboratories these types of checks are variable; sometimes a "quick check" by the second scientist rather than a full independent analysis. Not all laboratories include a second checking process; they require that the Clinical Scientist performing the data analysis will seek additional input from colleagues as required. In this circumstance the involvement of an additional scientist(s) should be recorded for audit purposes. This approach is consistent with the HCPC standards of proficiency that require a Clinical Scientist to be able to practise as an autonomous professional, exercising their own professional judgement.

As a first step towards adopting a more streamlined model that incorporates lean thinking principles(12), a retrospective audit of data analysis involving more than one competent Clinical Scientist is recommended. This will provide useful information regarding the error rate and type (missed diagnoses, misdiagnoses and incorrect variant classifications) and identify areas for additional training. The next step might be for Clinical Scientists to document those cases for whom they would request additional input and to prospectively audit the outcomes. Videoconferencing platforms provide readily accessible forums for discussion of complex ("edge") cases either with a senior scientist or a group of colleagues for training purposes. Reaching out to other laboratories to learn from their experience of greater Clinical Scientist autonomy is likely to be helpful. A data-driven approach to quality improvement is key.

Reporting of genomic test results

As described above, there is no requirement for more than one competent Clinical Scientist to check genomic data analysis and interpretation. This applies also at the stage of reporting results; the report authoriser is not required to re-check data analysis and interpretation performed or already checked by a competent Clinical Scientist. Their responsibility is to ensure that the report content is consistent with the result of the data analysis and interpretation.

Report templates for rare disease whole genome sequence (WGS) analysis are available on-line from the Members Area of the ACGS website(13). They cover various scenarios (including different modes of inheritance, variant classification categories and proband/parents) and include recommended report summary statements from Tables A and B of the ACGS Best Practice Guidelines for Variant Classification in Rare Disease. A set of report templates for inherited cancers has been developed through the Cancer Research UK funded CanGene-CanVar programme(14). These report templates are intended to increase consistency, clarity and efficiency of reporting and should be used wherever possible.

The set of template reports for rare disease were generated using the following principles:

(1) The report will be stored in the patient's notes and may be accessed by healthcare professionals from many different clinical specialties. Patients and their families may be offered or will request

a copy of the report. The report should be structured and written in a way that facilitates its use and understanding of the content.

(2) A one-page report is the goal, with supporting information included in an appendix or appendices. Appendices must include the patient identifiers (copied over from the top of the main page of the report). An appendix might include variant classification evidence, information about treatment/screening or gene panel(s) tested/read depth.

(2) Result Summary statements are included in the ACGS Best Practice Guidelines for Variant Classification in Rare Disease(7).

(3) It is important to know if the reported variant(s) explain part or all of the patient's phenotype. An exception-based approach is used i.e. only mention when the whole phenotype cannot be explained by the variant(s).

(4) The data items included in the report have been organised within a hierarchical structure that will facilitate electronic generation of reports using a formatting script.

(5) There are polarised views about including information on treatment or clinical management in a laboratory report because treatment and clinical management is the responsibility of the medically qualified referring clinician. A section entitled "Implications for treatment" is included as a way to signpost the referring clinician to information that may be relevant for a patient with a particular genetic diagnosis. This section of the report must be carefully worded to be clear that this is not direct clinical advice for the patient. An example of suitable wording: "High dose riboflavin supplementation has been reported to ameliorate the progression of this disorder (Foley et al 2014 Brain 137:44-56)."

(6) At a previous ACGS best practice meeting there was concern expressed about using the word "recommend" because it infers an obligation for the clinician to follow up a recommendation but in some cases this may not be possible. An example would be a recommendation to do mRNA analysis before it is known that such an assay is available for that gene variant. In this situation the preferred wording is "mRNA analysis might provide further evidence in support of the variant pathogenicity".

(7) The report templates will not cover every possible scenario, so occasional editing will be required and the report format may need to be modified for use within a LIMS. The aim is a more standardised overall appearance of reports with a simplified layout that facilitates better understanding of genomic reports.

REQUIREMENT 6: 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 disease-gene associations and mechanisms emerge(15-17), and to a far lesser extent when updated bioinformatics pipelines detect more types of (likely) pathogenic variants. Reanalysis is less costly than resequencing a patient's DNA sample given the Royal College of Pathologists' 2015 guidance to store genomic sequence data for at least 5 years. Reanalysis rather than resequencing will be faster if a result is needed urgently for clinical management.

Reanalysis can be performed either for individual families or at a cohort level by analysing the data for all families collectively. The development and implementation of a standardised national reanalysis pathway that integrates data reanalysis and advanced diagnostics approaches will reduce

the diagnostic odyssey for patients with rare diseases and their families. Genomic data must be stored for future reanalysis in a way that the data are readily accessible both for cohort-level reanalysis and for individual case reanalysis, for example in a clinically urgent situation. It is anticipated that guidance for individual case/family level reanalysis will evolve in parallel with the development and implementation of an accredited cohort level reanalysis, and the availability of additional financial and workforce resourcing. For example, the inclusion of family level reanalysis eligibility criteria that include informing reproductive decisions prior to a subsequent pregnancy.

Genomic testing in the UK and Ireland is delivered by UKAS ISO 15189 accredited laboratories with Quality Management Systems in place to document processes, procedures and responsibilities for achieving quality policies and objectives. Genomic and genetic data generated for the purpose of NHS diagnostic testing are analysed, interpreted and reported by Clinical Scientists working to the UKAS ISO 15189 accreditation standard. This applies to reanalysis too; other healthcare workers are not subject to such accreditation standards and should not access these data[1].

Patients who access WGS testing in England are given the opportunity to share their data for research purposes[2] through the National Genomic Research Library. The consent form used at the time of the initial diagnostic testing combines the diagnostic and research offering and is available from the NHS England website(18).

By making their data available within the research community, patients may benefit from the latest developments in genomic science and technology, and research work may identify new findings that lead to a genetic diagnosis. Candidate variants identified by researchers should be analysed, interpreted and reported by Clinical Scientists working to the UKAS ISO 15189 accreditation standard for reporting purposes.

Guidance for individual case reanalysis

National guidance for reanalysis of data for individual cases (R387 Clinical indication) is available for the Genomic Medicine Service in England. All requests must meet guidelines and clinical teams should understand that inappropriate use will divert resources away from those patients and families awaiting primary analysis.

Currently, reanalysis is only performed when there is:

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

Cohort level reanalysis

[1] In England access to NHS WGS data is governed by the joint data controller agreements between NHS England, Genomics England and NHS Healthcare Trusts who host Genomic Laboratories responsible for data interpretation and reporting. Data access is restricted to those professionals requiring it for this specific clinical purpose.

[2] Researchers seeking access to NHS genomic data with research consent will require the necessary information governance data protection agreements in place (e.g. Data Protection Impact Assessment, Data Deposit Agreements). Researchers may apply to join the Genomics England Research Network (academics, clinicians, students and charities or UK government departments that conduct research) or the Discovery Forum (industry partners). The Genomics England Research Environment secure workspace provides a place to carry out research on de-identified datasets in the National Genomics Research Library (Research and Partnerships | Genomics England).

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. This is pertinent since a lower diagnostic yield is anticipated for reanalysis (<5%) compared with primary analysis (~30% for WGS analysis in England). Cohort-level WGS reanalysis is highly efficient for identifying putative new diagnoses for new gene-disease associations and variants present in multiple patients with similar phenotypes. 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. Thus, an efficient approach for cohort-level reanalysis on an on-going basis is required to maximise the diagnostic yield from WGS analysis. It will also provide some reassurance to patients and clinical teams that there are further opportunities for diagnoses to be identified.

The Diagnostic Discovery pathway was established collaboratively by Genomics England, NHS England and the NHS Genomic Laboratory Hubs in England to enable putative diagnostic findings identified through research activities to be returned to NHS laboratories for clinical evaluation. Putative variants are reported by Genomics England to NHS Genomic Laboratory Hubs on a monthly basis for review and reporting if appropriate. The pathway now supports return of findings identified through cohort-wide reanalysis. To date >85% of findings reported by the laboratories have been classified as (likely) pathogenic.

A cohort-wide approach allows efficient analysis of genes that have recently been associated with rare disorders and incorporated into gene panels subsequent to a patient's previous analysis. It also enables reanalysis of a cohort using improved bioinformatic tools e.g. structural variant detection or mobile element insertions. Recurrent (likely) pathogenic variants within the cohort can be sought across the entire cohort and notified to laboratories to aid faster reporting through laboratory collaborations.

REQUIREMENT 7: PATIENT EXPERIENCE OF GENOMIC TESTING TO INFORM SERVICE DEVELOPMENT AND IMPROVEMENT

Engaging with patients, parents and carers

Each of the regional seven NHS GMS alliances have a Patient and Public Voice (PPV) panel to ensure that the views and opinions of patients, parents and carers are heard at all levels to inform decision making and input into the review and development of genomic services throughout the NHS. A PPV representative from each region is brought together in a quarterly meeting of the NHS GMS People and Communities Forum to share findings and best practice. The Participant Panel at Genomics England is a diverse advisory group whose role it is to ensure the patient voice informs all decision-making. A further opportunity for PPV input and engagement is through the rare and inherited disease NHS Genomic Network of Excellence.

Since 2018, Genomics Partnership Wales (GPW) have embodied patient involvement and co-production as a core function of NHS genomics services, engagement and research activity in Wales. The GPW 'Patient and Public Sounding Board' continues to develop in volume, demographics and engagement activities, keeping the patient 'voice' at the heart of all their work, and increasing the understanding of genomics' relevance to all.

REQUIREMENT 8: INNOVATION THROUGH RESEARCH AND DEVELOPMENT TO CONTINUALLY IMPROVE SERVICE QUALITY

Translational research initiatives, partnerships and infrastructure

The focus of the Rare and Inherited Disease NHS Genomic Network of Excellence is to help patients get a diagnosis faster; reduce genomic health inequalities; develop new testing approaches, especially for those patients with a suspected rare disease that remain undiagnosed using current genomic testing in the NHS GMS; increase the efficiency of analysis; and increase capacity for rare condition clinical trials.

This NHS Genomic Network of Excellence aligns with NIHR BRCs in Exeter, Manchester and Bristol and has industry sequencing provider partnerships including with Illumina, PacBio and Oxford Nanopore.

Supplementary Table 1: Annotation categories for variant interpretation and classification
Examples of annotations are provided, but this is not an exhaustive list.

Category	Examples
Population databases	○ gnomAD latest version (v4.1 at the time of publication) granular summary – frequency, number of het/hemi/homozygotes ○ Population level variants
Disease databases	○ ClinVar status ○ HGMD ○ CanVIG-UK
Gene-disease association(s)	○ OMIM ○ GenCC (Gene Curation Coalition) ○ DECIPHER
General annotations	○ Variant type (Sequence ontology terms) ○ Inheritance/*de novo* (if trio)
Predictive algorithms	○ Local constraint and local missense burden ○ Missense prediction e.g. REVEL ○ Splicing prediction e.g. SpliceAI ○ Haploinsufficiency scores

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