Quality management system in PGD/PGS: now is the time

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Abstract

Purpose Governments and international authorities require an accreditation of the PGD/PGS laboratories in order to ensure the safety and reproducibility of these analytical procedures. The implementation of a Quality Management System is the first mandatory step prior to accreditation. Our aim is to offer a detailed guidance to the PGD/PGS community that would like to implement this system in the future.

Methods The certification was based on the norm ISO 9001:2000 and requires the identification of procedures, definition of the flowchart, documentation of the processes,

recognition of the critical control points, establishment of quality controls, performance of validation and audit system. **Results** The achievement of ISO certification with the specific scope of “preimplantation genetic diagnosis”. **Conclusion** Certification of PGD/PGS allows to achieve evaluation of the efficiency to ensure the sensitivity and a continuous improvement of the genetic diagnosis of embryonic single cells.

Keywords Preimplantation genetic diagnosis · Quality management system · ISO certification

A detailed exposition of quality management system implementation in an external PGD/PGS laboratory based on the firsts international standards.

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Introduction

The main objective of implementing a Quality Management System (QMS) in a laboratory is to assess the effectiveness of the procedures; to identify and correct errors; to ensure the accuracy and sensitivity of different processes; and to assess the competence of professionals working in different areas. All this is aimed at maintaining under control a complex diagnostic process in continuous improvement, as well as achieving customer's satisfaction who demands reliable diagnostic services. Besides, in the health field, there are a number of objectives referring explicitly to the degree of patient satisfaction as the ultimate beneficiary of the process [1]. Therefore, in addition to the above criteria, it is necessary to offer the patient the best choice, the greatest diagnostic and the best information on the process, in this case Preimplantation Genetic Diagnosis (PGD) and Preimplantation Genetic Screening (PGS).

In most laboratories working with the basic principles of best practice, there are written protocols or procedures. However, the introduction of a QMS incorporates a differentiating element, the verification by an independently

recognized entity of the compliance of a series of requirements defined in regulations or technical specifications. Basically, obtaining a certification implies that the management system introduced in a laboratory has been subjected to audits by the Certification Authority, meeting the requirements defined in an international norm. In our case, the norm is UNE-EN ISO 9001:2000 [2]. Adopting the requirements of an international standard as the basis to implement a QMS provides the laboratory with an added value and an internationally recognised image of quality standards. The Certification Authority issues the Certificate of Registered Company and the IQNet Certificate (<http://www.iqnet-certification.com>) that facilitates international recognition of the certificate.

From the PGD/PGS point of view, the diagnostic process is a very complex reality. Nowadays in Spain, the PGD/PGS is being offered to couples who need it by in-vitro fertilization (IVF) centres and, in most cases, genetic studies are performed in an external genetics laboratory specialized in PGD/PGS. Generally, there is a physical separation between IVF and PGD laboratories, and in many cases this is a long distance. This highly specialized external PGD service should be formed by a multidisciplinary team where nurses, clinical embryologists, clinical geneticists, molecular geneticists and cytogeneticists are involved. The interaction of this group with experts in assisted reproduction is essential, not only for the coordination of cycles but also for the exchange of knowledge in order to offer couples and families the best diagnostic option at all times. The need for this interaction has been pointed out in various reports to both the European Union (EU) and the rest of the world [3, 4]. Secondly, from the regulation point of view, in the EU, there is no common European legislation. In Spain, this type of genetic studies are regulated by the recent law (14/2006 of May 26th) on Assisted Human Reproduction Techniques. Every country regulates these practices in a more or less specific way and, in some cases, there are no explicit laws. In addition, major differences have generated a significant flow of patients between different countries. In this scenario, it is very complex to determine what actions must be taken to ensure quality in the process of PGD. Thirdly, there is currently no standard of quality that can be applied directly to a service with the special characteristics of PGD/PGS. In recent years, various scientific societies [5–8] have proposed sets of guidelines, with greater or lesser detail, in order to standardize and achieve the highest levels of optimization, reproducibility and control of risks in genetic diagnosis in single cells.

Concerning the quality assessment, there is no clear and comprehensive information regarding the practice of PGD/PGS in Europe. The most exhaustive information about PGD practice is contained in the records of the PGD

Consortium of ESHRE (<http://www.eshre.com>) based on the different applications and results, in connection to clinical indications. However, no information is available on quality control programmes in PGD/PGS, and there are no external programmes of quality control targeted specifically at PGD/PGS. In this regard, two pilot programs of external quality assessment (EQA) in the context of PGD/PGS have been launched recently. On one side, the Cytogenetics European Quality Assessment (CEQA) has just started an inter-laboratory pilot program for quality control of the FISH-based PGD for aneuploidy screening and reciprocal translocations (<http://www.ceqa-cyto.eu>). Almost simultaneously, the UK National External Quality Assessment Service (UKNEQAS) has set up the first EQA pilot program for molecular-PGD of cystic fibrosis (<http://www.ukneqas-molgen.org.uk>).

Finally, the PGD application has seen an exponential increase since its emergence in 1990 [9]. Previous reports have shown an increase in number of cases, diseases studied and technologies of analysis developed [8, 10]. These advances have improved the diagnostic capacity and extended the implementation of PGD, not only for the most common single-gene disorders [11] but also for the most common aneuploidies in IVF patients at high risk (advanced maternal age and couples with recurrent abortions) [12–14]. Moreover, complex cases like the combination of aneuploidy screening plus monogenic diseases studies [15] and detection of HLA-matched embryos for therapeutic purposes [16–18] in combination with aneuploidy studies can be performed [19]. All these rapid advances make it difficult to standardize the analysis procedures and complicate the determination of the parameters for control and quality indicators that are crucial when it comes to implementing a QMS. This complex context collides with demands from users of these techniques, who request certified laboratories, and the requirements of the health authorities which requires accreditation of testing laboratories in many countries. It is important to note that the certification is the first compulsory step towards a system of accreditation. In this sense, the European Commission recently set up a working group formed by the European Society of Human Reproduction and Embryology, the Institute for Prospective Technological Studies and EuroGentest. Their mission is to collect comprehensive data about practice and legislation of PGD in Europe and to guarantee the quality of practices and procedures. This working group has published a very interesting and illustrative survey [20] which shows that 98% of the centres consulted considered it important or very important to have a QMS in PGD. However, very few laboratories have QMS or are in the process of implementation. The survey highlights a significant need for improvement in quality assurance in PGD centers.

The aim of this work is to showcase our experience of implementing the ISO 9001:2000 certification in an external PGD laboratory. This paper aims to be a practical guide to help future users. Nowadays in the European context, few laboratories have implemented a QMS in laboratories performing IVF plus PGD/PGS assays in an integrated scheme. However, we introduce a novelty that is the implementation of QMS in a satellite PGS/PGD laboratory. IVF centres outsource the genetic analysis to our centre. In this sense, to our knowledge, this is the first time in Europe that a satellite PGD laboratory gets the certification with the specific scope of “Preimplantation Genetic Diagnosis.”

The stages

In June 2004 the implementation process began for FISH-based PGD only. This was completed by the end of 2005. Later on, the scope was widened to PCR-based PGD and, by the middle of 2007, the ISO 9001 certification was achieved for the complete PGD service.

First of all, it is necessary to make the decision of having a certified service. It must be taken into account that this decision always requires a strong investment in human and material resources, and leads to a huge amount of additional work. Secondly, it is necessary to define how we want our “quality-based” PGD/PGS service to be. In our opinion, it should be a diagnostic service with high capacity, with maximum optimization and reproducibility of trials and with a control system based on the validation before and during the diagnostic process in single embryonic cells. The main limitation of PGD/PGS test is the inability to repeat the studies before embryo transfer (in most of the cases). In addition, this whole scheme should be supported by external quality controls. Then we need to know very well our work scheme.

At this point, it is important to clarify that our program is an external program. This means that some of the procedures involved in the work scheme occur outside of our laboratories, under the supervision and control of external professionals. The most important external stages are the IVF cycle, the embryo culture, the embryo biopsy (in some cases) and the embryo transfer.

Once our scheme is well defined, a sequential process begins which consists of *i)* assessment of needs, *ii)* identification of the processes, *iii)* documentation of the processes, *iv)* establishment of the parameters of control and *v)* submission to audits.

Assessment of needs

The assessment of needs is a critical step in implementing a QMS. The needs concern both personnel and equipment.

Regarding the personnel, it is essential to define the roles and responsibilities of each of the “jobs” in the laboratory, as well as the requirements for personnel who potentially could occupy these positions (academic training, previous experience, skills, etc.). All this information must be registered in one document called “job description”. Once these aspects are defined we must properly manage the process of continuous training and qualification of all personnel during their professional life in the laboratory. We must also define how to evaluate the effectiveness of the training method and qualification of the employees. All these activities must be registered in order to trace the professional activity of each person. Finally, there must be a commitment by the Direction Department with the continuous training of personnel, mainly in two very specific areas: genetics and embryology.

Concerning technological needs, it is necessary to identify the requirements in order to anticipate the acquisition of equipment and preparation or adaptation of spaces involved in the different processes. To do so, following international recommendations and requirements in general standards such as ISO 17025:2005 [21] for accreditation, there must be a physical separation of critical areas, thereby creating special laboratories for each process: coding samples, DNA extraction, cell handling, pre-analysis, analysis and post-analysis.

Identification of the processes

The QMS from ISO 9001:2000 is a management system based on processes. Therefore, it is important to make a detailed study of existing processes and clearly define three groups: *strategic processes*, *key processes* and *support processes*. The *strategic processes* depend entirely on the Management of the Centre and are aimed at making strategic decisions, such as business opportunities, interaction with customers, sales policy, etc. The *key processes* are those that take place between receiving the sample and issuing the results. In our case, the key processes are basically analytical and technical ones. The *support processes* help to comply with the norm in an ongoing and organized basis, and run in parallel with key processes. These support processes are related to purchasing policies, evaluation of suppliers, human resources management, equipment maintenance, etc.

In connection with this, it is necessary to develop a flowchart that will enable us to locate the different processes in sequence, to establish relationships between them and to locate possible control points (Fig. 1). It is important to say that this chart reflects the processes involved in the majority of PGD/PGS cases, both FISH-based and PCR-based PGD. It does not show the processes related to special cases of PGD such as predisposition to cancer and HLA-matching PGD. These cases require previous administrative steps (case by case) directed to obtain the legal authorization from the Spanish Health Authority.

Fig. 1 FISH and PCR-based PGD flowchart summary

Fig. 1 (continued)

As a result of this approach based on processes, we can establish indicators for each of the defined processes. We have a tool to measure the achievement of the objectives defined for each process. It is important that indicators are measurable and quantifiable. Besides, the

identification of the processes will allow us to define the "control points" on which we must act in order to implement improvements if necessary (see later). This way, we will begin to achieve a commitment to continuous improvement.

Fig. 1 (continued)

Documentation of the processes (writing the quality manual)

The procedures that appear in the flowchart have to be described in the quality manual. The development of this manual is one of the most arduous parts of the entire certification process. In the analytical laboratories the exhaustive description of the steps to follow carries special importance. The detailed description must be expressly embodied in a document of fundamental importance: the testing protocol. From the standpoint of documentation, a kind of "documentary hierarchy" exists, ranging from more generic to more detailed. The order is set up as follows:

- *General procedure*: gives its name to the entire set of documents and covers all the following.
- *Process*: general description of each step of the procedure.
- *Protocols test*: detailed description of each part of the trials.
- *Technical instruction*: description of a concrete action that takes place in one or more processes.
- *Laboratory register*: paper collection of data from different variables related to a particular process.

Functionally speaking, the drafting of these documents is as follows: all processes are described in a general procedure. The testing protocols show in detail the laboratory work and must always be updated and monitored by the responsible person. These documents include a step-by-step detailed description referring to the materials and reagents used. The most current version must be easily accessible. Under certain standardized actions, technical instructions are used (for example how to

prepare a solution). Regarding laboratory records, these are present throughout the entire procedure and must be easy to fill in. These documents must include all the variables that we need in order to identify the sample, patient, type of test, professionals involved, dates and times, and all data that guarantees the traceability.

Establishment of the control parameters

Prior to establishing our critical control points, it is very important to make clear what general requirements are reflected in the norm and what specific needs could be included. International guidelines, technical recommendations or quality standards (if it exist), must be considered. In this sense, the ESHRE PGD Consortium guidelines [6] give us a very valuable guide in setting up these control parameters.

In conclusion, it has to be very clear what we want to measure and record, where we store the records, what kind of measurement system we are going to use, who will be recording the data and, at all times, we must ensure traceability in each case. It is very important to remember that an external PGD programme necessitates the involvement of a clinical genetics unit, an IVF unit and genetic testing laboratories. To have our process under control, a smooth and continuous communication between these three elements is essential. In this sense, it is highly recommended that IVF laboratories operate under strict quality controls and have a well-established QMS [22, 23].

Concerning identification of the control points, the three types of processes described above should be defined. In Table 1 we can see different points of control that must be considered in each process. In addition, there are general remarks before starting the PGD procedure. These considerations apply mainly to high-risk PGD but is very important to take them into account in every case in order to define our inclusion/exclusion criteria and to ensure traceability. These are (i) reviewing the clinical indication along with the requesting clinic, (ii) collecting medical information (reports, family history, etc), (iii) asking for genetic diagnosis reports (if necessary), (iv) offering complete information to the couple/family (or requesting clinic in some cases), (v) offering a reproductive genetic counselling, (vi) ensuring signing an informed consent for the specific indication, and of the request for specific study.

Finally, it is very important to follow-up on the cases after embryo transfer to register a number of variables that we are going to use as quality control of the process, which will enable us to assess actions that may be of interest in our procedure such as reanalysis of pathological embryos to detect possible misdiagnosis or defining new quality indicators. This enables us to keep track of any prenatal genetic diagnosis performed in case of pregnancy and births post-PGD.

Table 1 List of the control points in relation with the processes

Strategic processes	Support processes	Key processes
Control of : <ul style="list-style-type: none"> • Policy interaction with the petitioner • Pricing • Competence study • Market research • Marketing and sales • Research and development 	Control of : <ul style="list-style-type: none"> • Codification of the samples and personal data protection • Equipment (calibration and maintenance) • Reagents, probes and primers (stocks, expiration and storage conditions) • Staff access to the different areas • Clothing at special areas (masks, gloves and labcoats) • Cleaning and sterilization (materials and surfaces) • Purchases (suppliers of equipment and reagents) • Professional qualifications of staff and continuous training 	Control of : <i>FISH based PGD:</i> <ul style="list-style-type: none"> • Quality control of the probes (performing preclinical test and validation) • Performing intra-assay controls • Correct storage post-analysis <i>PCR based PGD:</i> <ul style="list-style-type: none"> • Contamination test of primers with external DNA (before the first use) • Validation with single cells • Performing intra-assay controls • Amplification efficiency • ADO • Contamination during clinical PGD using blanks/cell

Special remarks: reporting results and external quality controls

Reporting results It is necessary to consider reporting of results as one aspect that requires the maximum interest in PGD/PGS procedure although this is not a requirement of the rule. The European Molecular Genetics Quality Network (EMQN) (<http://www.emqn.org>) and the Swiss Society of Medical Genetics (<http://www.ssgm.ch>) published very useful guidelines (Best Practice Guidelines on Reporting in Molecular Genetic Diagnosis Laboratories, see websites). It needs to be noted that, in most cases, the recipient of the report is not an expert in genetics. The interpretation of the results should always take into account the clinical context of the cases and the type of methodological approach that was used. The main features are that reports must be clear, concise, accurate, unambiguous and easy to interpret. The meticulous writing of reports is especially important on two levels: informativity or preclinical studies prior to PGD/PGS cycles and the results from the single cell analysis for the embryo transfer. In addition to the specifications appearing in the above-mentioned guidelines, it is imperative to clarify the definition of terms referring to the genetic status of embryos (normal, asymptomatic carrier, affected, normal/balanced) and knowing the implications in future newborns. Moreover, the final decision as to which embryo must be transferred depends not only on their genetic status, but other embryological variables that can not be assessed in a genetics laboratory.

External quality controls It is very important to compare our procedures with standards of a qualified and recognized external organization. Participation in voluntary inter-laboratory rounds gives a measure of the level of quality and enables us to fulfil one of the principles of the norm, which is to say, continuous improvement. Currently, there is a limitation to that effect in our field because there are not external quality control inter-laboratory schemes specifically addressed to PGD/PGS. Fortunately, there is a recent initiative of a pilot scheme for PGS as mentioned in the introduction. Participating in this kind of external control allows us to maintain a high standard in genetic diagnosis, and to improve the design of reports and handling of complex cases. It is very important to keep contact with other laboratories and expert groups to update our knowledge, to access documents and guidelines of good practice in genetic diagnostics and to make improvements in protocols.

Submission to audits

The completion of internal and external audits is a requirement of the norm. The internal audit is aimed at checking the implementation of the QMS. It is performed by the quality

management responsible of the institution or the person who has performed the implementation process. The frequency is annual and the Director of the Quality program communicates to the people involved what the purpose and scope of the audit are. This internal auditor will determine if the requirements of the ISO 9001 norm have been applied.

After the internal audit, an external audit is sought and all the documentation is forwarded to the auditors prior to their visit. During the audit, the auditors check the implementation of the requirements on the spot. The auditors have the right to determine corrective actions for possible deviations they detect. After the checks and application of these corrective actions, the Certification Authority issues the ISO Certificate which contains explicitly the scope of certification.

Conclusion

The PGD /PGS is undergoing a process of consolidation as a form of genetic diagnosis or screening in early embryos. Generally, both legislative and quality management is still in its beginning. At the moment, PGD/PGS community is witnessing the creation of the first working groups and networks aimed at specific management and quality control of genetic studies in the field of PGD/PGS. The international context demands the introduction of accreditation systems in laboratories as a way to unify the national and international standards. Particularly, the ESHRE PGD Consortium has a working group developing specific guidelines for the accreditation of PGD laboratories. The certification represents the first step towards an accredited system. The introduction of a quality management system in a PGD/PGS laboratory in this context is extremely useful when trying to standardize, validate and control processes as complex as those involved in the PGD/PGS.

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