

General Genetic Laboratory Reporting Recommendations

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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 Genetic 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, 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 typed, word-processed or created by computer.

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.

Ideally reports should fit onto one page. For any additional pages there must be patient identifiers. All reports must include pagination (e.g. page 1 of 5).

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

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 genetic 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 according to UKAS guidelines, if applicable.

2.4 Patient and Sample Identification

Patients must be identified on reports by at least two unique items of information e.g. full name and date of birth. It is recommended that the patient gender is also identified on the report.

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

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 mutation, investigation of inheritance of a genetic abnormality, in 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.

For infant samples labelled 'Baby <Family Name>', it is important to include the sex and date of birth of the infant as samples from future siblings may also be identically labelled.

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

2.5 Results and Interpretation

2.5.1 Correct and appropriate nomenclature

Nomenclature must be meaningful, unambiguous and consistent.

Karyotype designation should use correct current ISCN nomenclature where practicable. The use of 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.

Mutation nomenclature must be based on the Human Genome Organisation (HUGO) standard mutation nomenclature and Human Genome Variation Society. The use of HGVS nomenclature can be problematic for describing exon deletions/duplications (particularly where endpoints are unknown) and triplet repeat expansions. Therefore such mutations should be described in words rather than HGVS nomenclature.

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

The genome build should be included where this is pertinent to the interpretation of any results.

Genomic coordinates or an appropriate reference sequence should be included with additional notes for interpretation if necessary e.g. "base 1 = the A of the ATG translation initiation codon" shall be added where the numbering of the reference sequence starts elsewhere. Locus Reference Genome (LRG) sequences provide a stable genomic DNA framework for reporting mutations with a permanent identity and core content that never changes, thereby allowing consistent and unambiguous reporting of variants in clinically relevant loci. If a LRG is published then it is suggested that this is used as it can minimise the risk of misinterpretation of exon numbering (www.lrg-sequence.org/).

For triplet nucleotide repeat disorders, a clear key including the size ranges for normal, intermediate/premutation, and affected individuals must be included, with a reference for this information.

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

A clear 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

Any technical details relevant to interpretation 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.

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.

2.5.6 Clinical interpretation

The report must provide a full and clear interpretation of genetic 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 genetic 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 use of the terms 'positive' and 'negative' in relation to mutation status is not recommended but must be clearly defined if used.

In the context of a mutation, the term 'carrier' or 'carrying a mutation' 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 mutation 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 mutations are detected in a child, then confirmatory carrier testing of the parents (to exclude the possibility that both mutations 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 sex of the individual 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 unclassified variants (VUS)

When reporting unclassified variants, current guidelines must be followed (e.g. ACGS Practice Guidelines for the Evaluation of Pathogenicity and the Reporting of Sequence Variants in Clinical Molecular Genetics, (2013)).

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 mutation has been clearly linked to prognosis in large published series – or is classified in clinical trials - 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 obtained 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 2013). 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 (Firth HV and Hurst JA. 2005) 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.

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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 whole exome and whole genome sequencing

When reporting results from whole exome sequencing (WES) and whole genome sequencing current guidelines must be followed (e.g. ACGS Practice guidelines for Targeted Next Generation Sequencing, Analysis and Interpretation, (2014)).

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 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 must send the referral laboratory the report to file and 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.

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.

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.

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 familial mutation, 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

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

It is not considered necessary or desirable to mention the possibility of laboratory error or sample mislabelling on every report. 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

References must be given when published data have a bearing on the interpretation (e.g. a missense mutation) or risk calculation.

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 should 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

The OECD Guidelines for Quality Assurance in Molecular Genetic Testing (2007) recommend that results of molecular genetic testing performed in non-accredited (e.g. research) laboratories should be confirmed in an accredited laboratory.

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 ISO15189 section 4.13 standards for the control of records and other available guidelines e.g. from the Royal College of Pathologists

11. SOURCES

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

Association for Clinical Genetic Science (ACGS) Practice guidelines for Targeted Next Generation Sequencing analysis and interpretation, (2014).

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).

Clinical Molecular Genetics Society: Professional Guidelines for Reporting Times (26th Oct 2012).

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

Best practice guidelines on reporting in molecular genetic diagnostic laboratories in Switzerland; SGMG (2003).

Clinical Pathology Accreditation (UK) Ltd: Standards for the Medical Laboratory v2.02 (Nov 2010).

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OECD Guidelines for Quality Assurance in Molecular Genetic testing; OECD 2007.

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).

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ISCN 2013 Ed Lisa G Shaffer, Jean McGowan-Jordan, Michael Schmid. Karger ISBN 978-3-318-02253-7.

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Genetic Laboratory Reporting Time Targets

All laboratories should endeavour to maintain adequate reporting times (see Table 1). However it is recognised that the changes to reporting time measurement from working days to calendar days may affect the ability of some laboratories to meet all the expected turnaround times immediately. Therefore it is recommended that the reporting times stated in Table 1 are implemented by April 2016.

All targets should be for 90% within the given reporting time target for any category.

It is recognised that local clinical need may influence the reporting times for non-urgent work.

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. For samples transferred between local molecular and cytogenetic laboratories within the same organisation, day 0 is the date of initial sample receipt (e.g. for microarray testing, where DNA is extracted by the molecular laboratory and arrays are performed by the local cytogenetic laboratory within the same organisation, the time taken for DNA extraction is included within the reporting time target).

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

Reporting Time Target (calendar days)	Definitions
3 days	Rapid aneuploidy QFPCR/PCR/FISH testing for prenatal, postnatal or oncology referrals Rapid PCR/FISH testing for haemato-oncology referrals PCR-based tests where the result is needed urgently for prenatal diagnosis
10 days	Karyotype for urgent postnatal blood referrals
14 days	Karyotype results for prenatal referrals Karyotype results for urgent haemato-oncology referrals* Microarray results for prenatal referrals and urgent postnatal Southern blot tests where the result is needed urgently for prenatal diagnosis PCR-based tests for predictive testing and confirmation of neonatal results.
21 days	Karyotype results for routine haemato-oncology referrals
28 days	Karyotype results for routine postnatal blood referrals Routine testing of solid tissue referrals Microarray results for postnatal referrals Non-urgent PCR-based tests where the familial mutation is known, specific mutation tests, or gene tracking by microsatellite analysis
56 days	Mutation screening or tests that require Southern blot analysis Next generation sequencing panels of ≤10 genes
112 days**	Next generation sequencing panels of >10 genes** and other large scale sequencing work e.g. WES and WGS

*A diagnostic FISH or PCR result is adequate in this category, with confirmatory cytogenetics treated as for routine referrals.

**Temporary category to account for longer reporting times during implementation of new technology.