Best Practice Guidelines for Internal Quality Control in Genetic Laboratories

Zandra Deans¹, Joo Wook Ahn², Anne Bergbaum³, Kevin Colclough⁴, Ann Dalton⁵, Hazel Dinning⁶, Michelle Fenlon⁷, Will King⁷, Christopher Kettle⁸, Andrea Naughton⁹, Suzanne Page¹⁰, Rachell Robinson¹¹, Adele Timbs¹²

1. UK NEQAS for Molecular Genetics, Department of Laboratory Medicine, Royal Infirmary of Edinburgh, Edinburgh, EH16 4SA, United Kingdom
2. Genetics Laboratories, Guy’s and St Thomas’ NHS Foundation Trust, London, SE1 9RT, United Kingdom
3. Molecular Genetics Laboratory, Royal Devon & Exeter NHS Foundation Trust, Exeter EX2 5DW, United Kingdom
4. Sheffield Diagnostic Genetics Service, Sheffield Children’s NHS Foundation Trust, Western Bank, Sheffield, S10 2TH, United Kingdom
5. Nottingham Regional Cytogenetics Laboratory, Nottingham University Hospitals NHS Trust, City Hospital, Nottingham, NG5 1BP, United Kingdom
6. West Midlands Regional Genetics Laboratory, Birmingham Women’s NHS Foundation Trust, Birmingham, B15 2TG, United Kingdom
7. SW Thames Regional Genetics Laboratory, St. George’s University Hospitals NHS Foundation Trust, London, SW17 0RE, United Kingdom
8. Northern Genetic Service, Institute of Genetic Medicine, Newcastle upon Tyne, NE1 3BZ, United Kingdom
9. Genomic Diagnostics Laboratory, Manchester Centre for Genomic Medicine, St Mary’s Hospital, Oxford Road, Manchester, M13 9WL, United Kingdom
10. Molecular Haematology, Level 4, John Radcliffe Hospital, Oxford, OX3 9DU, United Kingdom
11. Leeds Genetics Laboratory (Molecular Genetics), St James’ University Hospital Leeds, LS9 7TF, United Kingdom

Recommendations ratified by the Association for Clinical Genetic Science Quality Subcommittee (1st September, 2015).

1. DEFINITION

Internal Quality Control (IQC) are the activities undertaken to detect, reduce and correct deficiencies in a laboratory’s internal analytical process which gives confidence that the test is performing well. IQC provides a framework of control measures to enable deficiencies in quality to be identified prior to release of patient results.

2. INTRODUCTION

It is assumed that the standards required by the regulatory body, United Kingdom Accreditation Service (UKAS) and Medical Laboratories, Requirements for quality and competence (ISO 15189:2012), or equivalent shall be adhered to by all accredited laboratories.

It must be noted that these recommendations are a minimum requirement 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 recommendations/guidelines, the most recently published should be taken to apply to all.
3. GENERAL RECOMMENDATIONS

3.1 Risk assessment
All stages of sample processing shall be risk assessed and appropriate action taken to minimise adverse incidents where there is a perceived risk which may potentially lead to incorrect results and/or incorrect interpretation of the results being issued. The quality management system shall include appropriate mechanisms to ensure if errors do occur they are detected immediately and are traceable.

3.2 Training
The work of the laboratory shall be carried out or supervised by suitably qualified, trained and competency-assessed staff or individuals with appropriate authority to ensure that service quality is not compromised. It is the responsibility of the Head of Laboratory to ensure that all roles are performed by suitably trained staff.

3.3 Transfer of information
Laboratories should minimise the use of manual transcription of patient information. Any transcriptions and transfer of labels shall be subject to an independent check.

3.4 Transfer of samples
The transfer of sample between tubes (i.e. tube transfers) shall be minimised. Transfers which are performed shall be checked by the operator. An independent additional check should be performed. If the risk to the patient outcome is high then an independent check is required. The use of bar coding and automated transfer of samples is recommended to reduce the risk of human error. Any automated or bar coding system shall be validated before use to ensure the automated process does not introduce any further risks.

3.5 Continuous IQC Improvement
The laboratory’s Quality Management System (QMS) shall contain the capacity to monitor, record and review all aspects of the variations in processes to provide an audit trail in the event of process failure.

3.6 Communication
Laboratories shall ensure robust communication with staff. Staff engagement should be encouraged and suggestions for improvement should be reviewed and appropriate action taken.

Sharing of lessons learned from audit and incident management is an important factor in continuous improvement.

4. PRE-ANALYTICAL PROCESSES

4.1 Acceptance of samples into the laboratory
Laboratories should define a minimum set of patient details which match on both the referral documentation and sample vessel before testing can proceed or results issued. Guidance on patient and sample identification is provided in the Association of Clinical Genetic Science (ACGS) General Genetic Laboratory Reporting Recommendations (2015)^4.

Initial data entry into a Laboratory Information Management System (LIMS) should be independently checked prior to sample processing.

The laboratory shall assign unique identifiers to patient samples, preferably generated automatically by the LIMS. The use of barcoding is recommended to reduce the risk of identifiers being misread and ultimately provide good traceability of samples.

Laboratories shall have rejection policies stating which samples will not be accepted or other reasons for sample or test request rejection.
4.2 Test selection
Procedures shall be in place to ensure correct test selection including the provision of reflex/secondary tests. Tests shall not be initiated without appropriate clinical information and must meet acceptance criteria as determined by the laboratory. If a test is outsourced, the sample acceptance criteria and testing criteria of the external laboratory shall also be met. The accreditation status of the outsourced laboratory shall be considered.

Prioritisation of tests should be determined by the clinical need, either by indication on referral information or discussion with the referring clinician.

Tests shall have the appropriate sensitivity to be clinically useful.

5. ANALYTICAL PROCESS
5.1 Validation and verification
Validation and verification are an essential part of a laboratory’s IQC process and are a formal requirement for accreditation against, for example, ISO 15189. Through the provision of objective evidence, it ensures that procedures are fit for purpose and/or perform as expected and enables internal quality control measures to be developed for each process.

Validation shall be conducted prior to the introduction of new laboratory developed procedures, non-standard methods and for standard methods used outside their intended scope. Validation is also applicable where significant changes to existing methods or procedures are subsequently made that may affect the quality of outputs. Furthermore, the clinical utility of the new test should also be considered including implications of results, e.g. termination of pregnancy, inappropriate/no treatment, patient management for pre-symptomatic or late-onset disease.

Verification applies to, for example, specific reagent kits, equipment, or commercial software applications/version updates and assesses whether the specified requirements of the kit or application have been met. Mattocks et al. (2010) and Berwouts et al. (2010) outline the implementation processes required to fulfil this requirement in detail, and present a generic framework to enable individual laboratories to systematically evaluate tests and procedures to a defined standard.

A comprehensive validation and verification process shall be adopted that includes:

- a description of the process/reagent/equipment/software being evaluated and it’s intended use.
- the aims and objectives of the validation/verification.
- a defined acceptance criteria.
- details of the evaluation process including the number and type of samples that will be tested.
- where appropriate, assessment of the uncertainty of measurement, and possible consequences for the final result.
- recording the process and review of outcomes.

The results shall include, as appropriate, assay trueness of measurement, reproducibility, detection and quantitation limits, diagnostic sensitivity and specificity, diagnostic accuracy and confidence limits for errors. The results shall be checked against the defined acceptance criteria to determine whether the validation or verification has been successful. Assays designed in-house, software that has not been commercially validated (including in-house developed software) and spreadsheets to assist with data analysis shall be validated, whereas commercially validated kits, probe sets and software shall be verified fit for intended use.

Aside from the analytical validation and verification of specific tests, performing laboratory procedures to a diagnostic standard requires the use of many independent components or systems. These also require individual consideration and assessment with specific IQ control mechanisms set in place to ensure optimal performance is maintained. The following sections aim to highlight some of these areas in more detail, recommending key IQC elements to be considered.
5.2 Equipment
All instruments or equipment used for routine diagnostic work that directly or indirectly affect the quality of the examination results, whether in an NHS laboratory or shared facility e.g. university/NHS, shall be recorded, monitored by the diagnostic laboratory and shall be maintained according to the requirements of ISO 15189\(^1\).

Prior to use for service delivery, internal verification shall be performed and documented to assess whether a newly installed, externally validated platform is fit for the intended purpose.

Measurement of uncertainty shall be determined for any equipment undertaking measurements that could affect the quality or accuracy of a test result.

Equipment shall be operated and maintained in accordance with the manufacturer’s instructions by staff with appropriate training and competence checked.

Acceptance criteria for internal maintenance checks should be defined and a procedure in place to rectify any equipment failures identified through such checks.

Maintenance logs and records of all trained operators shall be kept.

Performance of the equipment shall be monitored and reviewed on a regular cycle, the frequency of which is recorded in the laboratory's maintenance policy. Regular performance monitoring does not negate the requirement to perform an annual service/ performance assessment if recommended to do so by the manufacturer.

Comparability measurements shall be performed during validation for new equipment introduced for the same procedures to ensure results are consistent between platforms e.g. liquid handling robots, genetic analysers, thermal cyclers.

Performance results including the results of IQC samples should be periodically reviewed and trend analysis performed as part of the laboratories audit cycle. Results of IQC runs and error logs should be considered as part of the performance review procedure.

Following equipment repair, commercially validated software upgrade or modifications, verification shall be carried out prior to accepting equipment/software back in to service.

5.3 Reagents and Consumables
Detailed records of reagents and consumables shall be traceable to allow identification of sub-optimal reagents and or faulty consumables if a problem arises, and current guidelines e.g. from the Royal College of Pathologists\(^5\) shall be followed. Laboratories shall ensure that their reagents and consumables are appropriately verified or validated against defined laboratory standards and stored according to manufacturer’s instructions. As per the requirements of ISO 15189\(^1\), reagents shall be acceptance-tested before sample results are reported.

5.4 Data storage
The laboratory shall adhere to their local Information Governance and network security policy.

The appropriate storage location (drives) and naming convention for laboratory data files shall be documented and conveyed to all appropriate staff.

Appropriate back-up facilities should be periodically reviewed and considered e.g. output from machines which may not be supported by automatic institution network back-up as machines are upgraded and data out-put increases.

The laboratory shall have mechanisms in place to ensure that the integrity of data used for interpretation of patient results is maintained when transferred between systems e.g. to and from public or local databases, analysis platforms and servers.
5.5 Environment
Specimens, prepared samples, reagents, documentation and equipment shall be stored under appropriate conditions. All reagents shall be stored and equipment used according to the manufacturer’s recommendations. Optimum storage conditions for each specimen type shall be defined. Conditions may also be defined by the laboratory following risk assessment and/or validation and shall be subsequently adhered to.

Where specific environmental conditions are identified as critical e.g. temperature, this shall be monitored and records periodically reviewed. When not monitored, a risk assessment should exist stating why this is not performed.

Potential contamination sources which could compromise the integrity of diagnostic results shall be identified as part of the validation/verification process, for all laboratory processes. The optimum conditions to minimise such risk should be adopted e.g. defining pre- or post- PCR processes within a protocol. The areas should have separate pipettes, racks, reagents and laboratory coats, which should be distinguishable to prevent mix-up e.g. by colour.

The security of the environment should also be considered to ensure compliance with data protection requirements.

5.6 Assay quality criteria
The assay shall have a defined set of internal quality criteria established during validation that must be met in order to “pass”. These quality criteria are assay-dependent but can include one or more of the following:

- Template control (assay positive control)
- Mutation template control (mutation positive control)
- Non-template control (assay negative control)
- QC metric with validated thresholds, e.g. Phred score, DLRS, banding quality.
- QC thresholds should take into account any measurements of uncertainty where appropriate

Template intra-assay controls can be either a commercial or an in-house control such as a previous patient's sample (with the appropriate consent). For all in-house controls, suitability should be determined by a validated assay.

Depending on the test methodology, suitability/availability of intra-assay controls, clinical implications and perceived risk, the following independent confirmation tests should be considered appropriate:

- Confirmation by repeat testing on the primary or second sample
- Confirmation by testing using a second methodology

If intra-assay identifiers are assigned to samples, e.g. when batch testing samples in parallel, a batch identifier shall also be assigned. All identifiers shall be recorded.

The quality of analysis data shall be assessed and only results of sufficient quality will be reported. Analysis shall be performed by two independent suitably qualified, trained and competency-assessed staff. Concordance of analysis shall inform accuracy of results. All analysis and interpretation of results shall be documented.

6. POST-ANALYTICAL PROCESS

6.1 Reporting of results
All results and the content of the report shall be checked for accuracy and adherence to reporting recommendations and/or best practice guidelines and authorised by an appropriately trained (qualified) HCPC registered Clinical Scientist. If information required to interpret the results is not stated within the report and is available via an alternative resource e.g. lists of genes included in panel testing available via a website, then this information shall be document controlled. It is recommended that the report template is subject to version control to allow changes in reporting style to be traceable.

Guidance on reporting of genetic test results is provided in the Association of Clinical Genetic Science (ACGS) General Genetic Laboratory Reporting Recommendations (2015)⁴.
6.2 Issuing of reports
The laboratory shall record the individual(s) to whom the report is issued, the location of where the report is sent and the date of issuing the report. This information shall be recorded if the report is re-issued. The laboratory shall verify that the transmitted reports maintain integrity during transfer.

The laboratory shall record if an amended report is issued including the reasons for the amendment(s) and to whom/where/when the report is sent.

REFERENCES


5. 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)