General Genetic Laboratory Reporting Recommendations

Lara Cresswell[1], Yvonne Wallis[2], Graham Fews[2], Zandra Deans [3,7], Carl Fratter[4], Louise Monkman[5], Sian Morgan[6]

1. Cytogenetics Service, University Hospitals of Leicester NHS Trust, Leicester, LE1 5WW
2. West Midlands Regional Genetics Laboratory, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, B15 2TG
3. GenQA, Department of Laboratory Medicine, Royal Infirmary of Edinburgh, Edinburgh, EH16 4SA,
4. Oxford Genetics Laboratories, Oxford University Hospitals NHS Foundation Trust, The Churchill Hospital, Oxford OX3 7LE
5. Laboratory Genetics, Queen Elizabeth University Hospital, Glasgow, G51 5TF
6. All Wales Genetics Laboratory, Institute of Medical Genetics, University Hospital of Wales, Cardiff, CF14 4XW
7. Genomics Unit, NHS England, Skipton House, London

Recommendations updated by the Association for Clinical Genomic Science (ratified by ACGS Quality Subcommittee on 24/02/20). Version 1.1

1. INTRODUCTION AND SCOPE

These recommendations are intended as a reference tool for points to consider when writing reports which describe the results of genetic analysis, and should be used within local reporting arrangements (e.g. within a local laboratory and associated clinical departments) and in conjunction with other Association for Clinical Genomic Science recommendations.

Reports are specific formal documents from the laboratory to the referring consultant (or other health care professional) recording the outcome of genetic investigations on a patient. Reports should be accurate, clear and concise and contain where possible the features described in these recommendations.

These recommendations are minimum requirements and professional judgement is of paramount importance for many circumstances.

The use of 'must' in this document indicates a requirement and the use of 'should' indicates a recommendation.

Where there appears to be contradiction between available recommendations/guidelines, the most recently published should be taken to apply to all.

All diagnostic genetics laboratories must be accredited to nationally or internationally accepted standards.

2. REPORT FORMAT

2.1 General format

Reports must be clear, concise, accurate, fully interpretative including an explanation of the clinical implications of the results, and authoritative.

The overall result or conclusion must be clearly visible.

Reports should be in a typed format and handwritten alterations must never be made to the report.

When writing a report it is important to remember that the report will be inserted into the patient's notes and may be seen, not only by the referring clinician, but also by other healthcare workers, some of whom may not have a clear understanding of genetics and the report may also be made available to the patient.

Where laboratories use standardised template reports there must be a facility to edit automatic text as amendment is often required to tailor reports to a specific case.

Reports should be concise but where the report extends to more than one page any additional pages must include patient identifiers. All reports must include pagination (e.g. page 1 of 5). Supporting information should be included in an appendix or appendices. Any appendices must also include patient identifiers.

There must be processes in place that ensure that all reports issued reach only authorized recipients.

Standard report formats for constitutional genomic reports are available to download by logging in to the members area of the ACGS website www.acgs.uk.com/

2.2 Recipients of reports

The name and contact details (or other unique identifier), and referral unit of the requesting clinician, as well as those of any additional recipients of copy reports, must be clearly indicated on the report.

Reports should be sent only to appropriate clinicians with copies as appropriate to other healthcare professionals directly involved in the care of the patient or family.

A copy of the report should be sent to the laboratory requesting the test in cases where the analysis is performed out of region.

It is not recommended that reports are sent directly to patients, although the requesting clinician may provide the patient with a copy or local reporting pathways may require direct patient reporting.

Owing to the sensitive nature of genomic reports, care must be taken in issuing and archiving reports. All laboratories must comply with applicable law and regulations.

2.3 Laboratory Identification

The laboratory issuing the report must be clearly identified, with full contact details. The report should carry a title (e.g. results of genetic analysis) and include a date of issue (e.g. when available to the referring clinician).

The accreditation status of the laboratory test should be indicated in compliance with the laboratory's accreditation status and the National Accreditation Body's guidelines.

2.4 Patient and Sample Identification

Patients must be identified on reports by at least two identifiers e.g. full name and date of birth.

Inclusion of a unique laboratory number and/or NHS number, or equivalent (if applicable) is mandatory to ensure that the report unequivocally links to that specific patient.

Patient sex/gender should not be considered a unique identifier; however there may be instances where it is clinically relevant and, where appropriate, should be included on the report.

Each patient should be reported on a stand-alone basis and uniquely documented since the reports will ultimately be filed in individual patient or family files.

In restating family information, issues regarding personal privacy should be kept in mind, particularly when including the names of other family members. It is important that names and results of other family members are not included, unless they are pertinent to the report e.g. partner for an autosomal recessive disorder, parents when determining the inheritance of a variant, investigation of inheritance of a genetic abnormality, linked marker studies, or cancer predictive studies which restate the family relationship and names as a confirmation/quality check.

For prenatal samples it must be clearly indicated that the result is from the fetus and not the mother. It must also be clearly indicated if multiple samples are taken from one pregnancy or if multiple samples are taken from multiple fetuses during the same pregnancy and to which the result relates to.

For infant samples labelled 'Baby <Family Name>', it is important to include the date of birth and hospital or NHS number (or equivalent if applicable), as samples from future siblings may also be identically labelled. Inclusion of the phenotypic gender or genetic sex, where known, may also be useful in differentiating between siblings.

The type of primary sample and date of receipt in the laboratory must be recorded within the laboratory report.

2.5 Results and Interpretation

In accordance to the ACGS and BSGM Consensus statement laboratories must adopt the American College of Medical Genetics and Genomics (ACMG) guidelines for sequence variant classification and interpretation (11/11/2016).

2.5.1 Correct and appropriate nomenclature

Nomenclature must be meaningful, unambiguous and consistent. It is important to ensure that the results within clinical reports are clear to the clinician/user/reader.

Nomenclature for variants (from karyotype changes to single nucleotide substitutions) should use correct and up-to-date international nomenclature. This will be either ISCN (International System for Human Cytogenomic Nomenclature) or HGVS (Human Genome Variation Society) sequence variant nomenclature (http://varnomen.hgvs.org/), as most appropriate. However, there are a number of key categories where ISCN or HGVS nomenclature is not mandatory, since the meaning of such nomenclature is not generally clear or informative to the non-expert due to complexity:

- FISH: ISCN is not mandatory; results should otherwise be described as simply and clearly as possible, both in the headline summary and in the report text.
- Intragenic copy number variants, i.e. deletion/duplication of one or more exon: refer to paragraphs below.
- Repeat expansions, such as in triplet repeat expansion disorders: HGVS is not mandatory; results should be described in words, e.g. '42 CAG repeat expansion in the *HTT* gene associated with Huntington disease'. A clear key including the size ranges for normal, intermediate/premutation, and affected individuals must be included, with a reference for this information.

An appropriate gene reference sequence or genome build must be included whenever nucleotide coordinates, codon numbering and protein amino acid numbering are used. When genomic coordinates from a genome build are used, the genome build (e.g. hg19 or GRCh38) must be specified. When using gene specific coordinates, a reference sequence for the relevant gene must be provided. As recommended by HGVS, the preferred gene specific reference sequence is a Locus Reference Genomic (LRG) sequence (www.lrg-sequence.org). The transcript number, e.g. 'LRG_377t1', must also be included when reporting coding nucleotide numbering. LRGs provide a stable genomic DNA framework with a permanent identity

and core content that never changes, thereby allowing consistent and unambiguous reporting of variants in clinically relevant loci. However, only approved/finalised LRGs, that is those with status 'public', should be used (LRGs with status of 'pending' should not be used). Therefore, in many cases, an alternative reference sequence, such as an NCBI RefSeq, will be required. Additional notes to clarify the numbering used should be provided as necessary, e.g. 'nucleotide 1 – A of the ATG translation initiation codon' should be added where the numbering of the reference sequence starts elsewhere.

When exon numbering is included in a report, then a reference or explanation of the exon numbering used is required. LRGs provide exon numbering; therefore, use of LRG exon numbering is preferred (but not essential) where available. When using exon numbering from an LRG, laboratories should include a clear statement that exons numbering used is in accordance with the LRG quoted. It is important to note that LRG exon numbering may differ from historical exon numbering, and so laboratories need to take care to ensure that exon numbering is referenced and used correctly. If laboratories choose to use different exon numbering (e.g. historical/legacy) or if no 'public' LRG is available, then the numbering used must be clearly referenced.

Use of exon numbering in a report is particularly helpful for intragenic copy number variants, especially deletions or duplications of one or more exon, which may be detected by a number of techniques (including array CGH, MLPA, WES and WGS). Since the extent of the affected region often cannot be readily determined from the methods performed or through the use of ISCN or HGVS nomenclature, it is recommended that such variants are described in words, e.g. 'heterozygous deletion of exons 44 to 48 of the *DMD* gene' with an appropriate reference included as summarised in the paragraph above. In addition, it is acceptable (but not essential) to describe such variants using ISCN and/or HGVS nomenclature.

If alternative or common traditional nomenclature is used, it should be referred to as such and the ISCN or HGVS equivalent also included. It is recommended not to use solely protein nomenclature to describe the results of molecular testing, since this can only be predicted from the result seen at the DNA level.

2.5.2 Restate the clinical question being asked

The interpretation of genetic results depends entirely on the context. Therefore, reports must explicitly restate the clinical question being asked (or if the referral form is ambiguous, the question the report is answering).

Any additional information from the referral form which has a bearing on the clinical question must also be included.

2.5.3 A clear written description of the genetic abnormality

An unambiguous description of the genetic abnormality and the interpretation of the results of the analysis must be clearly stated. The use of the word abnormal should be avoided where a carrier has a constitutional balanced rearrangement.

2.5.4 The name of any associated syndrome/disease/prognosis

It is appropriate to include the name of any associated syndrome, disease diagnosis or prognostic information where relevant.

2.5.5 The basis of the test

The methodology of the test performed must be stated and any technical details relevant to interpretation of the result must be made clear or the information made available from the laboratory.

The technical sensitivity and practical resolution of the test must be provided where applicable and based on the laboratory's own internal data.

The sensitivity of the test may be influenced by information supplied on the referral form (e.g. ethnic/geographical information for CF or other recessive disorders). This is particularly important when

reporting negative results. Providing references to support sensitivity estimates, when appropriate and if available, is useful.

It must be stated if the testing is incomplete or where the minimum quality is not achieved.

If commercially available kits, probes or software are used, then the manufacturer, kit number, and version must be recorded by the laboratory, but not necessarily reported, as appropriate as long as the methodology has been stated.

2.5.6 Clinical interpretation

The report must provide a full and clear interpretation of the genomic test results.

Reports may be read by a variety of professionals involved in the care of the patient, many of whom will be unable to fully interpret genomic test results. Guidance should be sought from the latest disease-specific best practice recommendations / guidelines, if available.

In order to provide a full interpretation, results must be reviewed in the context of relevant clinical and family information available to the laboratory. It is therefore important to restate briefly any such information which is considered in the final interpretation. This may include the following:

- Relationship between the patient and the index case where there is a family history of the disease.
- Ethnic background where this is relevant
- Other laboratory investigations
- Unusual or suspicious clinical picture

The final answer to the clinical question is a statement of the interpretation of the results taking into account any appropriate additional information supplied. This can usually be expressed in simple concise statement and this statement must be accurate and not open to misinterpretation.

The genetic sex of the patient should be included in the report when tested or otherwise known and clinically relevant.

In situations where two pathogenic/likely pathogenic variants are detected in a proband, but it is not known if they are in *cis* or in *trans*, the report should state *'that assuming these variants are inherited in trans, the result is consistent with a genetic diagnosis of disorder X'*.

The use of the terms 'positive' and 'negative' in relation to a variant is not recommended but must be clearly defined if used.

In the context of a variant, the term 'carrier' or 'carrying a variant' should be used only in the context of autosomal or X-linked recessive disorders, or disorders where incomplete penetrance is evident.

2.5.6.1 Autosomal recessive disorders

If one pathogenic variant is detected in a diagnostic referral, then the interpretation should include 'this patient is at least a carrier'.

Depending on the clinical information provided, it may be appropriate to state that 'these results support the clinical diagnosis'.

If two pathogenic variants are detected in a child, then confirmatory carrier testing of the parents (to exclude the possibility that both variants are on the same haplotype) should be strongly recommended prior to offering prenatal diagnosis.

2.5.6.2 X-linked disorders

It may be important to state the phenotypic gender or genetic sex of the individual where known, particularly for prenatal testing.

It may be appropriate to offer prenatal testing (or state that prenatal testing is not appropriate), if the clinical question was raised in view of the patient (or partner of) being pregnant.

2.5.6.3 Reporting variants of uncertain significance (VUS)

When reporting variants of uncertain significance current guidelines must be followed (e.g. ACGS Best Practice Guidelines for Variant Classification).
If no clear diagnosis can be made from the evidence available, this must be clear in the report.

2.5.6.4 Acquired genetic abnormalities in leukaemias and solid tumours

The basis for genetic analysis of clonal neoplastic disorders may help to (i) establish diagnosis, (ii) risk stratification to aid in selection of treatment intensity, (iii) identifying eligibility for targeted drugs and/or (iv) monitoring response to treatment.

At diagnosis, it is important to consider carefully the specificity of a particular abnormality (the range of diseases in which it is found, and hence its value as a diagnostic feature), and also the reported incidence of the feature within a given disease type (in relation particularly to the diagnostic significance of not finding it).

Where a given rearrangement or variant has been clearly linked to prognosis in large published series or is classified in clinical trials then this can be cited in the report.

Results should be linked whenever possible to an assessment by the haematologist/pathologist of the proportion of neoplastic cells in the sample. However it is recognised that individual sections from the same tumour sample may vary in tumour cell content: This is particularly important to consider when normal results are obtain when testing solid tumours: if the results are reported without knowledge of the proportion of malignant cells, then the report must be qualified to point out the possibility that the malignant clone was not represented in the analysis, i.e. the possibility of a false negative result.

In karyotype analysis, the finding of a single abnormal metaphase, even if it includes a rearrangement of potential significance, cannot define a clone (ISCN 2016). Proof of clonality may often be possible by appropriate FISH and/or molecular studies. If this confirmation is not feasible, significant abnormalities may be reported with qualifications.

Where a karyotype abnormality of unknown significance is detected, the term ‘malignancy’ should not be used in reports. Terms such as ‘clonal proliferation’ or ‘neoplasm’ are recommended instead. Special consideration should be given to the reporting of –Y or +15 which can be found in elderly patients with no haematological disease.

Whenever possible, abnormal results should be classified according to World Health Organisation (WHO).

2.5.7 Family studies

A table can convey complex information much more concisely than text. This format is recommended for linked-marker studies or other investigations involving several family members and/or markers.

It is recommended that results of family studies are supplemented with a pedigree, if results are complex.

It is recommended to include a pedigree or family number (or equivalent), as appropriate, especially when reports include results on different members of a family.

Pedigrees must be drawn according to the Oxford Desk Reference - Clinical Genetics and Genomics (Firth HV and Hurst JA. 2017) including the use of a 'dot' to indicate the carrier status of an individual.

Pedigree diagrams should include only those individuals relevant to the interpretation, should have a date of issue and should include a key to any nomenclature used. The confidentiality of information about relatives of the patient being reported must be a consideration.

2.5.8 Assessment/calculation of risk/recurrence

When appropriate, genetic carrier risks should be stated. Risk estimates are usually most appropriately based on Bayesian calculations.

For diseases that show anticipation, a comment should be made regarding the risk of expansion on transmission to subsequent generations.

It is also important to state the implications of this result for other family members.

2.5.9 Reporting carrier status in prenatal samples

The Joint Committee on Genomics in Medicine, formerly known as Joint Committee on Medical Genetics recommends that for prenatal diagnosis for X-linked and autosomal recessive conditions, the genotype (and hence carrier status) of the fetus should at all times be reported to the referring clinician (JCMG, 2007).

2.5.10 Reporting of results from sequencing

When reporting results from clinical exome sequencing, whole exome sequencing (WES) and whole genome sequencing (WGS) current guidelines must be followed (e.g. ACGS Practice guidelines for Targeted Next Generation Sequencing, Analysis and Interpretation (2015).

2.5.11 Referral for genetic counselling

For cases referred from non-genetics specialities, when a genetic diagnosis is determined in an index case, referral of the patient and their family for genetic counselling should be recommended where appropriate.

As reports may be passed to clinicians other than the referring clinician, it is recommended that all reports state that support is available via/from Clinical Genetics. Where it is stated on a report that genetic testing can be offered to other family members, genetic counselling or referral to Clinical Genetics should be offered.

2.5.12 Further tests and/or information

If applicable, further tests may be indicated which could be undertaken to improve the accuracy or scope of the interpretation.

If the additional tests suggested are not offered by the reporting laboratory, it may be appropriate to suggest alternative specialist laboratories to perform the additional testing.

It may be important to state that no further testing is planned.

Reports may include an offer of opportunity to contact the laboratory directly to discuss the results.

2.5.13 No testing performed

Some samples are received within the laboratory for DNA extraction, cell banking and storage as no genetic test is currently available or they do not require immediate testing. Laboratories must issue a report to state that a sample has been stored.

2.5.14 Reporting of results performed by another laboratory

Procedures for correctness of transcription and accuracy of all information must be in place for any instance of re-reporting of results from another laboratory.

2.5.15 Reporting of results requested by another laboratory

Many laboratories receive samples from other laboratories for specific tests. The laboratory receiving the samples for testing may directly issue the report to the referring clinician and must send the referral laboratory the report to file. The testing laboratory may request the referral laboratory also forwards the report to the referring clinician.

2.5.16 Integrated reporting

Integrated reporting of results for a patient pathway or episode of testing is encouraged, if local facilities and networks allow. This may be multiple tests within one laboratory or several test results from different pathology disciplines for one patient event. An integrated report must contain an overarching interpretation in the context of all results obtained for the patient.

Procedures for accuracy of transcription must be in place for any instance of re-reporting of results from another laboratory.

3. AUTHORISERS OF REPORTS

Report authorisation is defined as the signing out of the report prior to issue by the person taking responsibility for the content of the report.

The authoriser must have appropriate professional registration and be deemed competent by departmental policies to release and take responsibility for the content of that report.

No signatures or named signatories are required on the report if this information is recorded within the individual laboratory's LIMS system that is issuing the report, however the report must indicate that authorisation has been given.

3.1 Competence

It is the responsibility of the Head of Laboratory to determine that any member of staff (including him/herself) is competent to authorise reports.

It is recommended that reports are categorised as standard/template based reports versus non-standard/non-template based reports. Competence to authorise reports may be for specific categories of report and/or for specific tests performed.

4. INTERIM/PRELIMINARY REPORTS

It may, in some circumstances, be useful to issue a report before all studies are complete (e.g. when indicative preliminary results have been obtained but a long delay is expected before the final results will be ready).

Interim/preliminary reports should be clearly marked as such and should be worded to avoid misinterpretation of their status.

The final report should always be issued to the requester.

5. ADDENDUM/REVISED REPORTS

It may be necessary to issue an additional/revised report which supersedes the initial report if further information becomes available e.g. details of a familial variant, further characterisation of an unclassified variant or if an error is identified in the original report.

An addendum/revised report should be 'stand-alone' and clearly identified as a revision, including reference to the date and patient's identity in the original report. The requester should be made aware of the revision. The revised report must state whether the report replaces or supersedes the original version and where it replaces the previous report the requester should be instructed to destroy the original report.

Results that have been revised should be retained by the laboratory in subsequent cumulative reports and be clearly identified as being revised versions.

6. DISCLAIMERS

No disclaimers (e.g. regarding correct samples/ family relationships) or statements about long term DNA storage are required in written reports.

Mention, only where appropriate, the possibility of errors due to factors beyond the control of the laboratory.

However, laboratories might wish to add a note of caution when reports are based on DNA samples or reports sent from another laboratory (particularly if the sample was obtained under research conditions).

7. REFERENCES WITHIN REPORTS

Selected references should be given when published data are key to assisting the interpretation (e.g. a missense variant), risk calculation or tandem repeat sequence reference ranges.

In general, references are necessary when the data are newly published or present information that is not widely known or accepted. Often patient leaflets are a good source of relevant clinical information and should be referenced where appropriate.

When different publications present conflicting data, it is important to specify which has been used as the basis for your interpretation.

References must be quoted in a format that allows the reader to easily identify the original article.

Where specific 'Best Practice' guidelines are available, it is recommended that reports reflect these guidelines, referencing them where appropriate.

8. REPORTING TIME TARGETS

All laboratories should endeavour to maintain adequate reporting times (see Appendix 1).

9. VALIDATION OF RESULTS FROM RESEARCH LABORATORIES OR PROJECTS

It is recommended that results of molecular genetic testing performed in non-accredited (e.g. research) laboratories are validated in an accredited clinical laboratory prior to their use in a diagnostic setting.

The validity of the research results with regard to interpretation (e.g. causative or VUS) should also be reviewed.

10. ARCHIVING AND STORAGE

Laboratories should follow all local and national guidance on Information Governance, Data Protection and Retention and Storage. Laboratories should ensure that all relevant clauses of ISO 15189 are met including Control of Records and Laboratory Information management; and that the requirements of The retention and storage of pathological records and specimens (5th Edition RCPath) are applied.

11. SOURCES

Association for Clinical Genomic Science (ACGS) Practice Guidelines for the Evaluation of Pathogenicity and the Reporting of Sequence Variants in Clinical Molecular Genetics, (2013).

Association for Clinical Genomic Science (ACGS) Practice guidelines for Targeted Next Generation Sequencing analysis and interpretation, (2015).

Association for Clinical Genomic Science (ACGS) ACGS Best Practice Guidelines for Variant Classification 2020

Richards S *et al:* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med (2015) May;17(5):405-24 . doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. PubMed PMID: 25741868.

Association for Clinical Cytogenetics: Professional Guidelines for Clinical Cytogenetics General Best Practice Guidelines (2007) v1.04

Association for Clinical Cytogenetics: Professional Guidelines for Clinical Cytogenetics. Haemato-oncology best practice guidelines (2007) v1.01.

Clinical Molecular Genetics Society: Best Practice Guidelines for reporting Molecular Genetics results (2011).

Medical Laboratories – Requirements for quality and competence (ISO 15189:2012).

Dalgleish R *et al*: Locus Reference Genomic sequences: an improved basis for describing human DNA variants. Genome Medicine 2:24 (2010).

The retention and storage of pathological records and specimens (5th edition) Guidance from The Royal College of Pathologists and the Institute of Biomedical Science (2015).

Gray KA, Daugherty LC, Gordon SM, Seal RL, Wright MW, Bruford EA. genenames.org: the HGNC resources in 2013. Nucleic Acids Res. 2013 Jan;41(Database issue):D545-52. doi: 10.1093/nar/gks1066. Epub 2012 Nov 17 PMID:23161694.

Oxford Desk Reference - Clinical Genetics. Firth HV and Hurst JA. 2017 2nd Edition Oxford University Press ISBN 9780199557509.

ISCN 2016 Ed Jean McGowan-Jordan, Annet Simons,Michael Schmid. Karger ISBN 978-3-318-05857-4.

Li, Marilyn M *et al*: Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer. The Journal of Molecular Diagnostics, Volume 19, Issue 1, 4-23.

Appendix 1

Genetic Laboratory Reporting Time Targets

All laboratories should endeavour to maintain adequate reporting times. All targets should be for 90% within the given reporting time target for any category.

NHS England (NHSE) have published TATs as documented in Table 1. Laboratories contracted by NHS England shall follow the turnaround times stipulated within the contract.

All reporting times are given in calendar days.

The reporting time targets are maxima and laboratories shall aim to report results as soon as practicably possible.

Day 0 is the day the sample is received into the laboratory with all appropriate information and all other required samples are received. This can also be the day that a specific investigation is activated if a request is made by a clinician for a test on a stored sample.
The end point of the test is measured when the results are available in an authorised state. This can be electronically stored and not yet sent out by the laboratory.

Table 1

Clinical Urgency	Category (mapping to test directory)	Sub-categories	Calendar Days	Examples
URGENT	**Ultra Rapid**	N/A	**3 days**	QF-PCR for rapid trisomy detection Urgent haemato-oncology FISH/RT-PCR PCR-based tests where the result is needed urgently for prenatal diagnosis
URGENT	**Ultra rapid**	NA	**7 days**	NIPT
URGENT	**Rapid**	Rapid	**14 days**	Microarray for prenatal / urgent postnatal (e.g. neonatal referrals) Urgent Haemato-oncology karyotyping Mutation specific molecular pathology tests Southern blot tests where the result is needed urgently for prenatal diagnosis PCR-based tests for predictive testing and confirmation of neonatal results
		Complex rapid	**21 days**	Urgent panels and exomes for relevant indications NIPD

NON-URGENT	**Standard**	Somatic Cancer	**21 days**	Standard HO karyotyping (e.g. MDS) NGS panels for HO referrals NGS panels for molecular pathology referrals Standard paediatric microarray Standard single gene and **small gene panel (<10 gene)** sequencing
		Rare Disease	**42 days (6 weeks)**	Known familial mutation testing Standard STR based analysis Postnatal karyotyping (e.g. fertility or familial microarray follow-up)
NON-URGENT	**Complex Standard**	Rare Disease	**84 days (12 weeks)**	**Large gene-panels (>10 genes)** or WES for standard referral indications
			Part a) 42 days (6 weeks)	**Expectation** for delivery of centralised WGS (from DNA sample receipt to return of vcf and/or filtered variants to GLH)
			Part b) 42 days (6 weeks)	Validation/reporting of centralised WGS results after receipt at GLH

Appendix 2

G- Banding Evaluation Score

At least three of the criteria to be obtained to apply banding scores 3-9

0	No banding
1	Identification of some chromosomes by morphology and major landmarks
2 POOR <300 band	Unequivocal identification of chromosomes due to major landmarks
3 300 band	2 dark bands on 8p (8p12 & 8p22) 3 dark bands on 10q (10q21, 10q23, 10q25) 20p12 visible 22q12 distinct
4 MODERATE 400 band	3 dark bands on mid-4q (q22-28) 3 dark bands mid-5q (5q14, 5q21, 5q23) 2 dark bands on 9p (9p21 & 9p23) 13q33 distinct
5 500 band	7q33 & 7q35 distinct 3 dark bands on 11p (11p12, 11p14, 11p15.4) 14q32.2 distinct 4 dark bands on 18q (18q12.1, 18q12.3, 18q21.2, 18q22)
6 GOOD 550 band	5q31.2 distinct 8p21.2 visible 2 dark bands on 11pter (11p15.2 & 11p15.4) 22q13.2 distinct
7 700 band	2p25.2 distinct 2q37.2 distinct 10q21.1 and 10q21.3 resolve 17q22-q24 resolves into 3 dark bands
8 EXCELLENT 850 band	4p15.31 & 4p15.33 distinct 5p15.32 distinct 11q24.1 and 11q24.3 distinct 19p13.12 and 19p13.2 distinct
9 900 band	11p14.1 visible 20p12.1 & 20p12.3 distinct 22q11.22 distinct 22q13.32 distinct
10	Banding Resolution higher than level 9 with additional bands to those seen at the 900bphs level (ISCN 2016)[3] seen consistently on both homologues.

Appendix 3

Minimum G Banding Score For Referral Reason

The recommended scores given below are defined as the **lowest standard acceptable** for a given reason for referral in constitutional analysis without issuing a qualified report.

	MINIMUM QUALITY G-Banding SCORE
Reason for referral	
Confirmation of aneuploidy e.g. direct lymphocyte, direct CV or solid tissue culture preparation	**2**
Exclusion of known large structural rearrangements. e.g lymphocyte, solid tissue, CVS direct preparation or amniotic fluid cell preparation	**3**
Identification and exclusion of small expected structural rearrangements e.g. lymphocyte, solid tissue, CVS culture or amniotic fluid preparation	**4**
Routine amniotic fluid and CV culture preparations	**4**
Abnormal ultrasound scan associated with AF, CV and solid tissue referrals	**5**
Blood referrals, not covered by exclusion criteria	**6**
For microdeletion syndromes (when no FISH probe is available and microarray testing not possible)	**7**

Sub-optimal quality / request for repeat samples

If analysis does not meet the minimum quality for the referral reason and no abnormality is detected, the report shall be qualified. When appropriate, the clinician should be invited to send a repeat sample.