PROFESSIONAL GUIDELINES FOR CLINICAL CYTOGENETICS AND CLINICAL MOLECULAR GENETICS

QF-PCR FOR THE DIAGNOSIS OF ANEUPLOIDY BEST PRACTICE GUIDELINES (2007) v2.01

December 2007
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Guidelines updated by S. Hamilton and K. Mann in consultation with the QF-PCR
email users group (meeting held 05/02/07).

Circulated and approved by all ACC Heads of Department and ratified at ACC Council
on 04/09/07.
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 UK. 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. In addition the use of ‘acceptable’ highlights an area where more than one approach is satisfactory and ‘unacceptable’ indicates areas where the quality of the service may be compromised.

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

The use of QF-PCR analysis of short tandem repeats (STR) for the detection of aneuploidy has since been validated and successfully applied for the rapid diagnosis of prenatal aneuploidy by a number of UK and European labs. The rapid result may be followed by full karyotype analysis of cultured cells.
2 SERVICE OVERVIEW

The testing of prenatal samples may be complicated by limited sample quantity, variable sample quality, mosaicism and maternal cell contamination. The processing of a number of prenatal samples requires stringent quality control measures to minimize the risk of sample mix-up. These aspects of prenatal diagnosis are taken into account in these guidelines.

Both cytogenetic and molecular genetic support should be sought for validation and implementation of a rapid aneuploidy diagnostic service by QF-PCR. Testing for trisomies 13, 18 and 21 should be routinely carried out. It is acceptable to test for sex chromosome aneuploidy in only a subset of referrals indicating a likely sex chromosome abnormality; the extent of sex chromosome testing carried out is decided at a local level in consultation with clinicians and other relevant groups.

In line with the National Screening Committee guidelines, 95% of samples should receive reports within 3 working days following sample receipt, as described in the report on Quality Management for screening page 110, which can be found at: (http://www.leeds.ac.uk/hsphr/nuffield_publications/documents/screening.pdf)
3 SAMPLE PREPARATION

As cell cultures may need to be established for karyotype analysis, only a proportion of the sample is available for QF-PCR aneuploidy testing in many cases.

Sample preparation (cleaning of Chorionic Villus samples and aliquoting of amniotic fluid samples) should be carried out accordance with good laboratory practice including no pre-labelling of vessels and the processing of only one sample at any one time.

Protocols should minimise the risk of sample mix-up. All tube-tube transfers should be checked by a second individual and the identity of samples shown to have an abnormal result should confirmed before results are issued. This can be done by in a number of ways, including analysis of a maternal DNA sample to confirm sample identity, a second assay on the original sample, or an interphase FISH test.

3.1 Amniotic Fluid Samples (AF)

Generally between 0.5 and 4 ml (or 1/10 of the sample) is used for QF-PCR analysis, though it is noted that the larger aliquot sizes suggested may compromise subsequent karyotype analysis, particularly for early gestation/small samples. The size of the aliquots taken routinely from samples is a local decision. All samples should be tested regardless of sample size/volume.

3.2 Chorionic Villus Samples (CVS)

For chorionic villus samples (CVS), an aliquot of dissociated villi (either digested or finely chopped) representing different regions of the sample should be processed in order to minimise the risk of misdiagnosis due to confined placental mosaicism (see Mosaicism section below). Such dissociated samples are likely to represent both cytотrophoblast and mesodermal tissue.

This is a relatively new method and data on the incidence of mosaicism is still being collated. In view of this, it is considered to be acceptable to continue to use the previous method of independently processing at least two small undissociated chorionic villi fronds taken from different regions of the biopsy, although care must be taken to ensure the majority of the sample is not comprised of villus tips.
3.3 Maternal Blood Samples

Maternal blood samples can be used to determine the fetal genotype in cases of maternal cell contamination in a prenatal sample, to confirm the identity of samples with abnormal results and occasionally to predict the clinical significance of anomalous results. It is a local decision whether maternal blood samples are requested with all prenatal samples or for individual cases.

3.4 Neonatal Blood Samples

Neonatal blood samples referred for trisomy 13, 18, 21 and sex chromosome testing can be tested by QF-PCR to provide a rapid result. The referral types for which testing is offered is a local decision.
4 DNA EXTRACTION

Any method must be fast, require a minimal number of tube-tube transfers and produce a standard quality of DNA, even from small samples that is reliable for use in PCR multiplex assays.

5 PCR REACTION

Commercial QF-PCR assays or commercial buffers (Abgene buffer/Qiagen multiplex buffer) suitable for multiplexing several primers are used for the PCR amplification. Laboratories using in house assays may prepare kits in advance by the addition of primers and H2O aliquoted into individual tubes. Batch testing of kits should be carried out using at least a trisomy and a normal DNA sample to ensure consistent assay quality and trisomy diagnosis.

A H2O control must be included in each PCR set-up to identify any DNA or PCR product contamination. It is acceptable to use DNA controls (trisomy or normal) with each PCR run in order to monitor variation between runs, but these are not necessary to validate the dosage results; the dynamics of an individual PCR will vary due to differences in DNA concentration/contaminants and therefore the quality of each result should be assessed independently (see analysis).

Post-PCR clean-up is not necessary.

5.1 Assay Design

A minimum of 4 markers should be tested for each chromosome. A lower number of Y specific markers is acceptable where testing for the sex chromosomes is carried out. Markers currently used by the service labs (2006/2007) are listed in appendix 1.

Basic principles of multiplex design should be followed in designing assays, including primers > 22 bp in length and avoidance of homology to repetitive DNA, SNPs and primer-dimer interactions by sequence comparison. Tri/tetra/penta/hexanucleotide repeat markers should be used as these have fewer stutter peaks, although it is acceptable to use dinucleotide repeat markers if few suitable markers are available within the tested region. All markers should have high heterozygosity within the population being tested. New markers not used previously for QF-
PCR aneuploidy diagnosis should be validated by testing a minimum of 100 chromosomes, including aneuploid samples.

5.2 PCR Programme

To ensure the reaction remains in the semi-quantitative phase, 24-26 PCR cycles should be carried out as standard practice. It is acceptable to use a higher number of PCR cycles if the normal number of cycles consistently gives low amounts of product as long as the assay is validated for that cycle number and both trisomy and normal controls show correct allele dosage ratios for all markers.

The annealing temperature should be set as low as is practical to minimise the effect of primer site polymorphisms.
6 ANALYSIS

6.1 Genetic Analysers

A genetic analyser capable of 2 bp allele resolution and peak area/peak height quantification should be used. ABI 310, 3100, 3130, 3700 and 3730 models (POP4/POP6/POP7/D matrix/G5matrix) and Beckman Coulter CEQ8000 (LPA1 gel) analysers have been used by service labs.

To ensure the quality of the data, minimum and maximum peak heights in accordance with the genetic analyser’s specification must be observed (eg. for the ABI 3100 markers with peaks above 6000 arbitrary fluorescence units should be excluded from analysis).

6.2 Interpretation of QF-PCR products

Both the electrophoretogram and peak measurements, which can be transferred to a spreadsheet for convenience, should be used for analysis. It is acceptable to use peak height, peak area or both measurements to calculate allele ratios, although for results obtained from an ABI genetic analyser it is peak area should be used to minimise the peak distortion caused to widely-spaced alleles. The use of POP4 polymer may result in reduced allele resolution in such cases peak height may be of additional use.

The area/height of the shorter length allele should be divided by that of the longer length allele to provide the allele ratio.

It is acceptable to fail individual markers if valid technical reasons such as electrophoretic spikes or bleed-through between colours are present on the electropheretogram.

If dinucleotide repeat markers are used care must be taken with analysis of stutter patterns. Dinucleotide repeat markers with alleles separated by 2 bp should not be analysed, as stutter peaks are incorporated into the shorter length allele and may misrepresent allele ratios. For alleles separated by more then 2 bp, it is acceptable to include stutter peaks areas in ratio calculations.
6.2.1 Interpreting allele ratios

The ranges outlined below allow for preferential amplification of the shorter length allele, which may be considerable if alleles are widely separated.

Occasionally both abnormal and normal allele patterns are obtained for a single chromosome. These results may represent clinically significant partial chromosome imbalance, copy number variants (CNV) Primer site polymorphisms (PSPs) or somatic microsatellite mutations (SMMs). The analysis and interpretation of such findings are detailed later in this section.

6.2.1.1 The Normal Range

The normal range for allele ratios should not exceed 0.8-1.4, however for alleles separated by more than 24 bp an allele ratio of up to 1.5 is acceptable and can be considered to fall within the normal range.

6.2.1.2 The Triallelic Range

Three alleles are evident by three peaks in a 1:1:1 ratio or two alleles in 2:1/1:2 ratios.

Values between 0.45 and 0.65, and between 1.8 and 2.4 define the triallelic range for alleles where two of the three alleles are of the same size.

6.2.1.3 The Intermediate Ranges

Values falling in the ranges (1.4-1.8 & 0.65-0.8) lying outside the normal and triallelic ranges are referred to intermediate ranges and the ratio calculations are referred to as inconclusive results. Such results can usually be resolved by re-testing using single marker assays.

Follow-up studies on single marker results falling in the intermediate range (where others for the same chromosome are normal) are carried out at the discretion of the individual laboratory. These inconclusive results may be caused by primer site polymorphisms (PSP); retesting using a lower PCR annealing temperature should correlate with greater amplification of the PSP allele and a change in the allele ratio.

Although a lower annealing temperature may result in a normal allele ratio, these marker results should not be used in interpreting the final
result, as amplification of the PSP allele may not be complete and may rarely represent an abnormal ratio.

6.2.1.4 Other Ranges

Sex Chromosome assays may give ratios above 2.4 or below 0.45, such ranges indicate the presence of more than 3 copies of the markers.

6.2.1.5 Somatic Microsatellite Mutations (SMMs)

Somatic microsatellite mutations may be identified by testing a different cell population such as cultured cells and observing altered allele ratios.

They arise when a mutation occurs within the microsatellite usually involving an increase or decrease of 1-2 repeats. As all cells should contain one copy of either the original or the mutated allele, the sum of the area/heights for these alleles should give a ratio in the normal range when compared with the unaffected allele.

6.2.2 Interpreting assay results

At least one clinical scientist registered with the Health Professions Council and with appropriate training, should analyse or check each result. Reports should be authorised by a State Registered Clinical Scientist at band 8 or above. This is consistent with other ACC BPG.

To interpret a result it is important that there is consistency between all markers on the same chromosome. The presence of only one allele for a specific marker indicates likely homozygosity at that locus and is considered to be uninformative.

6.2.2.1 Normal Results

At least two informative marker results consistent with a normal diallelic pattern (with all other markers uninformative) are required to interpret a result as normal.

It is acceptable to report cases where only a single marker shows a normal diallelic pattern, all other markers being uninformative as this is consistent with a normal chromosome complement. The report should state that the result is based on a single marker result and that this
result will be confirmed by another technique (either full karyotype or FISH on uncultured cells).

6.2.2.2 Abnormal Results–all informative markers

To interpret a result as abnormal, at least two informative marker results consistent with a triallelic genotype are required, with all other markers uninformative. It is unacceptable to interpret a result as abnormal if this is shown by only one marker.

(The presence of three differently sized alleles for one or more markers is consistent with a meiotic nondisjunction event generating the trisomy cell line, whilst the absence of such a result may indicate a mitotic nondisjunction event)

Confirmation of sample identity can be done by in a number of ways, including analysis of a maternal DNA sample to confirm sample identity, a second assay on the original sample, or an interphase FISH test.

6.2.2.3 Single abnormal markers

If discrepant abnormal/normal results are obtained for the most proximal or distal chromosome regions they may represent clinically significant regional imbalance. These findings should be detailed in the report and further testing recommended.

Abnormal markers that are flanked by normal markers may represent CNV. If the marker has previously been reported to represent a CNV inherited from a normal parent then it is acceptable not to report the abnormal marker result. A list of inherited CNV identified by markers used in QF-PCR assays is currently being collated and will be available on the CMGS and ACC websites.

For markers that have not previously been reported as representing inherited CNV, it is recommended that the abnormal and normal results are detailed in the report. QF-PCR analysis of parental samples may provide information regarding the significance of these results.
7 MATERNAL CELL CONTAMINATION

7.1 Blood-stained Amniotic Fluid Sample

It is acceptable to process all blood-stained samples, though care must be taken when interpreting the results as the blood may be fetal or maternal in origin. Levels of blood-staining in the cell pellet may also correlate with the level of the maternal genotype, though this should be carefully validated before being applied to interpret results.

The detection of maternal cell contamination in the absence of bloodstaining may indicate the presence of solid maternal tissue. This tissue may be a source of metaphases and care should be taken in the interpretation of karyotype results from these samples.

The presence of two genotypes in DNA from bloodstained samples is consistent with maternal cell contamination. Results from bloodstained samples can be divided into three categories;

7.1.1 Low Level maternal cell contamination

If a low level maternal genotype is present and the majority fetal genotype has no inconclusive allele ratios then the result can be interpreted as described in the Analysis Section.

7.1.2 Single genotype present

If a single fetal genotype is obtained then the result can be interpreted as described in the Analysis Section

7.1.3 Inconclusive allele ratios

If allele ratios are inconclusive (falls between the normal and abnormal range) due to the presence of a second genotype, the fetal genotype should not be interpreted.

For categories 7.1.1 and 7.1.2 the fetal genotype can be determined by analysis of a maternal DNA sample or by sexing the sample if the fetus is male.

In cases where a QF-PCR result is not available due to maternal cell contamination of the sample, karyotype analysis of cultured cells is usually possible.
7.2 Chorionic Villus samples

Maternal material may be present in CVS material prepared for QF-PCR analysis if the sample is of poor quality and/or the removal of maternal decidua is incomplete. Maternal cell contamination in CVS of reasonable quality is generally avoidable and may compromise the QF-PCR and/or karyotype results; every effort should be made to consistently remove all maternal decidua from CVS.

The fetal genotype can be identified by analysis of a maternal DNA sample or by sexing the sample if the fetus is male. If one or more allele ratio is inconclusive (falls between the normal and abnormal range) due to the presence of a second genotype, the fetal genotype should not be interpreted.

Whilst remaining maternal blood in the sample may be a source of maternal cell contamination in CVS, maternal tissue is the most likely source maternal cell contamination and also therefore of metaphases so care should be taken in the interpretation of karyotype results from samples indicating the presence of maternal cell contamination.
8 MOSAICISM

Mosaicism for trisomy and normal cell lines can be detected by QF-PCR analysis, evident as extra peaks and skewed allele ratios on a chromosome-specific group of markers. These results may be subtle; skewed allele ratios representing the mosaic chromosome may remain in the normal or abnormal ranges (i.e. ratios may all be borderline inconclusive or where the greater area/height is noted to be associated with the larger allele).

It is recommended that subtle but consistent skewing and/or small extra peaks on a chromosome-specific group of markers should be investigated further. Usually it is possible to distinguish between a mosaic genotype pattern and a pattern representing two genotypes.

If the QF-PCR result can be confidently interpreted the mosaic result should be reported, although the clinical significance of a mosaic result should be carefully considered in the report.

Rare completely discrepant QF-PCR and karyotype results due to placental mosaicism in CVS have been reported (see references below). In most of these cases QF-PCR testing of small or confined regions of the CVS was carried out and the result may represent predominantly cytotrophoblast material. Testing of dissociated cells representing the whole CVS has recently been introduced to the majority of UK labs and is now recommended practice (see Sample Preparation Section).
9 REPORTING

Reports should state the assumption that fetal material is tested. The fact that the test may not be detect mosaicism and the presence small segment imbalance for chromosomes tested should be included on the report, either in the main text or in a report rider.

The result may be described as preliminary or stand alone, however, if the QF-PCR test is to be followed by full karyotype analysis, this should be stated.

9.1 “Normal” reports

It is acceptable to list markers on a normal report, although this should be done in a way that does not ‘bury’ the result.

It is acceptable to report normal QF-PCR results as ‘consistent with a normal diploid complement for chromosomes 13, 18 and 21’, ‘an apparently normal complement of chromosomes 13, 18 and 21 was detected’, ‘no evidence of trisomy’ or similar phrasing.

9.2 Reports with triallelic results for autosomal aneuploidy

For abnormal reports, the locations of markers showing a triallelic result should be listed in the report to define the trisomic region.

It is unacceptable to report the QF-PCR result as trisomic for chromosome 13/18/21 as only specific sequences from each chromosome are tested. Report wording stating the result ‘indicates’ or ‘is consistent with’ trisomy 13/18/21 is acceptable, as is stating the result is ‘trisomic for at least the region represented by’ followed by the marker names and locations. Such abnormal reports should also include an interpretative statement such as ‘consistent with Down syndrome’, ‘associated with Down syndrome’, ‘indicative of Down syndrome’ or ‘predicted to be affected with Down syndrome’.

9.3 Reports indicating sex chromosome monosomy

It is important to be aware that the QF-PCR sex chromosome is a highly stringent screen for monosomy X but not a diagnostic test. A result consistent with monosomy X, where all polymorphic markers
have only a single allele peak and no Y sequences present, may represent a normal female homozygous for all markers tested.

Abnormal results should be confirmed using another technique, or reported as being consistent with monosomy X with the caveat that there remains a possibility that a normal female could give the same genotype.
10 Appendix 1 – References


### 11 Appendix 2 - Markers used diagnostically at the time of production of this version of the Best Practice Guidelines

Further information is available from Sue Hamilton (susan.hamilton@cmmc.nhs.uk).

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## 12 Version Control

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<td>Joint ACC/CMGS identity clarified with revised logos and text on page 1, amended header (all pages)</td>
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### Previous versions

| 10/09/2007 | QF-PCR for the Diagnosis of Aneuploidy Best Practice Guidelines (2007) v2.00 | Reformatted to standard ACC BPG style. Significant amendments were made to Section 3 - Sample preparation and Section 8 - Mosaicim | QF-PCR for Diagnosis of Aneuploidy (Apr 2005) (v.1.00) |
| April 2005 | QF-PCR for Diagnosis of Aneuploidy (Apr 2005) (v1.00) | no previous version                                                                                                           |                                                                                   |

Produced by ACC Professional Standards Committee