



Association for
Clinical Cytogenetics

PROFESSIONAL GUIDELINES FOR CLINICAL CYTOGENETICS

POSTNATAL BEST PRACTICE GUIDELINES (2007) v1.01

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1 INTRODUCTION

These guidelines should be used in conjunction with the Professional Guidelines for Clinical Cytogenetics: General Best Practice Guidelines (2007).

Professional guidelines for Cytogenetics laboratories incorporate the standards imposed by regulatory bodies (Clinical Pathology Accreditation (CPA) [1] and by statute (Clinical Governance) while taking into account current practice in the U.K.

Elements of the service not subject to statute may be varied in order to comply with local constraints and agreements. It must be noted that these guidelines are minimum requirements and that professional judgement is of paramount importance for many circumstances.

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

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

For prenatal testing using Fetal Blood Samples (FBS) also refer to Professional Guidelines for Clinical Cytogenetics: Prenatal Diagnosis Best Practice Guidelines (2005)

2 GENERAL

2.1 Reporting times

Reporting times given refer to the issue of the final report, and shall include documented authorisation by an appropriately trained and qualified clinical scientist, and completion on a departmental computer system in a form protected from revision.

Reporting times should be auditable.

2.1.1 Reporting Time Targets

	Calendar days to report	% Within guidelines
Urgent Bloods	10	95%
Routine Bloods	28	95%

2.2 Culture success rate

Overall success rate should be no less than 97.5%.

2.3 Urgent referrals

Blood samples submitted for constitutional chromosome analysis shall be prioritised according to urgency. The following referrals should be classified as urgent:

- Patient presenting in pregnancy with family history of chromosome abnormality
- Indeterminate gender at birth
- New born babies with a suspected chromosome abnormality
- Parents of a structural abnormality or unusual variant, found during prenatal diagnosis
- Request for a specific clinical need
- Fetal blood (associated with prenatal diagnosis)

Methods should be used to ensure that results are available to the appropriate clinician/department as soon as possible after authorisation (e.g. by using telephone or secure electronic methods such as secure fax). There shall be compliance with legal requirements and constraints applicable to the communication of confidential information. (e.g. Health Service Circular HSC/1998/153 etc).

2.4 Sample rejection

It is acceptable to reject samples that are in unsuitable blood tubes. The report should inform the referring clinician of the error and request a repeat sample in the correct tube. Urgent blood samples, sent in EDTA tubes, should be processed. Laboratories should have a protocol for the processing of EDTA samples.

2.5 Quality

Minimum acceptable quality for referral reason

Refer to Professional Guidelines for Clinical Cytogenetics: General Best Practice Guidelines (2007)

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.

2.6 Repeating previously analysed samples

Previously analysed referrals shall be repeated if the previous analysis was not to the current minimum quality standard.

2.7 Additional testing

Cases referred with features that are **strongly suggestive** of specific conditions should be considered for investigation by supplementary techniques. In some cases, the referring clinician should be contacted to discuss appropriateness of testing, or a recommendation for further testing should be included in the report.

2.8 Referral to molecular genetics

The laboratory should have a documented policy for dealing with referrals where molecular genetic testing is more appropriate.

2.8.1 Investigation for uniparental disomy (UPD)

All laboratories shall have a clear written policy on the application of UPD studies in a postnatal setting. This policy should be produced in consultation with the appropriate Clinical Genetics/Molecular Genetics Department.

Recommendation for UPD testing should be considered:

- In conditions where UPD is an established cause.
- When a structural abnormality / marker chromosome that involves a known imprinted region is identified in a patient with an abnormal phenotype.

3 ANALYSIS

3.1 Analysis definitions

Standard analysis shall be of a minimum of two metaphases and shall consist of every pair of homologues being cleared in full at least twice at the minimum quality level appropriate for the referral reason. It is recognised that additional cells of varying quality may be examined in the analysis process without affecting the overall case quality score. Independent checking is an essential part of the analytical process. A minimum of one further cell shall be analysed by the checker, using other cells when obscured regions of the karyotype need to be clarified, so that every pair of homologues is analysed at least once at the minimum quality level appropriate for the referral reason. In the checking of mosaic cases, one cell shall be analysed from each cell line.

The case quality is defined as the analysis quality of the minimum number of analysed and checked cells necessary for the reason of referral. Additional cells may be of a lower quality without altering the overall case quality score.

Either the analyst or checker shall be a registered clinical scientist (cytogenetics modality).

3.2 Mosaicism

If a single cell abnormality which could be clinically significant is identified during analysis, or potential mosaicism is suspected at referral, the abnormality should be excluded in a mosaicism screen of at least 30 cells.

A request for a second tissue may be appropriate when dealing with conditions which may have tissue specific mosaicism.

3.3 Female age related x chromosome loss

Sex chromosome mosaicism at, or below, the age related level should be interpreted on a case-by-case basis, taking into account the abnormality detected, the reason for referral, the age of the patient and published data (Gardner and Sutherland, 2004). On this basis, if

the mosaicism is interpreted as of no clinical significance, it should not be reported to the clinician.

3.4 Constitutional FISH analysis

Refer to Professional Guidelines for Clinical Cytogenetics: General Best Practice Guidelines (2007)

Checking should be carried out either on a raw image that has not been subject to enhancement, or down the microscope.

3.4.1 Minimum FISH Analysis Recommendation:

Metaphase FISH

A total of **5** cells should be analysed, of which **2** should be checked

Interphase FISH

	Total number of nuclei examined	Analysis (nuclei examined)	Check (nuclei examined)
Aneuploidy	30	20	10
Microduplication/microdeletion	15	10	5

A slide screening method should be employed to ensure that the analysis and check are performed on different nuclei. Alternatively, potential screening overlap can be circumvented by the 'total number of nuclei' being examined at both the analysis and check.

Depending on the quality of the preparations, higher numbers may be necessary to achieve a reliable result

3.5 Characterisation of ESACS (extra structurally abnormal chromosomes)

ESACS (extra structurally abnormal chromosomes) should be further investigated by appropriate methods and parental samples should be requested to determine inheritance.

4 REPORTING

When multiple cytogenetics techniques have been used, a single combined report should be produced whenever possible

All reports shall include:

- karyotype designation using current correct ISCN nomenclature where practicable
- the types of analysis used (eg. karyotype, FISH, CGH, special types of banding, QF-PCR, MLPA, etc).
- a clear written description of the karyotype result.
- when appropriate, a recommendation of referral to Clinical Genetics.

The report of an abnormal case shall include the following:

- karyotype designation using correct current ISCN nomenclature where practicable
- a clear written description of the abnormality, and whether the karyotype is balanced or unbalanced
- the name of any associated syndrome
- methods used in establishing the result
- clinical interpretation to include (as appropriate):
 - a. whether the cytogenetics result is consistent with the clinical findings, and/or an indication of the expected consequences of the abnormality
 - b. request for follow up of family members at risk of the same or related abnormality, starting with closest available relatives
 - c. an assessment of risk/recurrence
 - d. recommendation for consideration of prenatal diagnosis in future pregnancies
 - e. onward referral for genetic counselling

Where appropriate reports may include:

- citation of relevant literature
- consideration of reference to patient support groups acceptable to the local Clinical Genetics Department.

4.1 Risk assessment

Reproductive risks should take into account:

- mode of ascertainment of the family.

- personal segregation analysis from family history, if available.
- the predicted type of segregation leading to potentially viable gametes.
- the sex of the transmitting parent.
- haploid autosomal length of imbalance(s) with potential viability.
- review of literature describing viability for the specific imbalance(s), and/or established empirical risk figures.

Risk assessments should not give a false sense of precision but where there is well-established risk information from published data, specific figures can be used and the literature cited.

4.2 Reporting of variants

Well-documented polymorphic variant chromosomes may not require reporting or family follow up (Gardner and Sutherland 2004). Examples of variants that need not be mentioned in the report are:

- pericentric inversions with the breakpoints in the heterochromatic region, such as: $inv(1)(p11q12)$, $inv(1)(p12q12)$, $inv(9)(p11q12)$, $inv(9)(p11q13)$, $inv(16)(p11q11)$.
- heterochromatic size variants, including $1qh+$, $9qh+$, $16qh+$, $Yqh+$, Yqh^- ,
- acrocentric short arm variants resulting from the Yq heterochromatin translocation and satellited Y chromosome
- Acrocentric short arm variants, with the exception of cases in which further investigation of the possible involvement of euchromatin is required.
- fragile sites, excluding FRAXA and FRAXE.
- pericentric inversions that have been described as presumed harmless variants (Gardner and Sutherland, 2004); $inv(2)(p11.2q13)$, $inv(3)(p11q11)$ $inv(3)(p11q12)$, $inv(3)(p13q12)$, $inv(5)(p13q13)$, $inv(10)(p11.2q21.2)$
- $inv(Y)(p11q11)$.
- G-band euchromatic variants of 8p23.1, proximal 9p, insertion of euchromatin into 9qh, proximal 9q, 15q11.2 and 16p11.2.

It is recognised that specific clinical situations may require further laboratory investigations and/or family studies to enable clarification and certainty of coincidental status of these findings; this is subject to professional judgement.

5 RETENTION, STORAGE AND DISPOSAL

Laboratories should comply with relevant guidelines regarding consent for testing, storage and disposal of material including: -

- Royal College of Pathologists Retention and Storage of Pathological Records and Archives (3rd edition 2006)
- Statutory requirements of Human Tissue Authority
See: Consent and Confidentiality in Medical Genetics Practice (April 2006) prepared by Joint Committee of Medical Genetics.

6 REFERENCES

ACC Professional Guidelines in Clinical Cytogenetics 2007;
www.cytogenetics.org.uk.

Gardner R.J. and Sutherland G.R. Chromosome Abnormalities and Genetic Counselling, Third Edition, Oxford University Press, 2004.

7 Version Control

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03/09/2007	Postnatal Best Practice Guidelines 2007 v1.01	updated referencing between ACC Best Practice Documents	Postnatal Best Practice Guidelines 2007
	Previous versions		
07/03/2007	Postnatal Best Practice Guidelines 2007		No previous document

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