

# Draft Best Practice Guidelines for Reporting Molecular Genetics results

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## **Introduction**

These guidelines are intended as a reference tool for points to consider when writing reports which describe the results of molecular genetic analysis, and should be used within local reporting arrangements (e.g. within a local laboratory and associated clinical departments).

They are based upon the 'Best practice guidelines on reporting in molecular genetic diagnostic laboratories in Switzerland; SGMG (2003) and overall scheme reports from 2006-2010 from the UK National External Quality Assessment Service (UKNEQAS).

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

## **General format**

Reports must be clear, concise, accurate, fully interpretative, and authoritative.

The overall result or conclusion should be clearly visible (e.g. in bold or large text).

Reports should be typed, word-processed or created by computer. Hand-written reports may be misinterpreted when the author's script is poorly legible, and are likely to appear unprofessional and lack authority.

Increasing numbers of laboratories have access to integrated laboratory computer systems. These often have reporting modules which simplify report writing by using automatic text. Careful thought needs to be put into setting these systems up so that the text is accurate, appropriate and applicable to large numbers of reports. However, it remains important to have a facility to edit automatic text as amendment is often required to tailor reports to a specific case.

The page number (if greater than 1) and total number of pages should be indicated. Ideally reports should fit onto one page. However if additional pages are necessary then all patient identifiers must be present on each page (as individual pages could become detached).

## **Recipients of reports**

The name and address of the referring clinician/referral unit and recipients of copies should be clearly indicated.

Reports should only be sent to appropriate clinicians with copies to others as requested by the referring clinician. Reports should be sent to the local laboratory (e.g. NHS regional genetics laboratory) in cases where the analysis is performed out of region and the laboratory has requested the test.

Reports will be stored in patient files and therefore may be seen by other related health professionals caring for a patient and not just the initial referring clinician, therefore the clinical conclusion of reports should be understandable by medical professionals who may have little background in genetics.

Reports should not be sent directly to patients, although the referring clinician may provide the patient with a copy.

Due to the sensitive nature of molecular genetics reports, care must be taken in issuing and archiving reports. All laboratories must comply with applicable law and regulations, including those concerning the confidentiality of information (OECD guidelines, 2007).

### **Laboratory Identification**

The laboratory issuing the report should be clearly identified, with full contact details. The report should carry a title (e.g. results of molecular genetic analysis) and be dated.

The report should indicate who has written and authorised the report, including their job title/professional registration. It is recommended that reports are signed by at least two individuals.

The accreditation status of the laboratory should be indicated, if applicable.

### **Patient Identification**

Patients should be identified on reports by at least two items of information e.g. full name (initials are not recommended) and date of birth.

Inclusion of laboratory accession number and NHS number is strongly recommended to ensure that the report unequivocally links to that specific patient.

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

Care should be taken when dealing with prenatal samples (e.g. chorionic villi and amniocentesis) to ensure it is clear that the results pertain to the foetus and not the mother. The mother's date of birth should be included and the date the prenatal sample was collected (or, if date of collection not known, date of arrival in the laboratory). This will identify the prenatal sample if multiple samples are taken from one pregnancy and if the mother has prenatal samples taken for different pregnancies.

In addition for samples labelled 'Baby <Family Name>', it may be important to include the sex and date of birth of the infant in the main body of the report, as samples from future siblings may also be identically labelled.

For simplicity we recommend that individuals tested are referred to as the 'patient' within the interpretation text.

The sample type and date of receipt in the laboratory should be indicated.

### **Restate the clinical question being asked**

The interpretation of molecular genetics results depends entirely on the context. Therefore, reports should explicitly restate the clinical question being asked (or if the referral form is ambiguous, what the question is that the report is answering). This usually comprises at least the following three elements:

1. The disease/marker being tested (e.g. fragile-X syndrome, cystic fibrosis)
2. The request being made (e.g. diagnostic confirmation, carrier status)
3. The indication as to why the request is being made (e.g. developmental delay, known family history)

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

### **State the tests being used**

Include brief technical details about the tests performed and their limitations (e.g. exons screened for deletions in DMD, CF mutation spectrum). This information is important when a different laboratory is testing relatives of your reported patient and when testing procedures have changed over time.

The sensitivity of the tests (i.e. the proportion of affected individuals likely to be detected) should be provided. This may be influenced by information supplied on the referral form (e.g. ethnic/geographical information for CF or other recessive disorders). Again, this is particularly important when reporting negative results. It might be useful to provide references to support sensitivity estimates when appropriate, and if available.

If the testing is incomplete (e.g. for a gene screen when there is insufficient DNA), the percentage covered (and/or missing codons/exons) should be included.

If commercially available kits are used then the manufacturer, kit number and version should be included.

## **Presentation of results**

Results should be represented in a brief unambiguous form and separately from any text describing their interpretation.

The results should include sufficient precise data to be fully interpretable to other laboratories.

The interpretation of the results of the analysis should be clearly stated e.g. no mutation detected, two normal alleles (where clearly resolved), heterozygous/homozygous. If part of the analysis was performed by another laboratory this should be indicated on the report

Nomenclature should be meaningful, unambiguous and consistent. Mutation nomenclature should be based on the HUGO standard mutation nomenclature (den Dunnen & Antonarakis SE, et al 2001)(HGVS web site, www.HGVS.org). However the use of HGVS nomenclature can be problematic for describing exon deletions/duplications (particularly where endpoints are unknown) and triplet repeat expansions. If alternative or common traditional nomenclature is used, it should be referred to as such and the HGVS equivalent, if appropriate, also included.

The GenBank Accession number and version of the gene reference sequence used should be included with additional notes for interpretation if necessary e.g. "base 1 = the A of the ATG translation initiation codon" should be added where the numbering of the reference sequence starts elsewhere.

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

### ***Family studies***

A table can convey complex information much more concisely than text. This format is particularly 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. The diagram should include sufficient information to unambiguously identify the family (include family/ pedigree number) and to distinguish each relevant person. It is preferable to attach names to individual symbols on the pedigree diagram. Alternatively a numbering system can be used with a key supplied in the main report (care must be taken to ensure that individuals can still be identified in the event that the pedigree diagram becomes detached from the main report). The pedigree diagram should have a date of issue.

Pedigree diagrams should include only those individuals relevant to the interpretation. The confidentiality of information about relatives of the patient being reported must be a consideration.

Where pedigree diagrams display linked-marker haplotypes, the marker order presented should accurately reflect marker order on the chromosome e.g. from pter to qter or 5' to 3' within a gene as appropriate.

Include a key to any nomenclature used.

## **Interpretation**

The report must provide a full and clear interpretation of molecular genetic test results. Reports are destined to be read by a variety of professionals involved in the care of the patient, many of whom will be unable to fully interpret genotyping results.

Guidance should be sought from the latest disease-specific best practice guidelines, if available.

In order to provide a full interpretation, genotyping results must be reviewed in the context of relevant clinical and family information supplied at referral. 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 (e.g. CF)
- Other laboratory investigations (e.g. CPK results in DMD, chromosome results in PWS/AS, CHRPE status in FAP etc).
- Unusual or suspicious clinical picture (e.g. fetal echogenic bowel in CF).

In restating family information, issues regarding personal privacy should be kept in mind, particularly when including the names of other family members. It is recommended that names of other family members are not

included, unless they are pertinent to the report (e.g. partner for an autosomal recessive disorder, or parents when determining the inheritance of a mutation).

In the case where no mutation is detected, it is important to provide the sensitivity of the testing performed (i.e. the proportion of affected individuals likely to be detected). It may be relevant to include a statement such as 'We have confirmed the presence of the familial xx gene mutation in a DNA sample from an affected family member'.

### **Calculation of genetic risks**

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

### **Answer the questions in clear and concise text**

The final answer to the clinical question is a statement of the interpretation of the genotyping results taking into account any appropriate additional information supplied.

This can usually be expressed in simple concise statement. (e.g. "*This patient shows no evidence of a fragile-X expansion.*", "*This patient is a CF carrier.*").

Many laboratories highlight this statement (bold, underline, large font, text in a box etc) and therefore this statement must be accurate and not open to misinterpretation:

e.g. "*no evidence for a diagnosis of fragile-X*" might be more accurate than "*diagnosis excluded*", "*low-risk of being/unlikely to be a carrier*" might be more accurate than "*not a carrier*", "*normal-sized allele detected*" might be more appropriate than "*no pathogenic expansion detected*"

The use of the terms 'positive' and 'negative' in relation to mutation status are discouraged as these may be misinterpreted.

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

In a diagnostic referral, if no mutation has been detected it is recommended to state that the 'likelihood of a diagnosis is reduced', or if the clinical diagnosis is certain then 'this result does not confirm a diagnosis of XXX'

### **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.

### **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.

### **Prenatal diagnosis**

The Joint Committee on Medical Genetics (JCMG) recommends that for prenatal diagnosis for X-linked and autosomal recessive conditions, the genotype (and hence carrier status) of the foetus should at all times be reported to the referring clinician and their patient (JCMG, 2007).

### **Reporting unclassified variants (UV)**

When reporting unclassified variants, the CMGS "Practice guidelines for the interpretation and reporting of unclassified variants in molecular genetics, 2008" should be considered.

If no clear diagnosis can be made from the evidence available this must be clear in the report.

### **Further tests and/or information**

If applicable, further molecular tests may be indicated which could be undertaken to improve the accuracy or scope of the interpretation. This may include tests for additional disorders or additional tests to more fully investigate the disease in question (e.g. floppy baby – testing for SMA, PWS and DM1 may be appropriate).

If the additional tests suggested are not performed "in-house", it may be appropriate to suggest alternative specialist laboratories. It may be important to state that no further testing is planned.

When further testing involves other specialities (e.g. *cytogenetics, biochemistry*), it may be appropriate to include a suggestion that the referring clinician will need to contact the laboratory directly to establish sampling requirements etc.

Suggest any other information or testing which could be supplied or arranged by the referring clinician which might improve the accuracy of your interpretation (e.g. *arranging testing of the index case in a family to confirm a diagnosis or to determine which mutations are present, details of ethnicity, testing of other family members to help ascertain the status of an unclassified variant (UV)*).

### **Genetic counselling recommendations**

Where it is stated on a report that DNA testing can be offered to other family members, it is recommended that genetic counselling should be offered (or referral to clinical genetics is recommended). As reports may be passed to clinicians other than the referring clinician, it is recommended that this is stated on all such reports, even when the referring clinician is a Consultant Clinical Geneticist.

### ***For cases referred from non-genetics specialities***

When a genetic diagnosis is determined in an index case, it may be appropriate to advise referral of the patient and their family for genetic counselling.

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 e.g. for an autosomal dominant disorder 'if this patient has children then they will be at 50% risk of inheriting this mutation and developing xx'.

### **Authorisers of reports**

The report must identify the individual approving the report and the date of issue of the report. The authoriser must be deemed competent to approve the report.

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

### **Addendum reports**

It may be necessary to issue an additional report which supersedes the initial report if further information becomes available e.g. details of familial mutation, further characterisation of an unclassified variant.

An addendum report should be 'stand-alone' and may recommend destruction of the initial report (which is now invalid).

### **Reporting multiple patients**

Each *unrelated* patient should be reported on a separate and unique document since the reports will ultimately be filed in individual patient or family files. In the case of child with a de novo mutation, where parents have been tested, it is appropriate to mention the parental results in the child's report.

For linked-marker studies which only make sense in the context of alleles inherited by several family members, the report must include multiple family members (usually with a pedigree diagram). It is recommended to restrict the number of individuals reported to only those essential for accurate analysis.

For carrier testing for a couple it is recommended that separate reports are issued, with each indicating the name and date of birth of the current partner and the conclusion that the 'risk that this couple will have a child affected with disease (e.g. CF) is 1 in xx"

### **Validation of results from research laboratories**

The OECD Guidelines for Quality Assurance in Molecular Genetic testing 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 UV) should also be reviewed. We recommend this is only performed where there is a clear, published association between the gene and clinical disorder.

### **Disclaimers**

Mention, where appropriate, the possibility of errors due to factors beyond the control of the laboratory (e.g. *the risk of "non-paternity" and the need for family relationships and clinical information as stated on the referral forms being correct*).

It is not considered necessary or desirable to mention the possibility of laboratory error or sample mis-labelling 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).

### **References**

References should be given when published data have a bearing on the interpretation (e.g. a missense mutation) or risk calculation. In general references are only necessary when the data are newly published or present information that is not widely known or accepted. When different publications present conflicting data, it is important to specify which has been used as the basis for your interpretation.

Include enough information to allow the reader to obtain the reference themselves, e.g. Rousseau et al. *Am. J. Hum. Genet.* **55**: 225 (1994), rather than just Rousseau *et al.* (1994).

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

### **Sources**

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)

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