SYMPOSIUM: QUALITY MANAGEMENT IN ASSISTED REPRODUCTIVE TECHNOLOGY

Quality control standards in PGD and PGS

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Abstract Preimplantation genetic diagnosis (PGD) aims to test the embryo for specific conditions before implantation in couples at risk of transmitting genetic abnormality to their offspring. The couple must undergo IVF procedures to generate embryos in vitro. The embryos can be biopsied at either the zygote, cleavage or blastocyst stage. Preimplantation genetic screening uses the same technology to screen for chromosome abnormalities in embryos from patients undergoing IVF procedures as a method of embryo selection. Fluorescence in-situ hybridization was originally used for chromosome analysis, but has now been replaced by array comparative genomic hybridization or next generation sequencing. For the diagnosis of single gene defects, polymerase chain reaction is used and has become highly developed; however, single nucleotide polymorphism arrays for karyomapping have recently been introduced. A partnership between IVF laboratories and diagnostic centres is required to carry out PGD and preimplantation genetic screening. Accreditation of PGD diagnostic laboratories is important. Accreditation gives IVF centres an assurance that the diagnostic tests conform to specified standards. ISO 15189 is an international laboratory standard specific for medical laboratories. A requirement for accreditation is to participate in external quality assessment schemes.

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The current status of PGD and PGS

Initial clinical application of PGD

Preimplantation genetic diagnosis (PGD) was first introduced in 1989; since then, genetic testing has seen major advances. It was developed as an alternative to prenatal diagnosis, for couples at risk of transmitting a genetic abnormality to their children. Couples must undergo IVF procedures to generate embryos in vitro, even though many of the couples who undergo PGD are fertile. The embryos can be biopsied by the embryologists at the zygote stage (removal of the first and second polar body), cleavage stage (removal of one to two blastomeres from the six- to eight-cell embryo)
and blastocyst stage (removal of some trophectoderm cells) (Harton et al., 2011a).

Up until recently, almost all PGD cycles were carried out on blastomeres after cleavage-stage biopsy (Harper et al., 2012; Moutou et al., 2014). Numerous studies, however, have found that cleavage-stage embryos have high levels of chromosomal mosaicism, which means that biopsied cells may not be representative of the rest of the embryo (Fragouli et al., 2011; Harper et al., 1995; Munné et al., 1995; Taylor et al., 2014a). This is especially important when trying to conduct PGD for a chromosome abnormality. Polar body biopsy is rarely used as it only gives genetic information on the maternal genome. In recent years, the IVF community has seen an increase in the use of blastocyst transfer (Glujovsky et al., 2012), and this has been reflected in the increased use of blastocyst biopsy for PGD (Moutou et al., 2014).

Genetic testing should be carried out by a specialized genetic testing laboratory. The first cases of PGD used polymerase chain reaction (PCR) to detect a Y chromosome sequence for sexing for X-linked disease (Handyside et al., 1990).

Testing by FISH

Fluorescence in-situ hybridization (FISH) replaced PCR as the method of choice for embryo sexing (Griffin et al., 1994; Munné et al., 1995) and for chromosome analysis for patients carrying a Robertsonian or reciprocal translocation (Conn et al., 1998; Fridstrom et al., 2001; Mackie Ogilvie and Scriven, 2002). Individual tests had to be validated for each couple as separate probe combinations were needed for every translocation. Also, FISH is not an efficient technique to use at the single cell level (Ruangvutilert et al., 2000). At this time, some groups decided that PGD technology using FISH to analyse as many chromosomes as possible might be useful as an embryo selection method for patients of advanced maternal age, repeated implantation failure or repeated spontaneous abortion (when the chromosomes in the parents were normal) (Munné et al., 1995; Verlinsky et al., 1995). This technique is usually referred to as preimplantation genetic screening (PGS) and should be differentiated from PGD, as it is for a different group of patients and for a different reason.

Testing by PCR

For couples at risk of a single gene disorder, PGD is usually carried out using PCR (Harper and SenGupta, 2012). This technique has become highly sophisticated over the years, with one of the most important developments being multiplex PCR, which allows the analysis of the mutation and also a contamination check (Harton et al., 2011b). The causes of contamination are numerous, including cumulus cell contamination or from people handling the cells (SenGupta and Delhanty, 2012). Molecular-based analysis for PGD can either be carried out by direct PCR amplification of the biopsied embryonic sample or following whole genome amplification (WGA). For direct PCR analysis, inclusion of two informative short tandem repeat (STR) linked markers (within 1cM/1MB), flanking each side of the mutation site, minimizes the risk of misdiagnosis owing to allele dropout at any one locus or owing to contamination. Flanking markers allow the detection of cross-over events in the region and assessment of the reliability of linkage analysis in these circumstances. The haplotype of the STR markers in phase with the mutation can be determined by identification of the shared haplotype between family members of known disease status. The limitation of direct PCR analysis is that an individual test has to be developed for each couple, which is time consuming and expensive. Each test has to be validated before being applied clinically.

The mutation site can be included for amplification in the multiplex reaction. Minisequencing is a commonly used method for mutation detection (Fiorentino et al., 2006). For a de novo mutation in a male partner, the haplotype in phase with the germline mutation can be determined by analysis of a single sperm. Similarly, for a de novo mutation in a female partner, polar bodies can be used but these must be biopsied sequentially and analyzed separately. Alternatively, phasing of alleles can be carried out from the analysis of embryos during the PGD treatment cycle; however, problems can arise when only a few embryos are available for analysis. If all the embryos do not show the mutation and have the same haplotype, it is difficult to be certain that the mutation was not present or if allele drop out had occurred at the mutation site in all the embryos. In such cases, rebiopsy may be an option or cryopreservation of embryos that are blastocysts with analysis of whole embryos that arrest to confirm the STR phasing with mutational analysis.

Whole genome approaches

The introduction of whole genome amplification (WGA) methods have enabled high throughput technologies to be used, which have increased the amount and type of information that can be obtained from an embryo biopsy sample (Hughes et al., 2005). Coupled with this is a reduction in work-up time and the need for patient-specific protocols. Techniques using WGA products are being applied clinically, such as preimplantation haplotyping (PGH), which allows genotyping of multiple STR markers by PCR, or karyomapping (Single nucleotide polymorphism genotyping using an array) to carry out PGD by linkage analysis (Handyside et al., 2010; Renwick et al., 2010; Thornton et al., 2015). The haplotypes obtained using these methods can also identify monosomes and trisomies of meiotic origin, and can potentially be used to identify imbalances in embryos from translocation carriers and also distinguish between normal and balanced chromosome complements. Array comparative genome hybridization (CGH) identifies chromosomal imbalance in a WGA product, and has been used in both PGD for chromosomal rearrangements and for PGS. Next-generation sequencing (NGS) has also been applied for PGS (Tan et al., 2014; Wells et al., 2014). It is expected that NGS will become the method that is primarily used for detecting chromosomal imbalance and mutation analysis either as separate tests or combined together in one analysis (Tan et al., 2014; Treff et al., 2013). Currently, these whole-genome approaches rely on whole-genome amplification. The type of amplification used determines the artefacts that may be introduced into the sample and thereby affect the accuracy of the diagnostic test. Therefore, extensive validation of WGA in the context of the method of analysis (PGH, array comparative genomic hybridization, karyomapping or NGS) with the indication for testing
(chromosomal abnormality, single gene disorder) is required (Bergen et al., 2005; Gientis et al., 2009).

All direct multiplex PCR protocols require optimization such that the efficiency of amplification at each locus approaches 95% and allele drop-out is less than 5%. Optimization needs to be achieved using isolated single cells from each partner whereby false positive and false negative rates for the overall protocol can be determined. When whole-genome amplification is applied before PCR, then optimization at a single level is no longer necessary. The WGA, however, introduces artefacts into the sample and therefore more informative markers are required to ensure that the protocol is robust enough to overcome any resulting bias in the sample.

Causes of misdiagnosis in PGD and PGS

It is key that PGD is carried out using tests that have been validated and optimized for the couple, as several reports of misdiagnosis have been reported (Amagwula et al., 2012; Wilton et al., 2009). The causes of misdiagnosis include contamination, allele drop-out, mosaicism of the embryo, and transfer of the wrong embryo. Because of these risks, it is essential for the PGD laboratory to be adequately insured against the risk of misdiagnosis. Patients should be informed of the limitations of PGD when taking their consent to treatment and witnessing of appropriate stages during the procedure should be carried out and documented.

Developments in assisted reproduction techniques

In addition to the need for individual tests for most PGD cycles carried out to date, the diagnosis is constrained as there is a time limit for the results of the diagnosis. The latest stage that embryos are normally transferred in IVF is day 6, as current culture conditions cannot sustain embryos for longer, and embryos would normally be implanting around this stage, so they need to be transferred to the uterus. Cleavage-stage biopsy allows 2–3 days for the diagnosis, but blastocyst biopsy gives just 24 h. This means that PGD laboratories have to run a 7-day a week service as the diagnosis has been carried out within 24 h. Also, running a single test for an array or NGS is expensive; therefore, batching samples for these high throughput technologies makes it cost effective.

For many years, the freezing technique used in IVF did not support cryopreservation of biopsy embryos (slow freezing), but recent developments of the vitrification technique have allowed highly successful cryopreservation of biopsied embryos (Chang et al., 2013; Simopoulou et al., 2014). The use of vitrification is being tested to determine if cryopreservation of all embryos in routine IVF cycles gives a higher success rate, as it allows for optimization of the endometrium (Roque et al., 2015). These freeze-all cycles, open up the opportunity to cryopreserve all embryos after biopsy for PGD (Schoolcraft et al., 2011; Taylor et al., 2014b). This relaxes the time constraints on the PGD team to carry out the diagnosis and allows batching of samples, both of which make the test significantly cheaper and improves the quality of the test results.

Accreditation of a PGD laboratory

Accreditation is a laborious process to establish and even harder to maintain; however, it ensures good-quality management, which is essential in today’s diagnostic laboratories. ISO 15189 is the specific international laboratory standard to which PGD diagnostic laboratories need to conform (International laboratory standard specific for medical laboratories – Medical laboratories: particular requirements for quality and competence) (Harper et al., 2010; ISO 15189, 2012). The ISO has two parts: management and technical requirements. The European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium have recommended that PGD is only carried out in an accredited laboratory (Harton et al., 2011c), and the The Human Fertilisation and Embryology Authority in the UK have made this mandatory. Similarly, the Organisation for Economic Co-operation and Development Guidelines for quality assurance in molecular genetic testing (OECD, 2007) state that “All laboratories reporting molecular genetic testing results for clinical care purposes should be accredited or hold an equivalent recognition”. Unlike other forms of genetic testing, PGD is slightly more complicated as it requires a dialogue between the IVF centre and the PGD laboratory, and it can be constrained by a short time period required for the test result.

Under personal requirements, ISO 15189 states that the PGD laboratory shall be directed “by a person or persons having executive responsibility and the competence to assume responsibility for the services provided” (5.1.3) (ISO 15189, 2012).

The management requirements address quality management, including the quality policy and manual, document control, non-conformities and corrective actions, continual improvement, auditing, management review, contracts, referrals and resolution of complaints. Technical requirements include personnel competence (both technical and medical), equipment, accommodation and environment, and pre-analytical, analytical and post-analytical processes. Emphasis is placed on the particular requirements of patient care: notably sample identification and traceability, test validation and interpretation and reporting of results. Quality indicators must be developed to monitor contributions to patient care and continual improvement.

The reports required

In PGD, the protocol will need to be validated for the specific patient before the start of the treatment cycle. In PGS, each methodology (FISH, array CGH, NGS) requires separate validation before clinical application. This validation should be recorded and authorized for clinical application within a work-up report. For validation, appropriate control samples must be available. Equipment used must be in working order supported by documented evidence that it has been serviced and calibrated to the appropriate level for application of the PGD protocol. Quality control measures need to be specified to ensure that the diagnostic results are within the acceptable limits of the reagent kits and equipment that was used. Staff training records need to be readily available to ensure that those performing the diagnostic tests are sufficiently trained to do so. The final protocol should be validated
with the appropriate level of sensitivity for its intended use (polar body, single blastomere or five to six trophectoderm cells. Trend analysis of internal quality controls (diagnosis rates, contamination rates, equipment performance, staff training and root cause analysis of errors identified through audit) enables laboratories to identify good practice and potential problems. Acting on these findings can prevent misdiagnosis and improve the overall service.

For all cases, an authorized report must be produced for every PGD cycle, which is sent to the IVF unit. The report must have the name and addresses of the PGD unit providing the results and IVF unit to which the results are being reported. For document control purposes, the report should have a document name, number, the date of issue and the version number. The individual page numbers and the total number of pages of the report should be stated. At least two identifiers should be present for each partner, e.g., name, date of birth, hospital number or unique patient number, along with the date of oocyte retrieval. For single gene disorders, the report should have the disorder name, the gene involved and their respective Mendelian Inheritance in Man numbers. The mutation being tested for should be written using the latest Human Genome Variation Society mutation nomenclature along with the reference sequence used to identify the mutation. For chromosomal disorders, the chromosomal rearrangements should be described using the latest International System for Human Cytogenetic Nomenclature.

The date and time the samples are received in the PGD laboratory and the date and time the result reports are issued are important as they can help keep track of the turnaround times.

The results are best presented in a tabulated form and should include interpretative comments to indicate which embryos are suitable for transfer. An explanation of the results in the form of extra notes can be included, which describe the minimum criteria used to provide a result, including the expected error rates, which were determined during the work-up of the protocol.

The report should be signed by the persons involved in carrying out the diagnosis and authorized by an appropriately qualified senior member of staff.

### External quality assessment

A requirement for accreditation is to participate in an external quality-assessment (EQA) scheme, if available. This enables laboratories to compare their diagnostic workflow with that from other laboratories. There are a variety of EQA schemes that are available for PGD/PGS. Participants may be required to interpret diagnostic results, or design a diagnostic strategy for different PGD scenarios. All parts of the diagnostic process can be assessed including the information that a laboratory provides in its final diagnostic report. Wet external quality assessment schemes give laboratories the opportunity to test validated samples. Good practice and errors identified by the scheme assessors are summarized and circulated back to all participating laboratories in final scheme reports. It has the potential to identify both major and minor problems in staff training, and equipment maintenance as well as ensure that the laboratory is conducting tests that conform to current published guidelines (Harton et al., 2011b, 2011d). It is an excellent tool for laboratories to assess and improve the quality of their diagnostic service objectively.

 Participating laboratories are marked according to specific criteria, resulting in a satisfactory performance or poor performance score. Individual feedback is given to each laboratory, and laboratories can appeal poor performance scores. A panel of PGD experts (specialist advisory group) review the appeal and they may uphold or revoke it. A laboratory with poor performance is required to complete a root cause analysis of the reason(s) that led to poor performance. Unlike actual clinical work, identification of poor performance in EQA does not only arise as a result of misdiagnosis, but is often a result of a weak protocol that is vulnerable to misdiagnosis, or poor or over-interpretation of the actual results obtained. A review of the first three of the molecular PGD scheme run by United Kingdom National External Quality Assessment Service (UK NEQAS) showed a marked improvement in the diagnostic reports submitted by all laboratories as the scheme summary reports gave clear feedback on items to be included in them (Deans et al., 2013). User meetings for the schemes provide a forum for participants to meet and discuss any difficulties experienced in performing the EQA. This process allows the EQA schemes to evolve and to become appropriate to changes in clinical practice of the participating laboratories, such as the introduction of new technologies.

### PGD EQA for FISH-based diagnosis

The EQA for FISH-based diagnosis was started in 2008 as a collaboration between the Cytogenetics European Quality Assessment scheme and the ESHRE PGD Consortium. It has run annually as an online system since then. This scheme is in two parts. In part I, laboratories are sent two case scenarios and asked to select suitable probes for a pre-implantation genetic diagnosis work-up. Laboratories report the theoretical unbalanced and balanced products of the chromosomal rearrangement. A prediction of viable or frequently unbalanced products arising from the rearrangement enables laboratories to determine the appropriateness of their probe selection by assessing the limitations and their overall protocol and the risk of misdiagnosis owing to probe efficiency or number of rounds of hybridization. In part II, laboratories receive images of interphase nuclei from blastomeres with specified probe combinations for the case scenarios presented in part I. Laboratories report their scoring of the FISH signals and interpretation of the results. In addition to the two case scenarios, laboratories can also attempt an educational case, which is marked but not scored.

### PGD EQA for molecular-based diagnosis

The EQA for molecular based diagnosis was also started in 2008 as a collaboration between the UK NEQAS Service and the ESHRE PGD Consortium. It has run annually as a wet method for analysis of blastomeres and trophectoderm. The scheme has two parts. In part I laboratories are sent a mock PGD referral with genetics reports of parental mutations and appropriate relatives together with genomic DNA from these individuals. Laboratories design an appropriate molecular
protocol for the germline mutation(s). When the scheme first started, almost all laboratories carried out direct multiplex PCR for diagnosis. More recently, PGH and karyomapping are approaches that are being applied. Laboratories are required to submit a work-up report with evidence, such as the haplotypes of the DNA samples to show that the strategy taken conforms to current guidelines (Harton et al., 2011b). The strategy should ensure that allele dropout (heterozygous locus appearing to be homozygous owing to failure of amplification of one allele) or contamination (maternal or external) can be detected. In part 2, laboratories are sent single cells as mock embryos from the couple described in the referral. Laboratories carry out diagnosis on these samples and then submit their laboratory reports together with the haplotypes in a proforma. Laboratories could report on one or two cells from each “embryo sample” depending upon their normal practice. In recent years, laboratories have been offered the option of having four to five cells together as a mock trophoderm biopsy sample to reflect changing practice of participating laboratories.

This scheme has been run for cystic fibrosis, fragile X, Huntington disease and myotonic dystrophy type I.

**EQA for the detection of aneuploidy or chromosomal imbalance by molecular methods**

In 2013, two pilot schemes were offered for arrays as a collaboration between UK NEQAS and the Cytogenetic External Quality Assessment Service. Analysis for PB1 and PB2, blastosomie and trophoderm have been offered as wet schemes. Amplified DNA from PB1 and PB2 samples and single cells or groups of cells were sent to laboratories for testing. Laboratories reported chromosomal imbalances detected. Array CGH has been used in laboratories for analysis and, more recently, NGS has been used. These schemes are still being run as pilots to ensure that appropriate samples are provided to laboratories that give consistent results across a number of CGH or NGS platforms.

**Follow up of untransferred embryos**

One of the numerous difficulties in developing and validating PGD methods is that potentially affected embryonic cells are only available when the couple go through fertility treatment. Therefore, it is essential to make use of the untransferred embryos from a PGD cycle to confirm the diagnosis. An ESHRE study of follow up on 940 untransferred embryos from PGD of monogenic disorders found that 93.7% were correctly diagnosed in the treatment cycle. Diagnostic accuracy was statistically significantly higher when two cells were tested compared with one cell ($P = 0.001$). Sensitivity was significantly higher when multiplex protocols were used compared with singleplex protocols ($P = 0.005$); however, multiplex PCR-based methods on one cell, were as suitable as protocols involving two cells when the false negative rate was considered (Dreesen et al., 2014).

The shift to methodologies requiring whole genome amplified products has the advantage of enabling the robust validation of new technologies. This is because the same whole genome amplified product can be tested on different platforms (Fiorentino et al., 2014) and the effect on the results of altered conditions of analysis, such as hybridization time on arrays, can be verified. The shift to trophoderm biopsy at blastocyst stage has meant the effect of mosaicism in the sample needs to be validated for each new platform (Mamas et al., 2012).

**Internal controls**

**Biopsy, tubing, labelling, or spreading of cells**

Biopsy of cell(s) from an egg or an embryo is required for all PGD or PGS applications. The tubing and spreading of the biopsied cell(s) is the most crucial part of the PGD or PGS process. If the cell(s) do not enter the PCR tube or the spreading is not carried out optimally, the analysis of the DNA cannot be carried out leading to a no result or an inconclusive result. Oocytes and embryos that are donated for research and training can be used as controls by the embryologists to practice their tubing and spreading skills. For additional controls, DNA from the embryologists or scientists carrying out the biopsy and tubing should be included in the molecular tests being conducted to check for contamination. A log of this training should be kept and used to determine the competency of the staff performing these tasks.

Clear FISH signals can be used as internal quality control for optimally spread blastomeres. Consistency in successful amplification for samples from separate oocytes and embryos, without maternal or other contamination for molecular analysis, is a good indicator of competency in tubing the biopsied cells.

**FISH**

The main purpose of the FISH technique in PGD is to test for chromosomal imbalances. Before a FISH protocol can be applied clinically, it needs to be optimized on lymphocytes using the appropriate probe combination that will detect the chromosomal imbalance. Lymphocyte preparations from an unaffected partner and partner with chromosome abnormality can be used as controls to test probe strategy and to confirm reported chromosomal abnormality. Efficiency of optimized FISH protocol determined in work-up control samples can be used as a calibrator of the test and the acceptable values for the control samples during testing in the treatment cycle that were determined at workup can be used as internal quality control. For PGS, FISH is not an efficient technique, as often not all chromosomes are tested. When numerous chromosomes are tested, FISH is challenging. In most PGD cases, the resolution of whole genome approaches, such as array CGH and NGS, is sufficient to detect predicted imbalances that can arise in embryos from patients with chromosomal rearrangements without the need for patient-specific protocols. Whole-genome approaches also allow for the option of checking aneuploidy in other chromosomes not involved in the parental chromosomal rearrangement.

**Whole-genome amplification**

DNA from single cells or a clump of cells is whole genome amplified and used in different platforms to detect chromosomal
imbalances and single gene disorders mainly by linkage analysis. The reagents required for whole-genome amplification are generally provided as a kit by manufacturers. Because of artefacts or bias that may arise during WGA, it is important to validate which type of WGA kit is suitable for each workflow with consideration of the following parameters: the starting material (polar body, blastomere or trophectoderm), the indication for testing (single gene disorder, chromosomal rearrangement or PGS), the number of hours of WGA and the method of subsequent analysis using the WGA product (PCR, array or NGS). A positive control DNA sample of known concentration and a negative (no DNA) control can be processed and analysed with the test samples. The quality of the amplification can be assessed by visualising the size range and intensity of the amplified product on agarose gel electrophoresis or the double stranded DNA concentration of the product can be measured using an appropriate method such as Qubit. Recording these parameters of the control sample post WGA serves as an internal quality control by calibrating the efficiency of amplification.

**Array CGH**

Different array CGH platforms are used in PGD for the purposes of chromosomal imbalance detection. When available, samples with a known imbalance arising as a result of the chromosomal abnormality, such as from an affected family member or from a CVS, can be used as controls. For internal quality control, quality control measures as specified by array manufacturer for labelling, hybridization and scanning could be used. The quality and accuracy of the profile and results from reference male and female DNA samples should also be checked as an internal quality control.

**Multiplex PCR**

Multiplex PCR is used in PGD to detect single gene disorders, including dominant *de-novo* mutations known to be present in an affected parent. The PCR protocols need to be optimized on single cells for each family to include a mutation detection method along with linked microsatellite markers. Single cells from known normal, carrier and affected individuals (as appropriate and available) from the family are used during the work-up and during the treatment cycle as controls. Efficiency and allele dropout rates of each locus included in the final optimized multiplex PCR protocol developed in case work-up are calculated that can be used as calibrators for the PGD cycle. Similarly, false negative and false positive values for single cells of known mutational status are calculated and referred to during the PGD diagnosis.

The linked STR markers included in the protocol provide internal quality control measures to detect successful amplification, external and maternal contamination as well as any crossover events that might occur.

**PGH**

In PGD, PGH is used for detecting single gene disorders in which linkage analysis can be carried out. DNA samples from family members who have had genetic testing and have been found to carry the familial mutation are used as controls.

Suitable informativity of markers linked to the mutation site is required to use as calibrators. Sufficient amplification of linked informative markers to distinguish haplotypes in phase with familial mutation or the normal allele, together with contamination and crossover detection provide the internal quality control measures for PGH.

**Karyomapping**

Similar to PGH, DNA samples from family members with known disease status are used as controls in karyomapping. Suitable informativity of the SNPs linked to the mutation site is required. Sufficient amplification of linked informative markers to distinguish haplotypes in phase with familial mutation or the normal allele, together with contamination and crossover detection provide the internal quality control measures for karyomapping.

**NGS**

Next-generation sequencing has been applied to PGS. Reagent kits and software are available for different NGS platforms. For internal quality control, quality control measures as specified by the manufacturer of the NGS reagent kit and platform should be followed. The quality and accuracy of the profile and results, as well as the depth of the sequence read of a WGA product from a known euploid genomic DNA sample, can be used as a calibrator and an internal quality control.

**Audit**

Audits are an important part of quality control as they provide a means to monitor the service at regular intervals.

Three types of audits can be carried out: vertical, horizontal and examination audits. The aim of a vertical audit is to check the whole of the management system and processes, for example by following a PGD case from the referral stage all the way through to the point when the final PGD report is issued. This could include several parameters such as referral system, document control, standard operating procedures, equipment maintenance, health and safety issues and staff training.

A horizontal audit examines one component of a process on more than one item. For example, a number of reagents could be checked for logging in process, storage conditions and Control of Substances Hazardous to Health assessment.

An examination audit, where an examination process is witnessed while being carried out, not only audits the accuracy of the standard operating procedure and its related documents, but also provides an opportunity to assess the competency of the person carrying out the procedure.

Any non-compliances from any of the audits should be recorded and have a root cause analysis carried out. The outcomes of the audits can be used to rectify the shortfalls of the management system and provide more staff training if necessary and lead to quality improvements.
Key quality indicators

Key quality indicators are required so the laboratory can monitor its overall performance and capacity. Service improvements should be reflected in the key quality indicators, which can be used to formulate future plans for the laboratory, implement new technologies and change future practice. Key quality indicators could include turnaround times, diagnosis rates, contamination rates, EQA performance and staff competency testing.

In conclusion, quality control minimizes the risk of misdiagnosis. All parts of the work-up and diagnostic procedure from the initial referral to the delivery of the final report can be monitored with suitable controls and calibrators. Regular audit of these parameters enables the laboratory to assess the performance of their service and objectively measure improvements.

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