



Preimplantation Genetic Diagnosis in Europe

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List of acronyms

AEDP	Asociación Española de Diagnóstico Prenatal
ART	Assisted Reproductive Technology
BRCA1/2	Breast Cancer typegene 1/2
CF	Cystic Fibrosis
CMT	Charcot-Marie-Tooth disease
CPA	Clinical Pathology Accreditation
DMD	Duchenne/Becker Muscular Dystrophy
DM1	Steinert Myotonic Dystrophy
EAA	European Academy of Andrology
EMQN	European Molecular Genetics Quality Network
EQA	External Quality Assessment
ESHG	European Society of Human Genetics
ESHRE	European Society for Human Reproduction and Embryology
F8/F9	Haemophilia A/B genes
FISH	Fluorescent <i>in situ</i> Hybridisation
FRAXA	Fragile X syndrome
HD	Huntington Disease
HFEA	Human Fertilisation and Embryology Authority
HLA	Human Leukocyte Antigens
ICSI	Intra-Cytoplasmic Sperm Injection
IPTS	Institute for Prospective Technological Studies
ISO	International Organization for Standardization
IVF	In Vitro Fertilisation
JRC	Joint Research Centre
MD	Doctor of Medicine (degree)
MS	Member States
NF1	Neurofibromatosis type 1
NHS	National Health Service
PCR	Polymerase Chain Reaction
PCT	Primary Care Trusts
PGD	Preimplantation Genetic Diagnosis
PGDIS	Preimplantation Genetic Diagnosis International Society
PGS	Preimplantation Genetic Screening
PND	Prenatal Diagnosis
RATE	Regulatory Authority for Tissue and Embryos
SCD	Sickle Cell Disease
SMA	Spinal Muscular Atrophy
SOP	Standard Operating Procedure
QA	Quality Assurance
QAP	Quality Assurance Project
UKNEQAS	United Kingdom National External Quality Assessment Service

EXECUTIVE SUMMARY

Preimplantation genetic diagnosis (PGD) is used mainly in couples at high risk of transmitting a specific genetic anomaly. It involves genetic testing of embryos generated *in vitro*, with the aim of identifying embryos which are normal in terms of the anomaly in question and are therefore suitable for transfer. PGD is subject to different regulations, practices, professional standards and accreditation requirements across Europe.

In March 2005 the Institute for Prospective Technological Studies (IPTS) of the European Commission's Joint Research Centre (JRC), the European Society of Human Genetics (ESHG) and the European Society for Human Reproduction and Embryology (ESHRE) organised a workshop on the interface between genetics and reproduction in healthcare. In the course of this event it became evident that a full picture of PGD practice and provision in Europe was needed. The lack of quality assurance for these services in general was perceived as a potential problem. Questions were raised about the impact that different regulatory frameworks between Member States (MS) might have on these services and to what extent couples were crossing borders to gain access to treatment which is not available in their own country.

In response to these potential needs, IPTS, in collaboration with the European Science and Technology Observatory (ESTO), launched this study in an effort to address them and to obtain the missing knowledge on provision of PGD services in the EU.

The first stage of this study was a survey of centres potentially performing PGD or offering PGD-related services in Europe. The survey identified 53 centres across Europe offering PGD, most of them located in Spain, Belgium, the Czech Republic, Greece and the United Kingdom, which suggests that patients could potentially be travelling abroad to seek PGD treatment. The main **types of test** offered by laboratories performing PGD included tests for monogenic diseases, cytogenetic testing for chromosomal abnormalities and sex selection for X-linked monogenic diseases, whereas “social sex selection” was found to be performed at only one centre. Interestingly, tests are also performed for adult-onset diseases such as Huntington's disease and several cancer predispositions, showing that PGD laboratories agree to look for indications which are rejected in prenatal diagnosis. Finally, PGD is applied to HLA-typing.

Genetic counselling is offered by 94% of the centres, according to the survey. The majority offer counselling at the IVF centre and/or at the genetics centre, although the answers do not reveal whether or where counselling is actually given. The interviews conducted raised some concerns that counselling is not performed consistently. However, further investigation is required to obtain a clearer picture.

Quality assurance of PGD testing was evaluated by several criteria and was found to be inconsistent. For example, only about half the clinics and laboratories had a designated quality manager, suggesting a potential need for improvement and further education there. According to the survey, the majority of the centres rated external quality assessment (EQA) important or very important but only one third of them were actually participating in EQA schemes. Although there are no specific EQA schemes for PGD, ESHRE (2005) has recommended that a voluntary EQA scheme be implemented. This points to a clear need for development of EQA schemes specific to PGD (or for adaptation of existing schemes) to ensure that the

related technical aspects, interpretations and reporting of the results are properly assessed and comparable. A need for further improvement was also identified as regards **accreditation**.

The **EU Human Tissue and Cells Directive**¹ and the technical annexes to it introduce a broad range of quality management requirements to ensure that “each tissue establishment puts in place and updates a quality system based on the principles of good practice”. PGD laboratories and clinics fall within its remit. Although not all the specific requirements of the Directive were addressed in detail in the questionnaire or the interviews, the general message from the majority of respondents was that few clinics meet these criteria at present. The technical annexes were recently adopted as EU law, allowing clinics to implement the new requirements. The findings presented in this report suggest that many EU clinics will have considerable work to do in order to meet the requirements of the EU Human Tissue and Cells Directive. Nevertheless, this is a unique measure for **harmonisation** to ensure that patients who travel abroad for PGD can expect certain quality and safety standards if they are treated in an accredited centre. However, the standards are a minimum requirement and Member States are free to impose more stringent restrictions.

The quality and safety of technologies such as PGD cannot be assessed properly without data on the outcome of treatment, not only during pregnancy, but also at the neonatal stage and in the medium and long term. Such monitoring provides a wealth of information about safety and efficacy, in terms of both clinical- and cost-effectiveness. It can also help to improve understanding of the impact that PGD treatment has on families and their children. Together, such data can be used to shape clinical, scientific and counselling practices, but also policy and legislation in this field. However, the results of this study indicate that **monitoring and follow-up** are inconsistent across Europe. In most clinics neonatal and short-term follow-up is rare, and systematic long-term follow-up for PGD is limited to one centre in Belgium (possibly with some limited long-term follow-up in Spain). Another shortcoming appears to be that few of the follow-up studies that are carried out are linked or share data. Some clinics reported that they run their own studies, and the ESHRE PGD Consortium study is the only reported international data collection looking at neonatal data from clinics within Europe and some outside.

Lack of expertise and expense were pinpointed as the two main reasons why follow-up of PGD is not more common. Follow-up requires input from suitably experienced paediatricians, paediatric nurses and counsellors, working in collaboration with the treating clinic. In addition, a worthwhile follow-up study over the medium to long term requires a significant investment of time and other resources. This cost is higher still for a multi-centre international study collecting data from across Europe and beyond. Given the relatively small number of children born following PGD, an international study is necessary, but this would require significant sponsorship. The abovementioned ESHRE PGD Consortium is hoping to extend its current follow-up with those centres which have the infrastructure and financial means to participate. Ideally, further funding would facilitate wider participation, thereby adding to the value of the data.

As regards **trans-border flows**, the main receiving countries identified by the survey are Spain, Cyprus, Belgium and the Czech Republic. They all treated patients from a large number of European countries, but also from the USA, Lebanon and Israel. These cross-

¹ http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/l_102/l_10220040407en00480058.pdf.

border movements of patients were primarily the direct consequence of the regulatory differences across Europe. However, in addition to these legal reasons, test availability, quality of treatment and financial resources were cited as other drivers behind the flows observed.

Concerning **referral of couples and samples**, the survey indicates that countries referring either only provide information or directly refer couples abroad. Although it is not entirely clear how referrals are made, several ways and sources were mentioned in the interviews. For example, most of the foreign couples treated in the Czech Republic obtain information from the websites of IVF clinics or receive recommendations from other couples who have previously been treated, whereas in Switzerland information is frequently provided by medical genetics services (principally but not exclusively university services). One interesting point to note is that in certain countries (e.g. Germany) formal referral is prohibited.

In terms of **the regulatory framework for PGD**, there are obvious differences across Europe, which have a direct consequence on existing practice. The UK and Belgium, for example, allow IVF, PGD and related research in a regulated environment. By contrast, Ireland has a blanket prohibition on PGD. Germany and Switzerland have adopted similar positions, prohibiting PGD with the limited exception of polar body biopsies. The cross-border movements of patients seem to be a direct consequence of these regulatory differences, given the relatively free movement of people and goods around the EU. However, there are certain potential disadvantages to such cross-border flows from countries where such treatment is prohibited. If patients are not referred properly, they are left to identify clinics themselves, using only the information which is accessible and which they can understand, hence potentially depriving them of the benefit of medical advice, counselling and support at a vulnerable time. Secondly, even if patients are able to receive treatment abroad, the prohibition of PGD in their country of origin may complicate monitoring and follow-up. If patients have been self-referred, the fact that PGD has been practised abroad may go unnoticed. Clinics could also be reluctant to get involved in following up families and children born as a result of application of a prohibited treatment. Thirdly, in countries where PGD is prohibited, it is available only to more affluent patients who can afford expensive treatment abroad.

1 INTRODUCTION

1.1 Background

In vitro fertilisation (IVF) and preimplantation genetic diagnosis (PGD) are now well-established treatments and are provided in many European countries. However, regulations, practices, professional standards and accreditation requirements are often markedly different between Member States (MS). Differences between MS seem to be becoming especially pronounced because of the interface between assisted reproduction and genetics.

To assess the extent of these differences and try to obtain an initial picture of the overall situation in Europe, in March 2005 the Institute for Prospective Technological Studies (IPTS)² of the European Commission's Joint Research Centre (JRC), the European Society of Human Genetics (ESHG)³ and the European Society for Human Reproduction and Embryology (ESHRE) organised a workshop on the abovementioned interface⁴. The two-day event brought together 50 experts from different specialities to review current practices in Europe and discuss potential needs in this area. The first thing that became clear was that no full picture was available of PGD practice and provision in Europe.

Secondly, the lack of quality assurance for these services in general was perceived as a potential problem. The participants in the workshop unanimously agreed that European clinics should be certified or accredited and that licensing systems should be developed by professional self-regulation. Minimum quality standards should be set. The lack of common European rules and regulations to guarantee minimum standards was said to be adding to the problem. However, quality assurance and accreditation have taken on new significance in the light of the recent EU Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

Thirdly, as a result of the abovementioned differences between MS, patients are travelling abroad to gain access to treatment which is not available in their own country. This, in turn, sometimes requires movements of gametes (oocytes and sperm) and embryos within the EU. Whilst it is known that couples and reproductive tissue are moving around Europe, the extent is not known – especially in the new MS. Lastly, an overview of how the different regulatory frameworks are having an impact on the actual practices of PGD services was deemed necessary in order to gain a better understanding of the trans-border flows.

Having pinpointed some of the needs in this area, the IPTS launched this study in an effort to address them and to obtain the missing knowledge on provision of PGD services in Europe.

In 2003 the IPTS published the results of a study reviewing genetic testing in the EU which identified potential weaknesses⁵. Two years later an EU-funded network of excellence,

² <http://www.jrc.es/home/index.htm>.

³ <http://www.eshg.org/>.

⁴ Soini et al. The interface between assisted reproductive technologies and genetics: technical, social, ethical and legal issues. *Eur J Hum Genet.* 2006 May; 14(5): 588-645.

⁵ Ibarreta, D. et al "Towards quality assurance and harmonisation of genetic testing services in the EU" (2003).

EuroGentest, was launched with the aim of developing the necessary infrastructure, tools, resources, guidelines and procedures to structure, harmonise and improve the overall quality of genetic services in the EU. The EuroGentest network was therefore invited to participate in this new study on PGD services in Europe.

1.2 Aims

The aims of this study are two-fold:

- to obtain a clear picture of current PGD practice in Europe, including the quality of the services and cross-border activities (flows of couples or reproductive tissue);
- to carry out a comparative review of the different regulatory frameworks at MS level and identify potential gaps at European level and the impact these might have.

1.3 Steering Committee

The ESTO⁶ group conducting this study was made up of representatives from the following organisations:

- Epanan (UK-based research and advisory group specialising in reproductive and genetic technologies)⁷, Progress Educational Trust⁸ and Genetic Interest Group⁹;
- EuroGentest (network of excellence for medical genetics funded by the EU's Sixth Framework Programme (FP6))¹⁰;
- ESHRE (the European Society for Human Reproduction and Embryology)¹¹;
- Institut de Biomedicina de València-CSIC (Spanish Council for Scientific Research)¹²;
- Technology Centre AS CR, a consortium of legal entities/institutes of the Academy of Sciences of the Czech Republic¹³;
- University of Kiel¹⁴.

1.4 Definitions

Accreditation: formal recognition of a laboratory's competence to perform a test. It implies external audits carried out by an independent body, in accordance with internationally accepted standards such as ISO 15189 or 17025.

⁶ <http://esto.jrc.es/>.

⁷ <http://www.epalan.com/>.

⁸ <http://www.progress.ork.uk>.

⁹ <http://www.gig.org.uk/>.

¹⁰ <http://www.eurogentest.org>.

¹¹ <http://www.eshre.com>.

¹² <http://www.ibv.csic.es/es/Inicio.asp>.

¹³ http://www.tc.cz/home_/.

¹⁴ <http://www.uni-kiel.de/>.

Certification: attestation that a laboratory complies with the requirements for a quality management system, typically in accordance with standards such as ISO 9001. Unlike accreditation, certification does not evaluate the technical competence of the laboratory.

EQA (external quality assessment): a system in which laboratory results are scrutinised objectively by an outside agency in order to gain a general impression of the standard of laboratory practice and to achieve interlaboratory comparability.

FISH (fluorescent *in situ* hybridisation): use of fluorescent tags that glow under ultraviolet light to detect hybridisation of molecular probes with specific chromosomes and specific chromosome regions. FISH vividly paints chromosomes or portions of chromosomes with fluorescent molecules.

Licensing: a legal requirement in some countries: official or legal permission to perform testing.

PCR (polymerase chain reaction): a laboratory technique by means of which selected DNA fragments are amplified from a tiny sample to a large amount within just a few hours to allow analysis of (for example) a specific gene.

PGD (preimplantation genetic diagnosis): in the context of this study, which focuses on use of PGD in couples at high risk of transmitting a specific genetic anomaly, PGD means genetic testing of embryos generated *in vitro*, with the aim of identifying embryos which are normal in terms of transfer of the anomaly in question. Typical indications include one or both parents being carriers of identified mutations for a monogenic disease or of chromosomal anomalies (translocations, etc.). However, PGD has been used not only to diagnose and avoid genetic disorders, but also to select for certain characteristics, such as matching tissue type to an existing sibling for therapeutic purposes (e.g. HLA-typing).

PGDIS Guidelines: guidelines issued by the Preimplantation Genetic Diagnosis International Society (PGDIS) and designed primarily as an educational aid to help centres offering PGD to provide high-quality medical services.

PGS (preimplantation genetic screening): testing embryos generated *in vitro* for aneuploidy (i.e. one or more extra or missing chromosomes leading to an unbalanced set of chromosomes, which should be normal diploid), with the aim of identifying normal embryos for transfer. Unlike PGD, PGS involves screening for a range of anomalies, in the absence of one specific chromosomal anomaly. Five to nine pairs of chromosomes are usually examined. Also known as PGD-AS (aneuploidy screening). In the USA typically no distinction is drawn between PGS and PGD.

Proband: an individual or a member of a family being studied in a genetic investigation, through whom a family's history becomes evident.

2 METHODOLOGY

The first stage of this study was a survey of centres and clinics potentially performing PGD or offering PGD-related services in Europe. This took the form of an on-line questionnaire, which was sent to European PGD and IVF clinics identified by ESHRE and from the EuroGentest quality assurance survey (for further details on the survey, see Annex 1). The questionnaire focused on use of PGD to make it possible to transfer unaffected embryos for couples who carry or are themselves affected by serious genetic disorders: it did not aim to collect detailed data about other preimplantation genetic technologies, such as preimplantation genetic screening (PGS). The data from the survey are reported as the participants replied, without independent validation. In cases where there is a significant risk of error in the replies, this eventuality is specifically mentioned.

The results of the survey are presented in Chapter 3.

The second stage of the study was a more exhaustive analysis of PGD practice and provision in specific countries, namely Belgium, the Czech Republic, France, Germany, Greece, Ireland, the Netherlands, the Slovak Republic, Spain, Switzerland and the UK. They were chosen to include some countries with a relatively restrictive regulatory framework, others with a relatively liberal regulatory framework and some which allow practitioners to self-regulate. Some of the new EU Member States, about which little is known in this regard, were also included. This analysis was based both on data gathered from the survey and on information obtained from interviews with experts in this field in each of the abovementioned MS based on the short questionnaire in Annex 2.

The results of this analysis are presented in Chapter 4, followed by a comparison of the regulatory frameworks in these countries in Chapter 5.

A more detailed description of the methodology is provided in Annex 1. The complete questionnaire can be found in Annex 3.

A summary of this full report has been published in the *European Journal of Human Genetics*¹⁵.

¹⁵ Corveleyn A, Morris MA, Dequeker E, Sermon K, Lawford Davies J, Antiñolo G, Schmutzler A, Vanecek J, Nagels N, Zika E, Palau F, Ibarreta D. Provision and Quality Assurance of Preimplantation Genetic Diagnosis in Europe. *European Journal of Human Genetics*. (2007) In press. DOI number EJHG.2007.146.

3 SURVEY

3.1 PGD services

3.1.1 Centres

No comprehensive list of European centres¹⁶ providing PGD exists. A survey was initially sent to approximately 169 known or potential PGD providers. In addition, an invitation to participate in the study was sent to 1 515 IVF contacts from more than 30 countries. Table 1 lists the countries that participated in the survey broken down by area of activity as follows:

- IVF + PGD: centres offering both laboratory services;
- PGD only: laboratory performing PGD only, receiving samples from an IVF lab;
- IVF performed and PGD referred to external labs: IVF laboratories which act as gateways to PGD labs.

Table 1: Survey recipients and replies

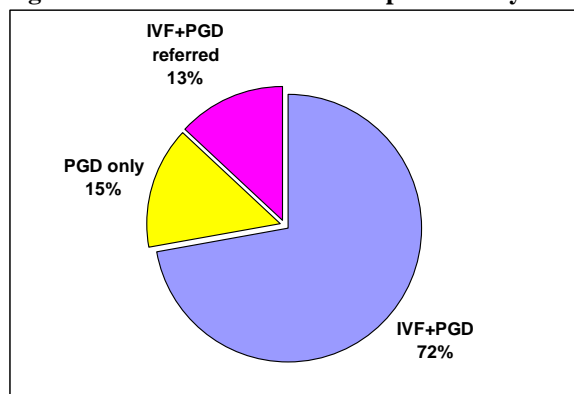
	<i>PGD contacts</i>	<i>IVF contacts</i>	<i>IVF + PGD replies</i>	<i>PGD only replies</i>	<i>IVF, PGD referred replies</i>
Austria	1	38		1	
Belgium	10	96	6		
Cyprus	2	4	1		
Czech Republic	36	25	5	1	
Denmark	3	67	1		
Finland	3	44	2		
France	8	116	3		
Germany	15	119	3		1
Greece	9	97	3	3	1
Hungary	1	20			
Italy	9	169			
Lithuania	-	10			1
Portugal	4	32	1		1
Slovakia	7	2	1		
Spain	15	76	5	3	2
Sweden	2	58	2		
Switzerland	20	59	1		1
The Netherlands	5	136	3		
Turkey	4	62	2	1	1
United Kingdom	14	136	5		1
Other	1	159			
Total	169	1 515	44	9	8

An on-line questionnaire (url) was developed and distributed to 169 known or likely PGD providers and to over 1 500 IVF professionals to ensure comprehensive coverage of centres potentially performing PGD. Ten of the centres which responded provide IVF only and were not studied further.

Sixty-one centres replied to the survey; the distribution of their services is shown in Figure 1; the majority are large centres providing a full service of both IVF and PGD.

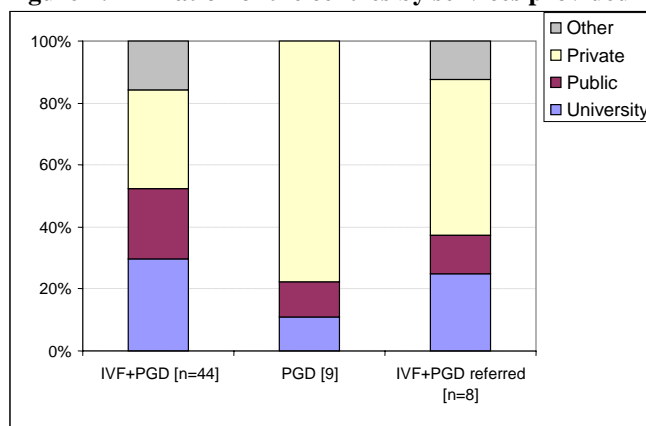
¹⁶ In this report “centre” means institutions (e.g. hospital, university or clinic) as a whole and, consequently, may refer either to a single laboratory/clinic or to a larger institution consisting of more than one unit (IVF lab, IVF clinic and/or PGD lab).

Figure 1: Distribution of services provided by the 61 centres responding



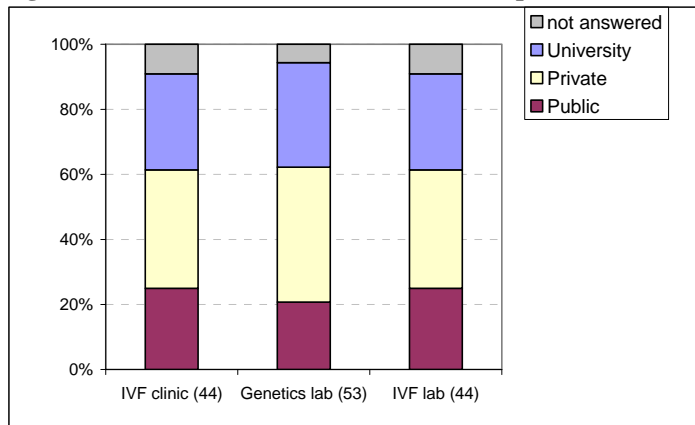
The affiliation (public, private or university) of the 61 centres responding is shown in Figure 2, broken down by services provided. Forty-four of the centres provide both IVF and PGD. Of these, 37 (84%) offer PGD and IVF facilities in the same sector (for example, all private), but three could be more appropriately considered as “virtual centres”, in the form of a university genetics laboratory collaborating with IVF in the public (1) or private (2) sectors. Four centres gave no indication of their affiliation. The more specialised providers, offering only PGD, were more likely to be in the private sector.

Figure 2: Affiliation of the centres by services provided



The 53 centres which replied that they provide PGD (IVF + PGD or PGD only) were made up of a total of 141 separate laboratories and clinics, distributed remarkably evenly between universities and the public and private sectors (see Figure 3).

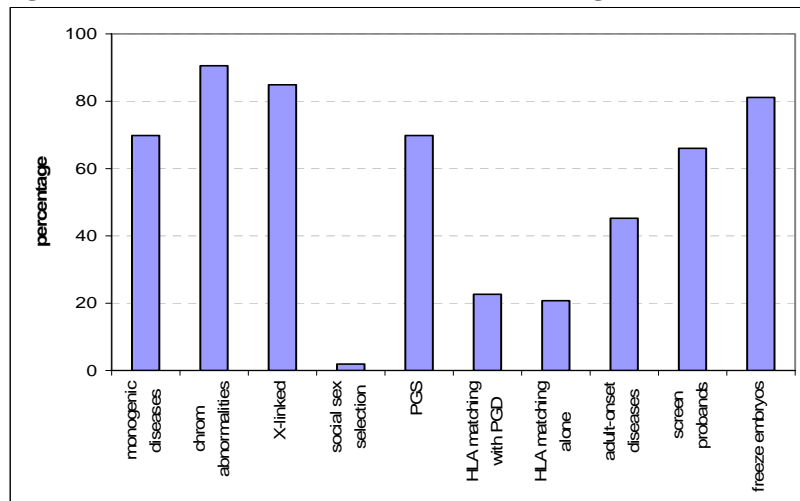
Figure 3: Affiliation of the individual service providers (labs and clinics)



3.1.2 Tests and pathologies

The centres performing PGD were asked to indicate the types of tests they provide, giving “yes/no” answers (see Figure 4). Thirty-seven of the centres (70%) offer PGD for monogenic diseases, 48 (91%) cytogenetic testing for chromosomal abnormalities and 45 (85%) sex selection for X-linked monogenic disorders. Only a single centre replied that it offers cytogenetic analysis for “social sex selection” (also known as family balancing, a form of social sex selection, where the family has to have at least one child of the opposite sex to the sex they want PGD for), but it is not known whether the centre offers full social sexing, i.e. for the first child.

Figure 4: Services available in the 53 centres offering PGD



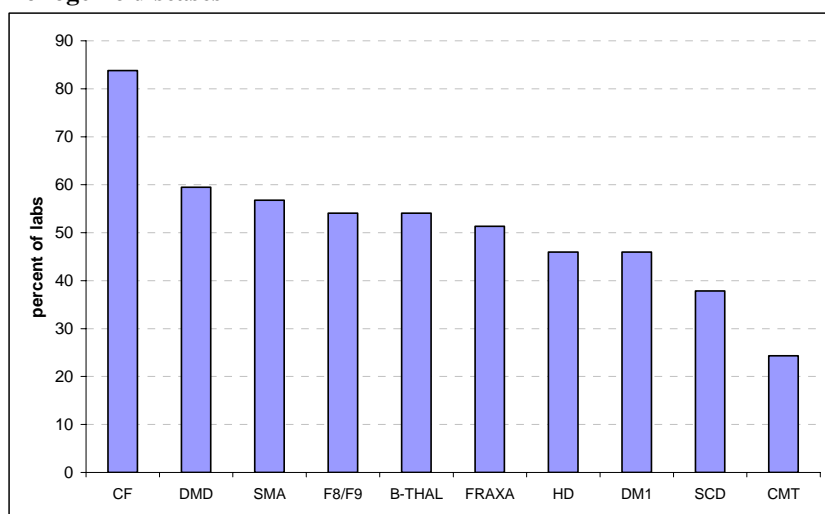
PGS for aneuploidy screening was performed in 37 of the centres (70%); two centres from the Netherlands perform only PGS and no PGD. It is possible that in this preliminary study further PGS-only labs were not identified within the “chromosomal anomaly” section. For instance, two centres which report to the ESHRE PGD Consortium did not reply to this survey, because they perform PGS only.

Fourteen of the centres (26%) offer HLA-typing for identifying embryos with histocompatibility antigens that would make them suitable donors for bone-marrow or stem-cell transplantation to an individual already affected by the same genetic disease or potentially by a non-hereditary disease such as leukaemia. Three of the centres perform typing only in association with PGD, but the remainder offer it either combined with PGD (12 centres, 23%) or as a test in isolation (11 centres, 21%).

Thirty-five centres, six of which do not at present offer monogenic PGD, answered that they offer mutation detection in probands/parents. Consequently, 29 of the 37 centres offering PGD for monogenic diseases also provide mutation detection in probands/parents (78%). Finally, 43 of the 53 centres (81%) freeze embryos for later use.

The 37 centres offering PGD for monogenic diseases were asked if they test for ten specific, relatively common diseases (see Figure 5). Cystic fibrosis (CF), spinal muscular atrophy (SMA) and β -thalassemia are, unsurprisingly, the most common autosomal recessive disorders, tested for by 50% or more of the labs. The X-linked diseases Duchenne/Becker muscular dystrophy (DMD), haemophilia A/B (F8/F9) and fragile X syndrome (FRAXA) are also covered by 50% or more of the labs. These diseases, together with Steinert myotonic dystrophy (DM1) and sickle-cell disease (SCD), are commonly requested in prenatal diagnosis and the distribution of answers would be expected to be similar were the question to be asked in prenatal labs.

Figure 5: Availability of testing for 10 common monogenic diseases at the 37 centres providing PGD for monogenic diseases



The provision of PGD for Charcot-Marie-Tooth (CMT) by nine centres (24%) is interesting, as conventional prenatal diagnosis for CMT is rare, because of its clinical heterogeneity and relatively benign course.

Twenty-four centres (65% of the 37 performing monogenic PGD) test for adult-onset diseases. Testing for Huntington's disease (HD), a neurodegenerative disorder with an onset typically in the fourth or fifth decade, is offered by 17 centres (46%); the other diseases were not formally identified but include a number of familial cancer predispositions (see Table 3).

No questions were asked in the survey about disease-specific technical details, for example the range of mutations covered for CF or whether mutation analysis or merely sex selection is provided for X-linked recessive diseases.

The detailed country-by-country analysis of these answers reveals a tendency for most laboratories in each individual country to diagnose most or all diseases, rather than to distribute the diseases between centres (see Table 2).

Table 2: Detailed results by country on availability of PGD for common monogenic diseases

	CF	DMD	SMA	F8/F9	βTHAL	FRAXA	HD	DM1	SCD	CMT
Belgium [n = 6]	3	3	3	1	2	2	2	2	3	2
Cyprus [n = 1]	1	1	-	1	1	-	1	-	-	-
Czech Republic [n = 6]	2	1	1	1	-	1	-	-	-	-
Denmark [n = 1]	1	1	-	-	-	1	1	1	-	-
Finland [n = 2]	-	-	-	-	-	1	-	1	-	-
France [n = 3]	3	3	3	3	2	2	2	3	2	1
Germany [n = 3]	1	1	-	1	-	1	-	1	-	-
Greece [n = 6]	4	1	2	2	6	1	1	1	3	-
Portugal [n = 1]	-	-	-	1	-	-	1	-	-	-
Spain [n = 8]	7	6	5	5	3	5	5	3	2	3
Sweden [n = 2]	1	1	2	1	1	1	-	1	-	-
Switzerland [n = 1]	1	-	-	-	1	-	-	-	-	-
The Netherlands [n = 3]	1	-	1	-	-	1	1	1	-	-
Turkey [n = 3]	2	2	2	2	2	2	1	1	2	2
United Kingdom [n = 5]	4	2	2	2	2	1	2	2	2	1

The figures in square brackets [] show the number of centres that provide PGD. The table indicates the number of centres per country testing for each disease.

Centres also reported the “Other” pathologies for which they offer tests. Table 3 lists the 51 pathologies/indications that were given as answers; in addition, some centres replied “more than 50 indications” or “custom-made analysis of any disease of known genetic cause”.

Table 3: Indications for monogenic PGD reported in the survey

Achondroplasia	Hypochondroplasia	Noonan
Angelman/UBE3A	Huntington	Pancreatitis, hereditary
BRCA1 & 2	HLA-typing	Polycystic kidney disease (AR & AD)
β-thalassemia	Incontinentia pigmenti	Polyposis coli (APC)
Cancer predisposition	Kell isoimmunisation	Retinoblastoma
Charcot-Marie-Tooth	Krabbe	San Filippo (MPS III)
Cystic fibrosis	Leigh	Spinocerebellar atrophy 1, 2, 3 & 7
Crouzon	Lesch-Nyhan	Sickle-cell disease
Diastrophic dysplasia	Leukodystrophy, metachromatic	Spinal muscular atrophy
Duchenne muscular dystrophy	Lowe syndrome	TH (tyrosine hydroxylase deficiency)
Epidermolysis bullosa	Marfan	Tuberous sclerosis 1 & 2
Ehlers-Danlos	Multiple endocrine neoplasia, MEN2	Tay-Sachs
Familial amyloidosis	Myotonic dystrophy	Von Hippel-Lindau
Fragile X	NARP	Wiscott-Aldrich
Haemophilia A & B	Neurofibromatosis 1 & 2	

The majority of the diseases listed are severe, and prenatal diagnosis is often requested by families; by contrast, prenatal diagnosis is relatively uncommon for some, for example BRCA (predisposition to breast cancer) or hypochondroplasia. This list cannot be regarded as comprehensive but clearly shows the wide range of tests available and a general trend towards making custom-made tests available, including for extremely rare disorders, together with PGD for some indications which may be less acceptable in prenatal diagnosis.

3.1.3 Counselling, consent and reporting

Genetic counselling is a communication process that provides genetic information in a non-directive manner, facilitates decision-making and supports the individual seeking counselling and the individual's family (American Society of Human Genetics, 1975). All patients entering a PGD/PGS programme need to receive counselling (ESHRE Guidelines, 2005).

Centres were asked if they provide counselling and, if so, whether it is “available at the IVF centre, the genetics centre or from partners?”. According to the replies, genetic counselling is offered by at least 50 of the 53 centres (94%). The majority offer counselling at the IVF centre and/or at the genetics centre, although the answers do not reveal whether or where counselling is actually given (see Table 4).

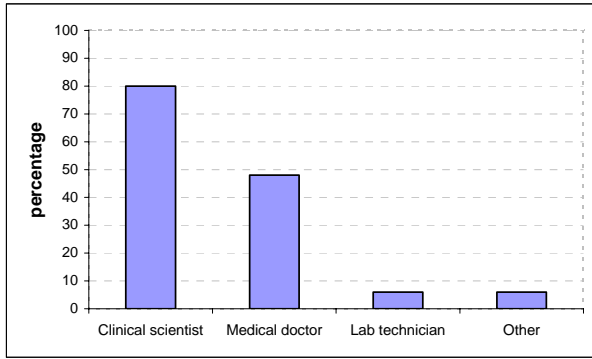
Table 4: Availability of genetic counselling services in centres providing PGD

Genetic counselling	Number (%)
at IVF centre	25 (50)
at genetics centre	38 (76)
from partners	8 (16)

The objective of **informed consent** prior to a medical procedure (e.g. in prenatal diagnosis) is to ensure that the patient understands the risks, discomforts and benefits of the procedure(s) to be performed and is aware of the alternatives, including the alternative of not performing the procedure. Informed consent means that the person consents voluntarily (WHO 2003). Written consent is recommended by the ESHRE Guidelines (2005). Informed consent from the patient is required by 94% of the centres; this survey did not address the questions of who is responsible for obtaining the informed consent or whether it is always in writing.

Reports are “specific formal documents from the laboratory to the referring doctor, recording the outcome of genetic investigations on a patient” (Swiss Society of Medical Genetics, 2003). The PGDIS (Preimplantation Genetic Diagnosis International Society) Guidelines (2004) state that “the IVF laboratory must receive from the genetics laboratory a written report of the performed analysis”. Fifty of the 53 centres performing PGD (94%) replied that they issue formal reports. The reasons why the other three labs send no reports were not identified by this study and, although the proportion is low, the lack of formal reports is potentially a cause for concern. Centres issuing reports were asked who “signed/validated test results?” (see Figure 6). Eighty percent replied “clinical scientist” and 48% “medical doctor”. The 50 centres gave a total of 70 replies, suggesting that results may be validated by more than one person.

Figure 6: Signature/Validation of PGD test results

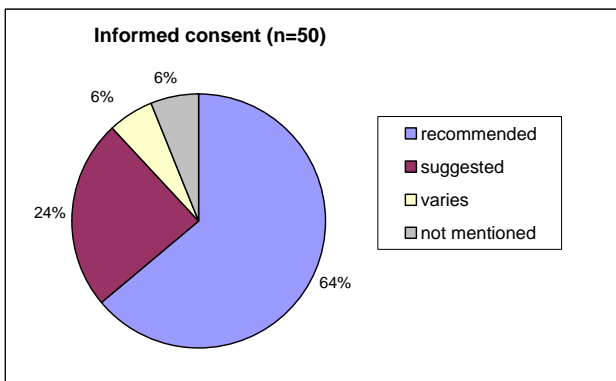
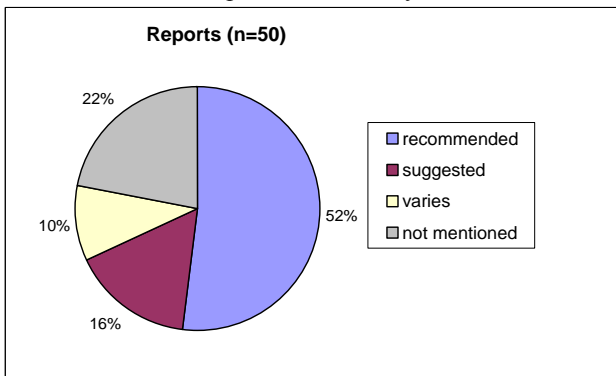


Fifty laboratories gave a total of 70 replies.

Participants were asked what recommendations they made on **follow-up confirmation of PGD** by choriocentesis or amniocentesis in their formal reports and in their informed consent documents. Follow-up can eliminate the small residual risk of diagnostic error with PGD, but at the cost of an invasive procedure which could lead to pregnancy loss. In the informed consent, follow-up confirmation by amniocentesis/choriocentesis is “recommended” or “suggested” in 88% of the centres (44 out of 50), presumably in association with genetic counselling. However, only 68% (34 out of 50) do so in their formal laboratory reports and 22% (11 out of 50) do not mention follow-up at all in their reports (see Figure 7).

Figure 7: Laboratory practice for recommending confirmation of PGD

Question: “Follow-up confirmation by amniocentesis/choriocentesis is:”

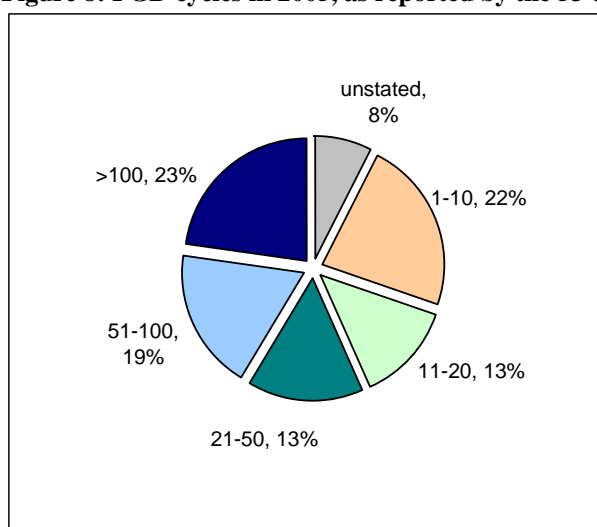


3.1.4 Number of PGD cycles in Europe

To gain better insight into the current extent of PGD activity in Europe, the survey also inquired about the number of PGD cycles performed. Participants were asked “How many PGD cycles did you perform in 2005 (monogenic diseases, chromosomal abnormalities, sex selection)?”

To obtain the highest possible response rate, the answer simply required selection of one of five possible ranges and participants were informed that the data would remain confidential “for anonymous research only”. The responses show an even distribution across the entire range of activities (see Figure 8). Detailed country-by-country analysis revealed no obvious differences.

Figure 8: PGD cycles in 2005, as reported by the 53 centres offering PGD



The replies reveal that the 49 centres which replied to the question performed a total of between 1 967 and 2 860 cycles in 2005. These data must be taken with caution given that they are not comprehensive and, although the survey question was designed specifically to exclude PGS from the replies, this cannot be firmly guaranteed.

As an informal validation exercise for the survey, the data can be compared with existing European figures. Given that 39 of the 53 providers surveyed replied that they report data to ESHRE, comparison with the ESHRE figures is valuable.

The centres which responded to both this survey and to ESHRE reported 886 PGD (plus 1 405 PGS) cycles to ESHRE for 2002 (the last data compilation available, Harper *et al*, 2006). The first conclusion is that the ESHRE figures are of a similar order of magnitude to the 1 967 to 2 860 cycles indicated by this study, suggesting that the two data collections are similarly comprehensive.

Secondly, the numbers support the general perception that PGD is an expanding activity and that many centres will have carried out more cycles in 2005 than in 2002. It is impossible to give a more precise estimate of how comprehensive the data are and, unless reporting cycles becomes a formal requirement for the majority of providers in the future, it will be difficult to obtain more reliable numbers.

Further comparisons of the data sets are worth noting. Seven centres appear to have over-reported, either by including PGS cycles or because the ESHRE data predate the numbers reported to ESTO. Six centres are relatively new members of ESHRE and therefore did not report their activity in 2002. The two centres in Italy are active members of the ESHRE PGD Consortium but reported in this study as “IVF only” because Italian law changed in 2003 and more recently submitted data are on polar body biopsy and PGS alone. One centre reports only monogenic disease data to ESHRE, but in this survey also reported PGD for chromosomal aberrations.

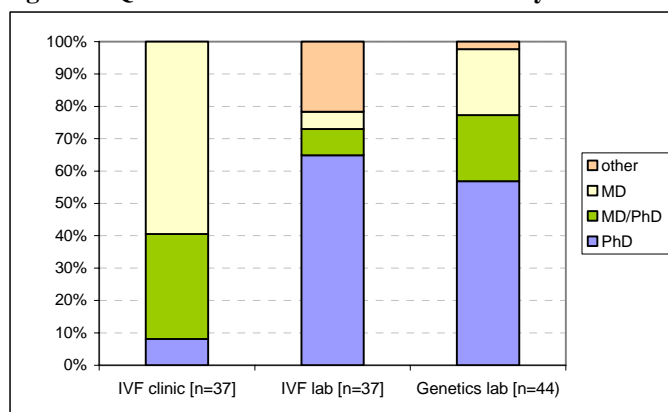
3.2 Quality assurance

3.2.1 Directors of PGD laboratories and clinics

Although current PGD guidelines (PGDIS 2004, ESHRE 2005) make no recommendations concerning the qualifications of staff, the degrees held by laboratory directors have been identified as a major criterion for quality assurance in molecular genetics laboratories (McGovern et al. 1999).

Participants were asked what qualifications the clinical and laboratory directors hold. Replies were obtained from 84% of the clinics and laboratories performing PGD. The results showed a trend towards PhDs directing the laboratories and doctors of medicine (MDs) the clinics (see Figure 9).

Figure 9: Qualifications of clinic and laboratory directors



The number of answers in each category appears in brackets. “Other” means different types of pre-doctoral degrees.

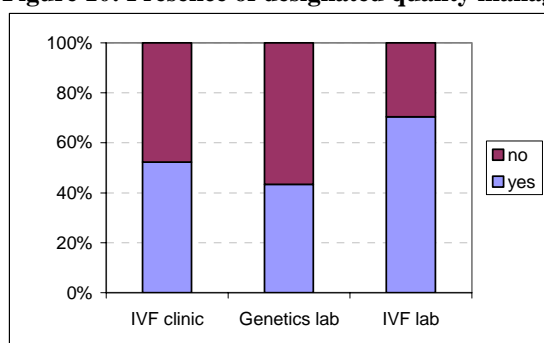
Thirty-four of the forty-four genetics laboratory directors (77%) are PhDs (25) or MD/PhDs (9) and nine are MDs. In the IVF labs, 27 of the 37 laboratory directors (73%) hold PhD (24) or MD/PhD (3) degrees, and only two are just MDs. Surprisingly, 22% of IVF laboratories (8 out of 37) have directors with neither MD nor PhD degrees but with Masters or similar post-graduate degrees. In the IVF clinics and genetics labs the figures are 0 out of 37 and 1 out of 44 respectively. Ninety-two percent of the directors of the IVF clinics replying (34 out of 37) are medical doctors (MD or MD/PhD); just 3 out of 37 have PhDs.

3.2.2 Quality manager

The quality manager is responsible for quality issues, and has the role of focusing on a consistent commitment to excellence and continuous improvement. The presence of a designated quality manager is a sign that a service recognises the importance of and is willing to invest in quality assurance and improvement.

According to the survey, only 77 out of 141 clinics and laboratories have a designated quality manager (55%). The situation is not so bad in the IVF laboratories (70% with a quality manager) as in the IVF clinics (52%) or the genetics labs (just 43%), but there is considerable room for improvement and perhaps education of the centres in this aspect (see Figure 10 and Table 7).

Figure 10: Presence of designated quality managers



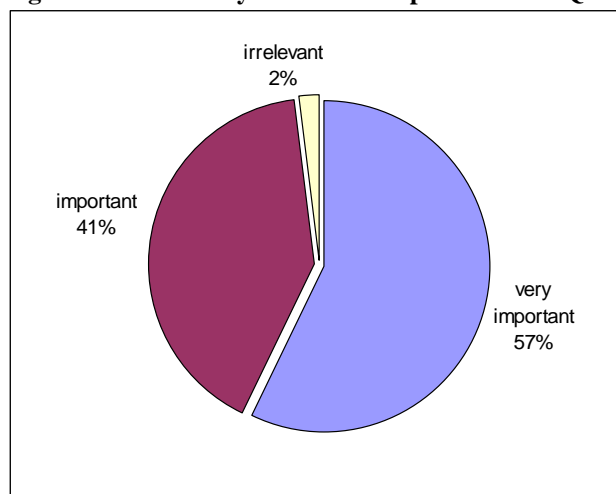
3.2.3 External quality assessment

External quality assessment (EQA) means a system in which laboratory results are scrutinised objectively by an outside agency in order to gain a general impression of the standard of laboratory practice and to achieve interlaboratory comparability (WHO). This assessment is retrospective and, consequently, the main aim of EQA is not to achieve day-to-day consistency but to help establish comparability of results between laboratories and between techniques.

Typical comprehensive EQA schemes in medical genetics assess the (a) technical aspects and (b) interpretation and reporting of results. As the ESHRE Guidelines (2005) note, there are no specific EQA schemes for PGD, but many European schemes exist for prenatal and postnatal testing, covering both molecular genetics and cytogenetics (EuroGentest 2005a,b). ESHRE (2005) recommended introduction of a voluntary EQA system that would solve this problem, with proficiency testing/assessment performed at least annually.

When asked “Do you participate in External Quality Assessment (EQA) schemes?”, only one third of the centres (18 out of 53) answered “yes”. One explanation is that some of the labs answering “no” may perform EQA for, for example, postnatal testing, but decided that this was not relevant. However, labs were also asked “How do you rate the importance of EQA?” (Answers: “very important”, “important” or “irrelevant”). 98% of the labs (48 out of 49) rated EQA as important or very important, and only one stated that it was “irrelevant” (see Figure 11). This indicates a clear necessity and desire for EQA schemes adapted to PGD; this needs to be addressed.

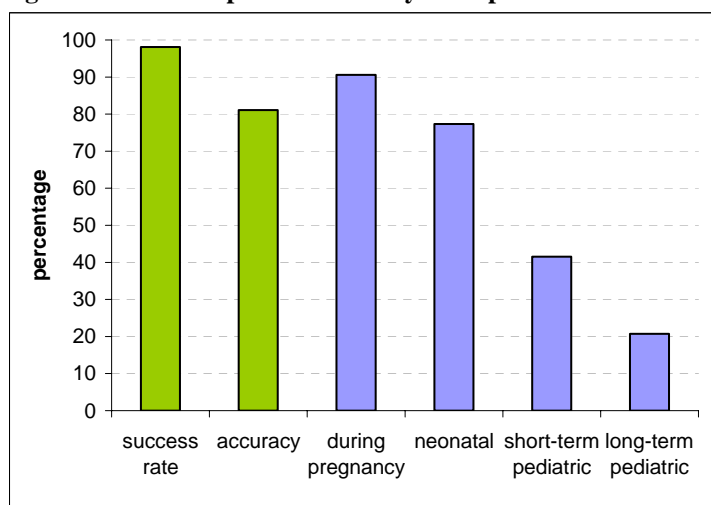
Figure 11: “How do you rate the importance of EQA?”



3.2.4 Quality management system

A series of questions were devised to evaluate critical aspects of the quality management systems of laboratories, including their record-keeping for important quality indicators such as success rate or accuracy and the existence of written instructions for two key quality parameters: validation of tests before diagnostic application and staff training. These procedures should be routine in accredited laboratories but, regrettably, are less common elsewhere. As shown in Figure 12, almost all the centres keep data on their success rate and 81% (43 out of 53) on accuracy. The majority of the centres follow pregnancies to the neonatal period, but few beyond this stage. Nonetheless, the finding that 19% of the labs (10 out of 53) keep no data on accuracy and 9% labs (5 out of 53) do not even follow up until birth is worrying and highlights a potential problem with quality assurance and patient safety.

Figure 12: Follow-up of outcomes by PGD providers



Answers from the 53 centres offering PGD services to two separate questions:
 Q1: “Your laboratory keeps data on ... :” (green bars); and
 Q2: “Your laboratory follows up ... :” (blue bars).

Most laboratories performing PGD keep analytical data for over two years, but again it is worrying that four do not even keep the data until the end of the pregnancy (see Table 5).

Table 5: Duration of data conservation

	Number of PGD labs (%)
< 9 months	4 (8)
9-12 months	4 (8)
1-2 years	1 (2)
> 2 years	43 (83)

Answers from 52 of the 53 centres performing PGD.

Q: “Analytical data are kept for ... :”

Finally, to obtain a preliminary picture of the state of their quality documentation the centres were asked “Do you have written protocols/policies for validating tests and for training staff?”. The answers showed a high degree of compliance (see Table 6).

Table 6: Documentation for validation and training

	Number of PGD labs (%)
validating tests	47 (89)
training staff	41 (77)

Answers from the 53 centres performing PGD.

Reporting to the ESHRE PGD Consortium is a further established method for following up PGD quality at European level. Of the 53 centres performing PGD (PGD + IVF or PGD only) who answered the survey 39 (74%) replied that they contribute data to the ESHRE PGD Consortium; conversely, ESHRE says that it has data from 33 (not 39) of the centres. The reasons for this discrepancy are not clear but could lie simply in the timing of the reporting to the two data collections.

Overall, these data highlight the need for more thorough and longer-term follow-up and documentation of results, to improve knowledge of the security and accuracy of PGD and thereby increase patient safety. It is hoped that ESHRE will become a cornerstone for building up monitoring of both PGD technology and long-term follow-up of babies. This survey has identified centres that do not report to ESHRE and highlights a need for ESHRE proactively to seek active participation by PGD centres.

3.2.5 Accreditation

Official recognition of the quality management system in the form of accreditation (including process management and technical competence) or certification (process management only) is an important step because it demonstrates the competence of the laboratory and its personnel in a clear, objective and independent fashion. Accreditation (based on international standards such as ISO 15189) is the single most effective way of assuring the quality of a medical laboratory.

The survey asked about the current status of accreditation and certification of the centres and their individual departments. It revealed that penetration of formal recognition of quality management is low in PGD centres (see Table 7). Thirty-three percent of the laboratories and clinics (46 out of 141) have or are preparing at least one form of formal recognition, although

only 17% (24 out of 141) are either accredited or working towards accreditation. One third of the genetics laboratories (18 out of 53) have or are preparing some form of recognition and 23% (12 out of 53) are accredited or working towards accreditation. The survey also asked about the licensing status of the centres. Only 11% of the labs and clinics (15 out of 141) are licensed, which is generally a legal requirement that may or may not be based on quality criteria.

Table 7: Accreditation, certification and licensing in PGD centres

	All	IVF clinic (44)	IVF lab (44)	Genetics lab (53)
Quality manager	55%	52% (23)	70% (31)	43% (23)
Accreditation ¹	17%	7% (3)	20% (9)	23% (12)
Certification ¹	17%	27% (12)	9% (4)	15% (8)
Accreditation and/or certification ²	33%	34% (15)	30% (13)	34% (18)

¹ Accredited/certified or working actively to this end.

² Some services replied “yes” to both accreditation and certification.

Uptake of accreditation is significantly stronger in the private sector: 73% of the accredited centres and 57% of those working towards accreditation or certification are private. Similarly, large centres are more likely to adopt a formal quality system: 31% of the centres which performed over 50 cycles are accredited and 37% are preparing for accreditation/certification, against only 13% and 19% respectively for smaller centres. Appropriately, given the different priorities of laboratory testing and patient care, IVF laboratories prefer accreditation to certification, whereas IVF clinics prefer the opposite; genetics laboratories are equally divided between certification and accreditation.

3.3 PGD procedures

A series of questions were asked to determine current practice for a number of steps which are critical in assuring quality of service in PGD laboratories. Firstly, centres were asked if they **confirmed the identification of mutations** when families were referred for PGD. This is important for two reasons: (1) it guarantees identification of the mutation, which is good practice until accreditation and unambiguous mutation nomenclature are widespread and (2) it provides valuable validation of the mutation assay within the laboratory, which is often custom-developed for a single family. Mutations are confirmed by the large majority of the centres; only three of the 49 centres confirm mutations in less than 50% of cases (see Table 8).

Table 8: Confirmation of mutation reports: replies from 49 of the 53 PGD centres

	Number of PGD labs (%)
In all cases	34 (69)
>50% of cases	11 (22)
<50% of cases	3 (6)
Always trust external report	1 (2)

Q: “Does your laboratory confirm the nature of familial mutations and/or chromosomal anomalies?”

A series of technical questions were asked (see Table 9 and Figures 13 and 14) which allow identification of consensus procedures in European centres:

- 48 of the 53 PGD centres analyse one or two blastomeres (34% and 57% respectively) (see Table 9); polar bodies are analysed in Austria, Germany and Switzerland, in response to the ban on direct embryo testing.

- All 48 centres biopsy blastomeres on day 3, mostly from the five- or six-cell stage onwards (52% and 35% respectively) (see Figure 13); blastomere biopsies are performed at the seven-cell stage in several centres in Estonia, Greece and Turkey.
- Embryo biopsies are always performed by a biologist/embryologist, either alone (36 out of 48) or with a technician (12 out of 48).
- PGD embryos are transferred on days 4 (20 out of 48) and 5 (25 out of 48) (see Figure 14).

Table 9: “Number of cells analysed per embryo per diagnosis?”

n=53

	Polar bodies		
	0	1	2
0	-	1	4
1	18	-	-
2	30	-	-

Figure 13: “Which embryos do you biopsy?”

n = 48

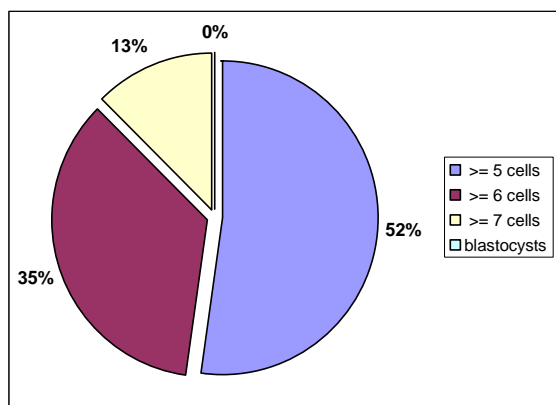
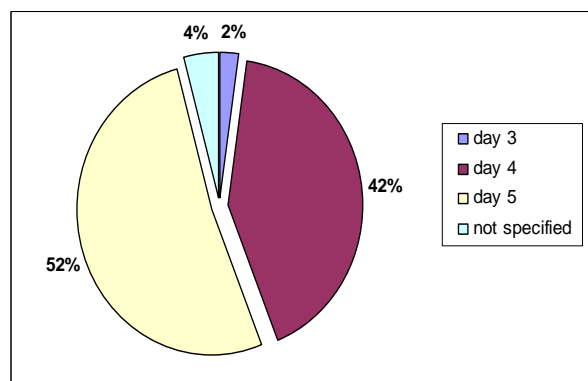


Figure 14: “On which day do you usually transfer fresh embryos following PGD?”

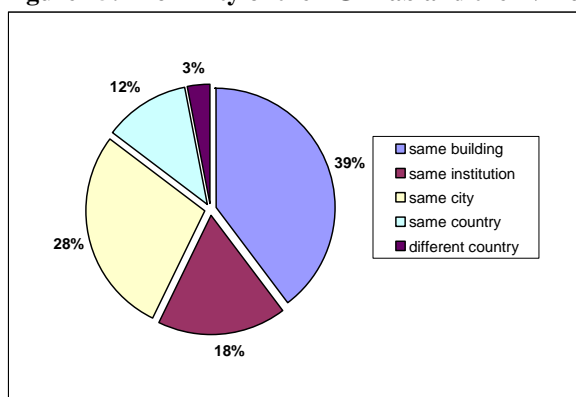
n = 48



Although the ESHRE Guidelines (2005) state that use of controls is contentious and is merely “acceptable” for PGD, use of **positive controls** for FISH probes and, particularly, **negative controls** for PCR is very valuable. Such controls are used by 43 of the 53 centres, indicating that this is common practice.

In order to gain a better understanding of the organisational details in relations between the genetics laboratories and IVF clinics, the centres were asked about the relative proximity of the laboratories – “How close is the PGD lab to the IVF clinic?” A total of 68 replies were obtained from 53 centres, as some labs or clinics work with different partners. Although the majority of tests were performed nearby, 15% are carried out only in the “same country” or in a “different country” (12% and 3% respectively); proximity therefore does not seem to be a critical issue.

Figure 15: Proximity of the PGD lab and the IVF clinic



68 replies from 53 centres.

Availability and use of strictly separated working zones are of prime importance in PCR to avoid contamination, particularly for monogenic PGD with its reliance on single-cell PCR. Only 65 to 78% of the centres performing PGD for monogenic diseases (and 49 to 57% of all the PGD labs) have such dedicated working zones in place (see Table 10). Furthermore, five centres performing monogenic PGD answered “no” to all three questions.

Table 10: Dedicated working zones to avoid contamination

	% monogenic PGD labs (n)	% PGD labs (n)
pre-PCR	78 (29)	57 (30)
PCR	65 (24)	49 (26)
post-PCR	70 (26)	51 (27)
	n = 37	n = 53

Q: “Do you have dedicated rooms for...?” (n = 53)

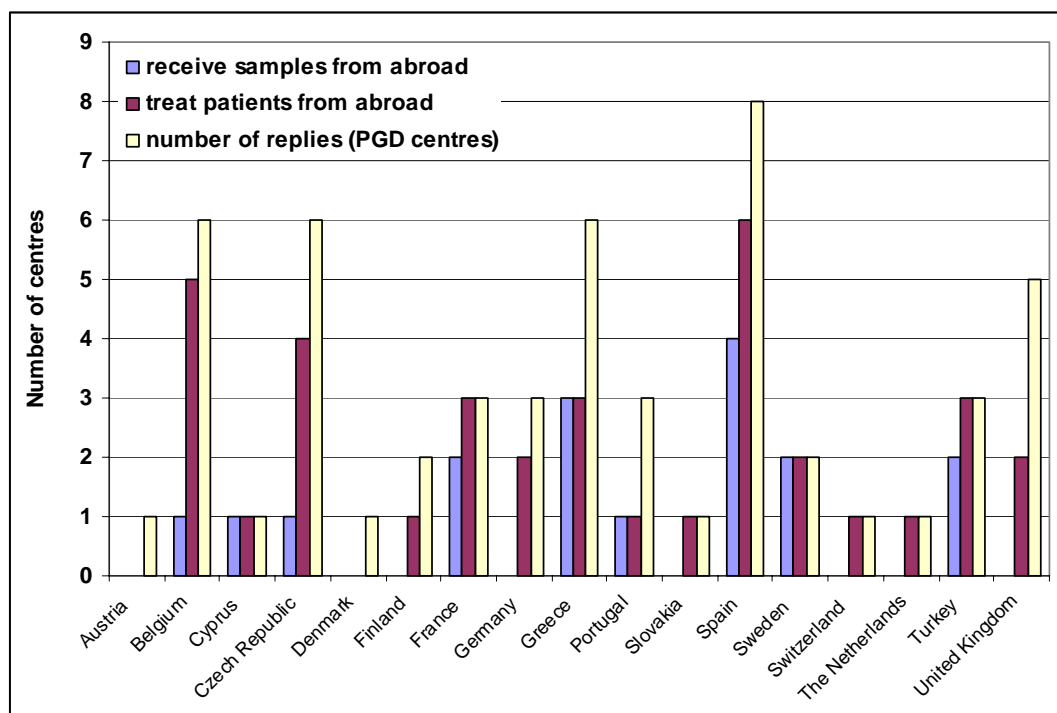
Although the ESHRE Guidelines (2005) call for “physical separation of pre-PCR, PCR and post-PCR laboratories and the biopsy laboratory”, the results of this survey indicate that some laboratories are not appropriately equipped and reveal a potential safety problem, which will need to be addressed.

3.4 Trans-border flows

A series of questions were asked to determine the current situation with trans-border flows related to PGD, i.e. the level of movements of couples (and/or samples) from one Member State to another in order to gain access to these services.

First, centres were asked if they receive samples and/or treat patients from abroad. To further elaborate, centres were also asked approximately how many patients come from other countries each year, from which countries, and for what specific reasons they typically travel abroad seeking PGD services (four options were suggested: legal reasons, test availability, financial reasons and other reasons).

Figure 16: Centres receiving samples or treating patients from abroad



Out of a total of 53 centres which replied to the survey that they offer PGD (PGD only and IVF + PGD), 17 receive samples and 36 treat patients from abroad. A detailed country-by-country breakdown of the centres receiving samples/treating couples is provided in Figure 16.

Spain is the leading receiver of patients within Europe, with around 332 patients treated per year in four of the six centres that replied (the two remaining mentioned that they receive patients from Italy but did not specify how many) (see Table 11). Other major receivers include Belgium and the Czech Republic. Cyprus is emerging as a key player in this activity, having treated 150 patients in just one centre. Germany, Greece, Slovakia and Turkey also treat patients from abroad but fewer than received by the leading countries listed above (see Table 12).

Table 11: Trans-border flows: main receiving countries

	Number of centres that treat patients from abroad	Number of patients treated
Belgium	5	127
Cyprus	1	150
Czech Republic	4	110
Spain	6	332

The number of foreign patients received by Sweden and France may be underestimated as only one centre from each country reported figures. Austria and Denmark reported that no samples or patients are received from abroad. Other centres (two in the UK and one in

Switzerland) reported that they treat patients from abroad, but did not say how many each year.

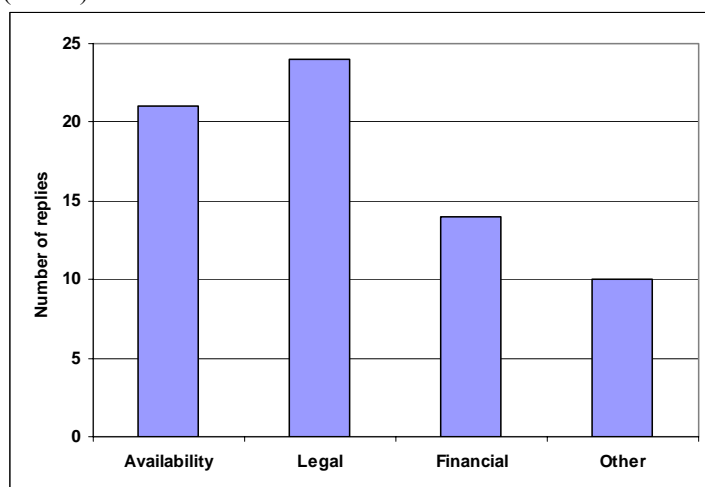
Table 12: Trans-border flows: other receiving countries

	Number of centres that treat patients from abroad	Number of patients
Finland	1	1
France	3	10
Germany	2	22
Greece	3	18
Portugal	1	2
Slovakia	1	20
Sweden	2	3
The Netherlands	1	2
Turkey	3	35

Indicative trends were also observed in where the patients come from, potentially indicating geographical restrictions on the flows observed. For example, patients treated in Greece come from only Albania and Italy, patients reported to have been treated in Slovakia are all from Poland and patients received by Sweden come either from Iceland or Norway. By contrast, the major receiver countries (Spain, Belgium, the Czech Republic and Cyprus) treat patients from a broader range of nationalities.

Legal reasons and test availability were identified as the main drivers behind the flows of patients observed within Europe. Financial reasons were also cited in a large share of the replies. Other reasons mentioned by respondents included: quality of service, experience and success rates, expertise on certain diseases, length of waiting lists and the reputation of the clinic (see Figure 17).

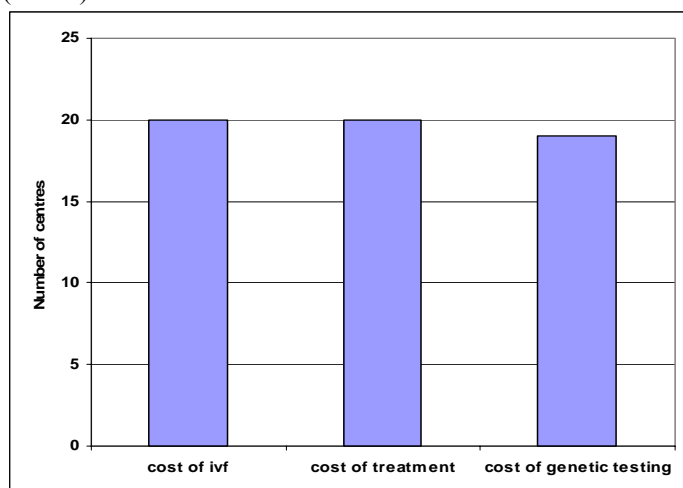
Figure 17: Patients' reasons for travelling abroad for PGD
(n = 53)



3.5 Financial aspects

To gain further insight into the reimbursement situation for PGD across the EU, participants in the survey were also asked whether couples receive public funding or reimbursement for PGD and, if so, what percentage of the cost is reimbursed. As the question was not mandatory, it remains unclear whether the countries that offer PGD but did not answer (e.g. Austria, Cyprus and Greece) actually offer reimbursement. Nevertheless, 22 centres from a broad range of countries replied positively. Twenty of them reimburse the cost of IVF and/or the cost of treatment and 19 also reimburse the cost of genetic testing (see Figure 18). As the survey reveals, in the majority of cases the procedure (i.e. cost of IVF and treatment plus cost of genetic testing) is reimbursed either completely (e.g. Spain) or partly (ranging between 80% and 90%, with only one UK centre reporting reimbursement of 30% to 40%). In this context, it is important to note that from this data it is difficult to distinguish whether the respondents are referring to reimbursement for couples from abroad. Another question that remains open is whether reimbursement – where offered – is available for couples treated in their own country or in another.

Figure 18: Centres offering reimbursement for PGD-related services
(n = 22)



3.6 PGD referral

Eight centres in seven countries (see Table 13) replied that they perform IVF and refer PGD. In some countries this is certainly because PGD is not permitted; other reasons given included:

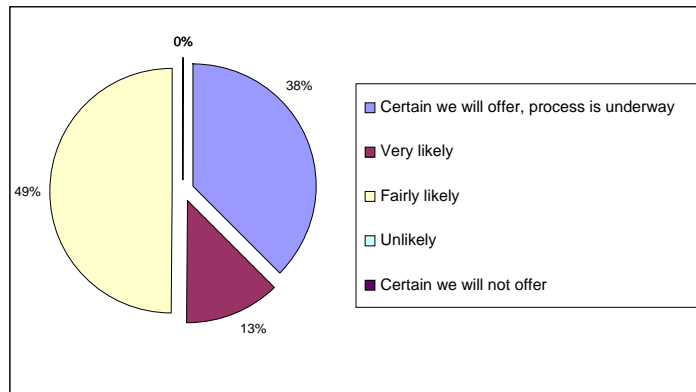
- “would like to offer PGD but do not have the resources/staff/money/expertise to make it available” (4);
- “unfamiliar with PGD” (1);
- “PGD is experimental” (1).

Half the centres in this category were “very likely” or “certain” to offer PGD in the future (see Figure 19), and no laboratory excluded this possibility.

Table 13: Countries with IVF labs that refer PGD

Germany
Greece
Portugal
Spain
Sweden
Turkey
United Kingdom

Figure 19: “What is the likelihood you will offer PGD in the future?”



Referrals can be made in a number of ways (see Figure 20). Seven of the eight centres give information to couples about foreign PGD labs, four actively refer couples and one sends samples abroad.

Figure 20: Mechanisms of foreign referrals

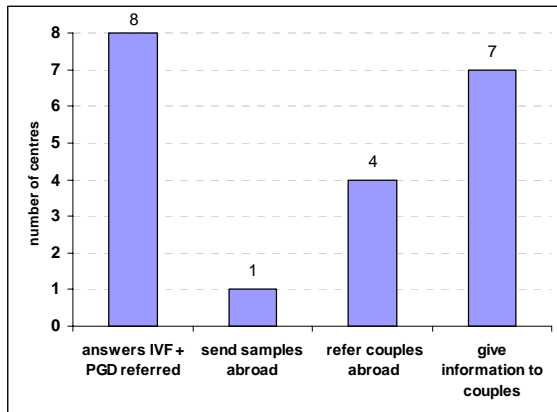


Table 14 shows that referral was most commonly for legal reasons, and less commonly because of test availability.

Table 14: “What are the reasons to refer couples abroad?”

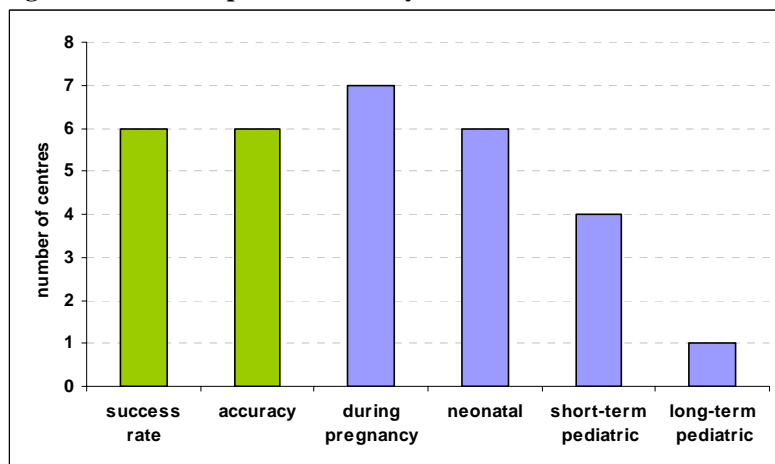
	legal reasons	test availability	financial reasons
refer couples abroad	4	2	0
give information to couples	5	3	0

In terms of traceability, six of the eight centres receive formal reports from the genetics laboratories. Six keep data for more than two years, and one for one to two years (one lab did not answer).



The data that are kept are shown in Figure 21; the survey did not distinguish whether this concerns all cases handled by the laboratory (principally IVF) or only the referred PGD cases. Four centres have written protocols for validating tests, and five for training staff.

Figure 21: Follow-up of outcomes by laboratories



Answers from the eight centres offering IVF + referred PGD to two separate questions:

Q1: “Your laboratory keeps data on: ...” (green bars);

Q2: “Your laboratory follows up: ...” (blue bars).

4 CURRENT PGD PRACTICE IN EUROPE

This chapter presents a more exhaustive analysis of PGD practice and provision in specific countries (Belgium, the Czech Republic, France, Germany, Greece, Ireland, the Netherlands, the Slovak Republic, Spain, Switzerland and the UK). This analysis is based on data gathered from the survey (see Chapter 3) and from interviews with experts in the field in the countries mentioned above (for details of the questionnaire used for the interviews see Annex 2).

4.1 Belgium

4.1.1 PGD services

Six PGD centres replied to the survey. All six are “B-centres” for reproductive medicine (i.e. accredited for the whole IVF process), five of them are publicly funded university centres combining an IVF centre and a genetics centre on the same site, while the other is a private IVF centre collaborating with one of the other Belgian genetics centres or with a genetics centre abroad (Italy). Staff from all except one of the centres were interviewed.

All the centres offer PGS and PGD for chromosomal abnormalities, plus sexing for X-linked diseases using FISH technology. Three of the centres also offer PGD for monogenic diseases, two offering IVF plus PGD with two private centres offering IVF only and sending samples to a genetics laboratory. Two centres also send samples to Italy, mainly for treatment of Italian patients who undergo IVF in Belgium and for whom the genetic diagnosis is carried out in Italy.

One centre offering PGD for monogenic diseases is one of the largest in the survey and offers PGD on request, i.e. for rare diseases, as well as for the more common diseases (CF, β -thalassaemia, SCA, SMA, DM1, HD, FRAXA, DMD, etc.). The second offers PGD mainly for frequent monogenic diseases.

In the five university centres, there is close interaction between the IVF and the genetics centre: diagnosis is developed and carried out in the genetics laboratory, and the IVF itself and the biopsy are performed at the IVF clinic. The two private IVF centres collaborate very closely with external genetic diagnosis centres. Regular meetings are organised and day-to-day communication is electronic. Diagnoses are validated by geneticists. The intake of patients is usually through the genetics centre or, alternatively, genetic counselling is provided before the start of treatment. Throughout treatment, and during the follow-up of the patient, genetic counselling is available.

4.1.2 Education and quality assurance

Of the six centres responding, one IVF lab is accredited and one certified, but none of the IVF clinics or genetics laboratories is. Four IVF clinics, six IVF labs and two genetics labs have quality managers. Although only one centre is participating in external quality assessment schemes, but five thought that EQA is important. The one centre responding positively is participating in EMQN schemes, EAA and ESHRE schemes for sperm analysis and QAP Online for embryo scoring. It is clear that several other Belgian centres are also participating in these, or similar, schemes, but did not report them as the schemes are not specific to PGD.

Moreover, all six centres responding report data to ESHRE; two reported that they do so although they are not members, which reflects their intention to join in the near future. As further support for this argument, most centres follow some external guidelines, e.g. HFEA or ESHRE Guidelines, although some have developed their own.

Only the accredited/certified IVF labs monitor the quality of the centre through constant quality control by the quality manager. However, all the other centres strive to keep up quality through monitoring, self-evaluation, feedback, control systems and standardised protocols.

With regard to staff training and education, all the centres make an effort to send their staff abroad to internationally recognised centres and then continue their education, either by sending staff to workshops or through in-house training. All six centres have written protocols on staff training and on validation tests before clinical application.

4.1.3 Trans-border flows and financial aspects

One Belgian centre receives no patients or samples from abroad. All five other centres treat patients from other countries but only one also receives samples. Three centres offer PGD, mainly for chromosomal abnormalities, to Dutch couples who prefer to turn to a Belgian centre because of limited test availability and long waiting lists in their own country. One centre reports that it received Dutch couples for legal reasons, i.e. because use of testicular sperm is not allowed in the Netherlands, and because these patients are proposed as an indication category for PGS.

One large PGD centre accepts patients and samples from different EU countries and from outside the EU: couples from Germany, Italy, Switzerland, Austria, Ireland and Norway for legal reasons and couples from Denmark, France, Greece, Luxembourg, the Netherlands, Portugal, Sweden, the UK, the USA and Israel for reasons to do with test availability. The total number of couples accepted from abroad makes up about half the total number of couples treated in this centre (i.e. as many couples from abroad are treated as from Belgium).

It is not very clear how the patients obtain information on where to seek PGD. Those who are referred for reasons of test availability are obviously referred by practitioners in their own country. However, in the case of patients who come for legal reasons, it is difficult to ascertain how they were referred, as referring patients is often perceived as problematic by health practitioners in countries where PGD is not allowed.

IVF is now covered by the Law on IVF Services. Accordingly, for example, six IVF cycles are completely reimbursed through the social security scheme, provided a number of conditions (e.g. on the number of embryos transferred) are met. For the genetic part of PGD, no specific reimbursement arrangements are in place in Belgium, so most of the centres report that the patients have to cover that cost themselves. However, one large centre reported that the preliminary test (e.g. family linkage analysis) and the PGD itself are counted by the social security system as part of genetic services and prenatal diagnoses. Foreign patients bear the full cost of IVF and PGD themselves, but sometimes obtain public or private funding in their home countries.

4.1.4 Monitoring

The organisation of the PGD centres in Belgium mainly depends on whether they are university or private centres. University centres usually provide IVF and genetic diagnosis in the same institution, often in the same building, while private labs are IVF labs collaborating with other genetics labs, whether university or private (abroad).

All the centres reported that they have good channels of communication between the genetics labs and the IVF labs, through daily contacts by electronic means (e-mail, cell phones and on-line systems) or regular monthly meetings. Technical barriers encountered include lack of personnel and the difficulty of coordinating such a complicated procedure as PGD. However, it is felt that reproductive specialists do not fully comprehend the complexity of genetic diagnosis, and often counsel patients wrongly or schedule IVF cycles prematurely. Another frequent problem is how to obtain accurate and complete information from patients referred from abroad. As also mentioned by a French centre, obtaining DNA samples from countries such as Germany is sometimes difficult.

One Belgian centre reported that it provides no follow-up at all, although patients are encouraged to undergo prenatal diagnosis: two centres provide prenatal, neonatal and short-term follow-up, whereas the others also offer long-term paediatric follow-up. The largest PGD centre provides long-term follow-up with the aid of EU support for research.

It is clear from the interviews that the PGD centres where the patients are best monitored and followed are those which provide IVF and genetic services at the same site. Communication between the two groups is felt to be crucial, but could still be improved. In particular, education of fertility specialists on the intricacies of single-cell diagnosis would increase their understanding of what is possible and, more importantly, what is not.

Up to now the only follow-up of PGD babies has either come from individual centres with a research programme in this area or from the ESHRE PGD Consortium. Some individual centres have also provided long-term follow-up, i.e. up to five years of age for children born after ART in large multi-centre studies (Bonduelle et al., 2005). The ESHRE PGD Consortium has collected only neonatal data, because many PGD centres are unable to provide more than that, and even neonatal data are impossible to obtain from many centres. The PGD Consortium plans to extend the follow-up with a small number of centres which have the infrastructure and financial resources to provide long-term follow-up, but the whole endeavour is hampered by lack of funding for, for example, logistical help (websites, database design and use, etc.) and for professional help with examining the children (paediatricians, paediatric nurses, genetic counsellors, etc.).

4.2 Czech Republic

4.2.1 PGD services

Altogether there are 23 IVF clinics in the Czech Republic. Seventeen offer PGD, 13 of which are private and four public. Currently about 250 to 300 PGD cycles are performed every year. However, so far only five clinics have reported successful pregnancy and birth of children after PGD.

Out of the total of seventeen IVF clinics operating in the country, six completed the international survey. Interviews were conducted with three of these clinics plus three others. Altogether some kind of a direct response was received from nine IVF clinics. Importantly, the respondents included the two largest IVF clinics in the country, each performing more than 1 500 IVF cycles a year. Together they carry out about 50% of all IVF cycles performed in the whole of the Czech Republic. Equally important for this study was the participation of the third largest clinic, located in Brno, which belongs to the pioneers of PGD in the Czech Republic and offers the widest range of genetic tests in the whole country.

All nine centres responding offer PGD. All of them can detect chromosomal abnormalities, but only three of them offer testing for monogenic diseases. The diseases tested for include cystic fibrosis (CF), haemophilia, Duchenne muscular dystrophy (DMD), neurofibromatosis 1 (NF1) and hereditary breast/ovarian cancer (BRCA1/2). Two other centres indicated that they are planning to start monogenic testing within six months.

In five centres, the IVF clinic and the genetics laboratory belong to the same institution, and in four of these both are located in the same building. Four other centres contract services from external genetics laboratories which do not belong to the same institution. In three cases, this laboratory is located in the same city. Most IVF clinics collaborate with only one genetics lab, but one collaborates with two (one for FISH and another for PCR). Interaction between clinics and genetic laboratories is quite frequent, depending on actual need. No technical barriers were reported in communication between IVF clinics and genetics centres. One IVF clinic indicated that it has to place orders for specific genetic tests in advance.

Genetic diagnosis is performed and validated by geneticists. Genetic counselling is offered in eight centres. The IVF clinic is responsible for counselling in three centres, while in another three the genetics laboratory is responsible. In the two remaining centres counselling is offered by both the IVF clinic and the genetics laboratory. Written informed consent is generally required before any PGD procedure. It is usually the responsibility of the clinical geneticist to obtain consent. However, two IVF clinics reported that their embryologist is responsible for obtaining informed consent in their institution.

4.2.2 Education and quality assurance

Currently, there is no formal mechanism in place for internal or external quality control or quality assessment for PGD diagnostic laboratories. Czech legislation does not require any obligatory quality schemes or accreditation systems for laboratory practice on PGD testing. A new law (in force since June 2006) requires all IVF clinics to obtain a licence from the Ministry of Health. Nevertheless, at least 12 IVF clinics in the Czech Republic already have ISO 9001 certification and at least five genetics laboratories have ISO/IEC 17025 accreditation. In our international survey, 5 out of the 6 responding IVF clinics have indicated they do not participate in EQA schemes. However, this answer must be due to some misunderstanding, because four of these clinics stated in the same survey that they have ISO 9001 certification and they also display the certificate on their web pages.

In line with this finding, four of the clinics also consider EQA important, one very important and only one irrelevant. Only one respondent has a quality manager for the IVF clinic, the IVF laboratory and the genetics laboratory. Another has a quality manager for only the IVF clinic and the IVF laboratory. The third centre has a quality manager for only the IVF clinic

and the fourth for only the IVF laboratory. Five centres keep data on success rate and accuracy for a significant length of time, the sixth keeps data on accuracy only.

There are no legal requirements on the sensitivity, specificity and predictive value of the genetic tests. It is the responsibility of each genetics laboratory fully to assess the sensitivity, specificity and predictive value of its methods before applying them to PGD. In this context, five out of the six centres responding stated they have a written protocol for validating genetic tests before application.

Education of the healthcare practitioners in the ART centre complies with the Ordinance from the Ministry of Health. Gynaecologists must have a medical degree, a certificate in either gynaecology and obstetrics or, more recently, assisted reproduction, and practice in this area. Education in clinical genetics is included in their specialisation (certificate). The minimum training required of the chief gynaecologist is second-grade certification in gynaecology and obstetrics and experience in endocrinology, vaginal sonography and endoscopy. He/she must also have at least two years' experience in assisted reproduction and practice corresponding to the requirements of the European Board and College of Obstetricians and Gynaecologists. Chief embryologists must have a university degree in medicine or biology, two years' practical experience in reproduction biology and experience of independently conducting 200 IVF cycles. Geneticists must have a degree in medicine and certificate in medical genetics. Four centres have written protocols on staff training. Three refer to the ESHRE and follow the Best Practice Guidelines for Clinical PGD/PGS Testing.

4.2.3 Trans-border flows and financial aspects

No samples are sent outside the Czech Republic for PGD and only one centre reported receiving samples for genetic testing from abroad. Similarly, no couples are referred abroad from the Czech Republic either for IVF therapy or for PGD. The main reasons reported are that the quality of the treatment in the Czech Republic is sufficiently high and the costs are much lower than abroad.

Foreign couples from various countries (mainly Croatia, Denmark, France, Italy, Israel, Lithuania, Germany, Austria, Slovakia, Ukraine and the USA) frequently come to the Czech Republic to receive IVF therapy (five of the nine clinics responding treat foreign couples). According to the experts, about 300 to 500 foreign couples come to the Czech Republic for IVF every year. However, a much lower number of foreign couples come for PGD (according to the experts, only about 20). A considerable proportion of foreign couples coming to the Czech Republic for IVF and PGD are recruited from countries with more restrictive regulation of IVF and PGD services (e.g. Italy or Germany) than the Czech Republic, where a new law was recently approved for regulation of PGD (which, according to one interviewee, “only legalised the established practice”). Nevertheless, the clinics interviewed report that the main reason for cross-border flows into the Czech Republic remains the lower cost of the treatment.

There are no statistics on how the information reaches foreign couples. According to the centres interviewed, most of the foreign couples obtain the information from the web pages of the IVF clinics in the Czech Republic. Quite frequently they also come on the recommendation of friends who have been successfully treated in the Czech Republic, whereas referral by foreign IVF clinics or physicians is more of an exception.

The national healthcare system covers three cycles of assisted reproduction regardless of the indications. The health insurance system pays most of the costs of drugs and transfer of the embryo. PGD is generally not covered by the national health insurance. However, three of the nine clinics responding stated that, depending on the indication and their type of agreement with the health insurance company, the cost of genetic tests but not of the embryology services may be covered, at least partially. Private health insurance is either non-existent or very rare in the Czech Republic, and the clinics surveyed therefore have no experience of any payment for PGD from private health insurance schemes. Most of the clinics stated that the costs of IVF and PGD may be restrictive for some low-income couples.

4.2.4 Monitoring

All but one of the IVF clinics responding strongly recommend prenatal testing in pregnancies after PGD, but the final decision depends on the patient. Postnatal follow-up in neonates is performed in six of the nine clinics responding. Only two indicated that they also carry out short-term postnatal monitoring. No long-term postnatal monitoring is performed, because it is not required by law and not favoured by parents. However, the recently approved Law on Assisted Reproduction set up the new register of assisted reproduction which should allow long-term postnatal monitoring.

The only international cooperation on monitoring offspring after PGD is organised by ESHRE. Three of the clinics responding report to ESHRE. However, no reliable long-term, multi-centre, multi-generational studies are being conducted in the Czech Republic. The main barriers to long-term monitoring include the reluctance of parents to take part and insufficient funding (e.g. the health insurance companies tend not to cover expenses for such monitoring).

4.3 France

4.3.1 PGD services

As stated by the “Agence de Biomédecine”, only three licensed laboratories offer PGD in France: one centre in Paris, one in Strasbourg and one in Montpellier. All three replied to the survey and to the interview questionnaire. They are all publicly funded university centres, each consisting of an IVF centre closely linked to a genetics laboratory, within the same institution.

All three are major IVF and genetics centres, with a long track record and broad experience. Two of these three centres offer PGD for monogenic diseases and chromosomal abnormalities. All the centres offer PGD for several common monogenic disorders plus some diseases of particular interest to the centre, e.g. Charcot-Marie-Tooth type 1 or retinoblastoma. Some of the centres also offer sexing for X-linked monogenic diseases. However, none of the centres offers sexing for social reasons or preimplantation genetic screening (PGS), both of which are forbidden in France.

In all three centres the interaction between the ART clinics and the genetics centre is very close, and the whole process is highly regulated from patient intake to the cycle and follow-up

of the patients and their children. Genetic diagnosis is performed and validated by geneticists. Counselling is provided by the genetics centres making up the PGD units. However, staff at one of the centres interviewed remarked that collaboration between the genetics centre and the IVF centre could be closer and felt that the IVF centre does not fully comprehend the difficulties encountered in single-cell diagnostics.

To quote one of the geneticists interviewed: “In my point of view, in France, PGD is too much considered primarily as part of IVF procedures and not enough as primarily a "genetic diagnosis". This situation may lead to inappropriate information to couples, at all steps of the procedure. It is considered more advisable to treat PGD, like PND, primarily by a genetic analysis performed on a cell biopsied by the IVF clinics”. This feeling is also present in other large EU PGD centres.

Nevertheless, the three PGD centres in France collaborate closely and meet twice a year to exchange results and experience as part of continuous quality assessment. The uniformity of these three PGD centres most probably reflects the choices made by the government when designating the three PGD centres to be licensed in France.

4.3.2 Education and quality assurance

Since the “Agence de Biomédecine” licenses the PGD laboratories, a certain degree of know-how has to be built up by the labs before they acquire a licence. Only one of the French respondents has a quality manager for the IVF clinic, the IVF laboratory and the genetics laboratory. The second centre has a quality manager for the IVF lab only and another for the PGD lab, while the last has no quality manager at all. Although all three professed that they think that external quality assessment (EQA) is important, only two of the three are participating in such a scheme. The success rates are followed by all three respondents, although only two also assess accuracy. All three keep analytical data for a significant time, and two out of the three report their data to the ESHRE PGD Consortium. All three have written policies on training staff and/or on validating tests.

One PGD centre trains its staff at workshops and also organises in-house training and follows ESHRE PGD Consortium Guidelines on assessment of sensitivity, specificity and predictive value. The second PGD centre receives help from the industry to organise its QA and has written guidelines for staff. The third PGD centre regrets that not enough funding is provided by its institution for adequate QA, staff training and test assessment.

4.3.3 Trans-border flows and financial aspects

One centre reported that it receives patients and samples from abroad, i.e. from Germany and Switzerland. Since this centre is close to the French-German and French-Swiss border, this is not surprising. The obvious reason for these cross-border flows is the legal situation in both Germany and Switzerland. The second French centre also receives Swiss patients for legal reasons, while the third has treated one patient from outside the EU (Lebanon) for reasons related to test availability. The three centres put the number of patients from abroad at not more than ten percent, and closer to one percent. French patients are mainly referred to other French centres because the indications and workload are divided between the three centres. If none of the three centres can help the patients, they are usually referred to Belgium.

PGD costs for French patients are completely covered by the government, while foreign patients may receive part-funding for PGD in France. One major criticism of this situation was voiced by one interviewee: “The bad point of complete coverage by the public health system is two-fold: (1) couples do not have any idea of what is the real cost (both human and financial) of PGD and (2) the three PGD centres in France do not have appropriate means to cover all the PGD requirements, so the "waiting list" for couples is very long.”

4.3.4 Monitoring

In all three centres participating, the IVF centre and genetics centre are part of the same institution (but not in the same building), which facilitates day-to-day communication. However, one respondent said that PGD is seen too much as an IVF activity, although it is primarily a genetic activity. The same sentiment was also expressed by other centres (e.g. another French centre mentioned that patients’ cycles sometimes have to be cancelled because the genetic test is not ready) and in other countries.

Different labs are contacted on a regular basis if necessary, e.g. to obtain information on the patient’s genotype. One lab mentioned that it is difficult to obtain DNA samples from foreign patients, probably reflecting the reluctance of German doctors to participate in PGD.

In two centres genetic counselling is provided by the genetics department, while informed consents are also presented by the genetic counsellor and signed during a genetic counselling session, whereas the third centre provides a combined first consultation and presents the informed consent at oocyte retrieval. One centre reported that IVF centres sometimes give patients erroneous information, which then has to be corrected by the genetic counsellor. Sometimes a separate informed consent is signed for the IVF part of the procedure.

Two of the three centres participating complained that there is no follow-up of either couples or offspring after PGD. The third mentioned that follow-up is carried out by a paediatrician in the framework of research, with money provided by the government. It is clear that follow-up can be identified as problematic in France for two reasons: lack of interest on the part of those qualified to perform the follow-up (i.e. gynaecologists and paediatricians) and, on the other hand, lack of funding.

4.4 Germany

4.4.1 PGD services

Eleven centres, three of which are public university-based, offer PGD or PGS of females by polar body biopsy on a regular basis. They all offer PGS, six offer detection of translocations and three offer single-gene detection. Estimates suggest that approximately 20 to 50 cycles with translocation or single-gene disorders and approximately 500 cycles with PGS are carried out each year.

Typically the IVF clinic and genetics laboratory are not in the same building, and in 70% of the cases they are not part of the same institution. However, there is always regular close communication between the two parts of the treatment. By contrast, genetic counselling and analysis are often carried out on the same premises. Only in exceptional cases (17%) does an

IVF unit cooperate with different genetics laboratories. Normally there are no technical problems with cooperation. However, distance (13% of the cases) and transport are sometimes reported as a problem. Genetic counselling is performed by the genetics centre/experts in two thirds of all cases and by both the IVF and genetics centres/experts in one third. Informed consent is normally given by the patient signing the written genetic information. In one third of all cases, only a written report is sent to the patients.

4.4.2 Education and quality assurance

All IVF labs in Germany need to be licensed. This requires qualified personnel (the head of lab must be an academic qualified in the field of IVF) and the right material (rooms and equipment must be appropriate and need to be approved). Genetic analysis must be under the responsibility of a board-certified human geneticist and it is obligatory to report IVF results to the German IVF Register. Specific PGD results are reported on a voluntary basis. An increasing number of IVF labs are certified in line with the ISO 9000ff standard. There is no specific licensing system for PGD.

Ninety-one percent of the centres reported special training requirements for PGD. Seventy-five percent think that counselling and analysis must be carried out by a human geneticist. Seventy percent perform retrospective analysis, 20% external controls and 20% prospective evaluations. Sixty-five percent follow international guidelines (PGDIS and/or ESHRE). In spite of this, there is no proper legal framework for quality assessment of PGD apart from the requirement that it must be carried out by a human geneticist.

4.4.3 Trans-border flows and financial aspects

PGD of embryos is forbidden, but PGD by polar body biopsy, which is generally considered difficult and less reliable, is allowed for hereditary diseases and for PGS. The majority of the interviewees were convinced that no worthwhile treatment can be applied in Germany. Consequently, patients go abroad, especially as detection of hereditary diseases transmitted by the father is not allowed in Germany. The centres advise patients on the situation abroad (85%) and perform diagnostics (39%) and monitoring (46%) for cases treated abroad. Formal referral is forbidden under German law but, as one interviewee pointed out, “patients inform themselves via the internet.” These patients (129 per year from 18 centres) normally go to the Benelux countries (35), Austria (12), the Czech Republic (21) or western (26) and southern (26) Europe. All the interviewees expected no changes to the law within the next 18 months.

Eleven of the 25 centres receive patients from abroad for polar body biopsy. Patients (73 per year in 25 centres) come from the Benelux countries, France, Switzerland, Poland, western, southern and eastern Europe and from outside Europe. One of the main reasons reported is good value for money.

Costs are covered by public and private insurance companies only if ICSI is indicated (69%). Exceptionally, private insurance companies will pay in other cases (12%). Treatment abroad is covered only in special cases when ICSI is indicated. According to one interviewee, patients “have to pay for everything themselves”. This situation potentially leads to the perception on the part of the interviewees that less treatment is performed than medically indicated (89%),

also for PGS (62%), and that cooperation with a public institution with research funding is necessary.

4.4.4 Monitoring

Fifty-two percent of the centres monitor the children born. In 67% of all cases the IVF centre is responsible for monitoring both IVF and genetics. “It is not regulated!”

However, long-term monitoring is still lacking. On malformation, there is international cooperation but there are no reliable long-term, multi-centre, multigenerational studies. The main barrier is that there is no funding for such activity, which is time-consuming and expensive. The point of view of the families will certainly be taken into account in prospective monitoring programmes.

4.5 Greece

4.5.1 PGD services

A total of six centres replied to the survey. Three of these were genetics laboratories performing PGD only, and the rest were clinics offering PGD in addition to their main IVF activity.

Five of the six centres offer PGD for chromosomal abnormalities but all six offer PGD for monogenic disorders. They all test for β -thalassemia and four of these six centres also test for CF. Additional diseases for which PGD is offered in Greece include CF, DMD, SMA, F8/F9, FRAXA, HD, DM1, HLA matching and sickle cell anaemia (HbS). PGD sex selection for X-linked disorders (not social sexing) is offered by all the centres.

In most cases, according to the replies to the survey, the genetics laboratory is in the same city as the IVF clinic, and sometimes in the same building (in two out of the six cases). According to the interviewees, in most cases the IVF clinic and the genetics lab are neither in the same building nor in the same institution. Although this could potentially influence interaction between the two, the interviewees indicated that this is not necessarily the case and stated that communication is frequent (“it has to be”). Moreover, no technical barriers affecting interaction between the genetics lab and collaborating IVF clinics were identified.

Genetic counselling is offered by all six respondents. In most cases it is offered at the genetics centre, although in one case it is offered only by the IVF clinic. The staff of the genetics lab interviewed reported that they perform genetic counselling, whereas informed consent is more typically the responsibility of the IVF clinic. In this context, all but one respondent confirmed that informed consent is requested.

4.5.2 Education and quality assurance

The Assisted Reproduction Law requires that services be provided in specially authorised centres staffed with at least one gynaecologist, a scientist with a degree in biomedical

sciences, a nurse (all with at least two years' experience), and an anaesthesiologist. Nevertheless, no specific official training currently exists, and geneticists in this field are trained mostly in the laboratory, gaining their experience by practice, as one interviewee said. No continuing education programmes exist, although most professionals in this field keep up with developments through conferences. The missing genetics speciality is therefore considered necessary. In this context, a Special Committee on Genetics in the Ministry of Health has proposed an inter-disciplinary speciality (for clinical geneticists and geneticists with a background in biology, biochemistry and pharmacy), including optional training in genetic counselling.

Although no specific QA framework exists or is currently provided for by law, four out of the six centres have quality managers, and four are participating in at least one EQA scheme (UKNEQA, EMQN and the CF network are the most common). In spite of this, all respondents believe that participation in EQA schemes is either important or very important, and half of them report data to ESHRE. Moreover, the laboratory interviewed follows the guidelines published by the ESHRE PGD Consortium on assessment of sensitivity, specificity and predictive value (Thornhill et al, 2005).

Although there are no official guidelines on QA and accreditation of genetic services, all the centres responding have written protocols on staff training and validating tests before application. In addition, they all perform both positive and negative controls during testing, and the test results are typically validated by a doctor and/or a clinical scientist.

4.5.3 Trans-border flows and financial aspects

Two of the three genetics laboratories that responded receive samples from abroad and one treats patients from other countries. Out of the three IVF clinics that replied to the survey, one treats patients only, whereas another receives embryo samples from abroad in addition to accepting patient referrals. Based on the survey, a total of 18 couples per year from Italy and Albania were reported to be treated. However, only one centre indicated that it had received one or two cases referred from abroad, so far only from Italy. According to the survey, in most cases these patients go to Greece because of test availability and the legal situation in their own countries, but much less for financial reasons. The survey also indicated that some IVF labs in Greece provide information to couples on foreign PGD providers.

All respondents reported that no public funding is available for this activity. All the interviewees further confirmed that, at the moment, neither IVF nor PGD (performed in Greece or abroad) is covered by the national healthcare system or by private insurance schemes. However, the new legislation provides for some coverage for both.

4.5.4 Monitoring

Although all the respondent centres recommend follow-up, only a single centre indicated that long-term monitoring has been initiated. So far this centre has evaluated about 30 children for follow-up, with a team that includes at least one paediatrician and a psychologist. This centre recommends annual follow-up, although largely this is still not universally applied, partly because no funding is available and partly because it also requires cooperation by the families.

4.6 Ireland

4.6.1 PGD services

PGD is not currently available in Ireland as a result of constitutional protection for the human embryo. Patients who require PGD are therefore referred to clinics outside Irish jurisdiction.

The only genetics centre in Ireland is the National Centre for Medical Genetics, located in Dublin. This is based in a paediatric hospital. It has no direct link to an IVF clinic but does accept referrals from IVF clinics for genetics issues. Interaction between the IVF clinic and the genetics centre is regular and frequent, and the system reportedly works very well, with the relevant clinicians knowing one another well and having a low threshold for discussion in relation to individual patients. It was reported that there is a long waiting list for laboratory genetic testing within the country, laboratory services being perceived as unfriendly to clinicians and patients. Some tests are sent to facilities in the UK but returned very quickly, sometimes sooner than those sent to the genetics centre in Ireland. The choice of genetics laboratory depends on the type of testing required since no centre in Ireland is able to provide all the tests requested.

It was reported that some genetic counselling is provided by the genetics centre. Where PGD is provided by clinics outside Ireland, it is seen as the joint responsibility of the referring centre and the treating clinic to obtain consent and ensure that counselling for PGD is provided. The final decision about whether or not to proceed with PGD is made by the treating clinic.

4.6.2 Education and quality assurance

As PGD testing is not provided, Irish clinics do not work to specific education and training requirements for PGD.

It was reported that quality management systems are used by some clinics but that the current schemes are under review to meet the requirements of the EU Human Tissue and Cells Directive. There are also some brief guidelines produced by the Irish Medical Council.

4.6.3 Trans-border flows and financial aspects

The status of the embryo remains uncertain in Ireland and, as a result, PGD is not provided by Irish clinics. All patients who request PGD are referred to clinics outside Irish jurisdiction. There is anecdotal evidence that some patients who might benefit from PGD are not being offered this option because of unfamiliarity with the procedure on the part of some practitioners and/or because of the difficulty of gaining access to the service. One clinician suggested that the service is made available to patients “who have persisted in requesting it.” It was reported that referrals are usually made to a clinic in Brussels and sometimes to London. The total number of referrals made within Ireland is not known but the number of referrals for PGD made by the National Centre for Medical Genetics is known to be approximately 20 cases over the last two years.

PGD funding in Ireland is a matter of some controversy. It was reported that, until recently, some couples received funding for PGD abroad under the Irish healthcare system which offers funding for certain treatments which are not available in Ireland. One clinic suggested that the system for obtaining funding was complicated and not all couples who applied received funding, but it did allow some families to be treated abroad who would not otherwise have been able to afford it. However, it was reported that since December 2005 public funding has not been available for PGD, since it is now classified by the Irish government as a fertility treatment. As such, patients seeking PGD abroad are not eligible for public funding. It was further suggested that a clinic applying for public funding for PGD could be liable to prosecution.

As a result of these difficulties, and the fact that Irish clinics cannot offer PGD themselves, the number of couples who can actually receive PGD is limited and likely to become more so: “those who receive PGD are now only those who can afford to pay to travel and be treated abroad”.

4.6.4 Monitoring

On the one hand it was suggested that there was no monitoring for children born after PGD. This has not been considered by some of those responding because it was felt that it would not be worthwhile to follow up PGD provided abroad. However, by contrast, the interviews revealed that one clinician routinely contacts all families who have successfully conceived by PGD to offer follow-up testing during and after pregnancy, at the discretion of the family.

4.7 Netherlands

4.7.1 PGD services

As in France, PGD practice is highly regulated in the Netherlands, where only one centre has been designated by the Healthcare Board and the Ministry of Health to provide PGD. This was part of a pilot study to provide the government with information on specific demands and needs and a cost-benefit analysis compared with prenatal diagnosis. PGD was recently recognised as a medical treatment and not as part of a pilot study. The centre designated by the government to offer PGD answered the survey and the interview. Another large IVF centre that provides only PGS also replied to the survey and the interview. Both centres are publicly funded and belong to a university. A third centre closely collaborates with the former and provides PGS only.

In the Netherlands PGD is offered for monogenic diseases and for chromosomal abnormalities. The monogenic diseases covered are either the more frequent genetic diseases (CF, SMA, DM1, HD and FRAXA) or specific requests from patients (e.g. Machado-Joseph disease, tuberous sclerosis types 1 and 2, and Marfan’s syndrome). Sex selection is offered exclusively for X-linked disorders.

There is a close physical (same institution and campus) and working relationship between the IVF centre and the genetics centre. Practitioners from both groups interact daily, and regular more formal meetings are also organised between the two groups. Genetic diagnosis is

performed and validated by geneticists. Genetic counselling is offered by the genetics centre involved in the PGD unit and is easily accessible. The intake of patients is channelled through the genetics centre after referral from other genetics centres.

4.7.2 Education and quality assurance

The Dutch centre offering PGD has a quality manager for the IVF clinic, the IVF laboratory and the genetics laboratory. However, none of these facilities is accredited. Data are kept on success rate and accuracy, and written protocols have been developed for training new staff and validating tests before application. The centre is not participating in EQA, but finds EQA important. Possibly it meant that no specific EQA for PGD exists, although this genetics department is probably participating in EQA for genetic diagnostics.

In this centre PGD tests are assessed for sensitivity, specificity and predictive value before clinical application. These procedures are written down as SOPs and follow the ESHRE PGD Consortium Guidelines.

4.7.3 Trans-border flows and financial aspects

The centre offering PGD has accepted patients coming from Germany for legal reasons. However, due to a growing waiting list, this centre now accepts only Dutch couples. Other couples have been accepted because of test availability. As a result, the cross-border flow to the Netherlands is limited (two couples per year reported). However, patients for whom the test is not available or for whom there are legal restrictions (e.g. testicular biopsy to obtain sperm for ICSI is forbidden) are referred to Belgium.

For Dutch patients both PGD (as a health service) and PGS (as a research activity) are completely covered by the government.

4.7.4 Monitoring

Communication is facilitated by the fact that the IVF clinic and genetics lab are part of the same institution, on the same campus. Genetic counselling is offered at the genetics department, whereas the comprehensive informed consent is signed during consultations at the IVF clinic.

The three Dutch centres participating mentioned prenatal, neonatal and short-term follow-up (two years). Notably, the centre performing PGS also provides long-term follow-up of children, but solely in the context of a research project. It can therefore be concluded that in the Netherlands, as in other countries, long-term follow-up is not organised systematically and does not benefit from country-wide funding.

4.8 Slovak Republic

4.8.1 PGD services

Altogether there are six IVF clinics in the Slovak Republic. One is public and five are private. Four of these IVF clinics (all private) are currently offering PGD for chromosomal abnormalities using FISH. However, no clinic currently offers detection of monogenic diseases using PCR. The other two clinics are planning to offer PGD as transport centres soon. According to an expert estimate, 60 to 70 PGD cycles were performed in 2005.

The international survey was completed by one centre and the same centre was the only participant in the interview. However, it is the most important PGD centre in the Slovak Republic because it alone performed 55 PGD cycles in 2005. It is also the only centre performing genetic testing in its own laboratory. Other Slovakian IVF clinics send their samples for genetic testing outside, either to this main centre or to other collaborating centres in the Czech Republic.

In one case the IVF clinic and the genetics centre belong to the same institution and are even located in the same building. The remaining three IVF clinics contract the services of an external genetics laboratory, which does not belong to the same institution. Two of these IVF clinics send samples to genetics labs in the Czech Republic. The interaction between clinics and genetics laboratories depends on actual need. Communication is naturally better when the laboratory and the clinic are located in the same building. However, no potential technical barriers were reported that could influence communication between other IVF clinics and genetics laboratories.

In the centre which responded, the genetic diagnosis is performed and validated by geneticists. Genetic counselling is also provided by the clinical geneticist. The same person is also responsible for obtaining written informed consent, which is required before any PGD procedure.

4.8.2 Education and quality assurance

A licence from the regional authority is required both for performing IVF and for genetic testing. However, the legislation does not impose any obligatory quality schemes and accreditation systems for laboratory practice in PGD testing. Nevertheless, the IVF clinic which responded has ISO 9001 certification. This centre has a quality manager for the IVF clinic, the IVF laboratory and the genetics laboratory. The centre keeps data on its success rate for a significant period of time.

There are no legal requirements on the sensitivity, specificity and predictive value of the genetic tests. It is the responsibility of each genetics laboratory fully to assess the sensitivity, specificity and predictive value of its methods before using them for PGD. The centre which responded stated that it has a written protocol for validating genetic tests before application.

Education of healthcare practitioners in ART centres is not regulated by law or ministerial ordinance, but a recommendation has been issued by the Assisted Reproduction Section of the Slovak Gynaecology and Obstetrics Society. Staffing is usually assessed by the regional authority during the licensing process for ART clinics. Gynaecologists must have a degree in medicine (MD), certification in gynaecology and obstetrics and practice in assisted reproduction. Education in clinical genetics is included in their specialisation (certification). Embryologists must have a degree in medicine or PhD and experience with assisted

reproduction. Geneticists should have a degree in medicine or a PhD and certification in genetics.

4.8.3 Trans-border flows and financial aspects

Three IVF clinics have contracts with clinics in the Czech Republic for sending couples for PGD of monogenic diseases, although this is rarely used as the procedure is quite expensive. Nevertheless, two centres send samples to the Czech Republic for genetic testing.

Few foreign couples are reported to go to the Slovak Republic for PGD. They come mainly from countries with restrictive PGD regulation, such as Austria and Italy. The foreign couples obtain information about Slovakian IVF clinics from the webpages of the IVF clinics.

PGD in the Slovak Republic is not covered either by the national healthcare system or by private health insurance. Patients are therefore responsible for payment of all PGD costs. According to the only respondent, the cost of IVF and PGD could be too high for some low-income couples. On the other hand, the same respondent concluded that patient payments have a positive influence on clinical practice.

4.8.4 Monitoring

In general, monitoring of couples and offspring after assisted reproduction is not required in Slovakia. In the only IVF clinic interviewed, the prenatal check on the genetic diagnosis is always performed and early postnatal monitoring is strongly recommended after PGD. Long-term postnatal monitoring is not carried out.

There is no international cooperation on long-term monitoring of offspring after PGD cycles. No reliable long-term, multi-centre, multi-generational studies are being conducted in the Slovak Republic. The main barriers to such monitoring are the reluctance of parents to participate and lack of funding. One additional barrier is the lack of a central register of assisted reproduction.

4.9 Spain

4.9.1 PGD services

Out of the ten centres surveyed in Spain, eight are private (five IVF clinics and three genetics laboratories) and the other two belong to the National Health System and offer both genetics and reproductive medicine services. Five of the six IVF clinics offer both IVF and PGD, whereas just one outsources PGD.

Mutation detection is offered by only one genetics centre, while another offers embryo freezing. Analysis of chromosomal abnormalities is more common (offered by seven of the eight). PGD is also frequently offered for monogenic diseases, although the range of diseases covered varies between centres. Two genetics centres offer PGD “à la carte”, i.e. “any disease of known genetic basis” and “any other required”. The most frequent diseases for which PGD is offered are cystic fibrosis (6), Duchenne muscular dystrophy (6), fragile X syndrome (5),

haemophilia (5), spinal muscular atrophy (4), myotonic dystrophy 1 (4) and Huntington's disease (4). All the centres offer sex selection for X-linked disorders but none of them performs PGD for social sexing.

The interaction between genetics laboratories and ART clinics on PGD is better when they belong to the same institution. In line with this observation, the survey found that in four of the five IVF clinics offering PGD in Spain the genetics laboratory is in the same building, whereas in the other one it belongs to the same institution. Nevertheless, genetics centres interact with different IVF clinics not only in the same city and country but also in other countries.

In cases where the IVF centre collaborates with an external genetics centre on PGD, technical barriers may exist, particularly as regards material requirements, for example for cell biopsy preparation (in which case the embryologist from the genetics centre has to travel to the IVF centre). To address this problem, one IVF centre, with ten clinics in different cities in Spain, has appointed a biologist in each clinic to perform the embryonic biopsy, although PGD remains centralised (i.e. is offered by only one clinic belonging to this centre).

All eight centres that perform PGD also provide genetic counselling, informed consent and formal reports. However, who actually provides the counselling varies widely in both IVF and genetics centres. Despite this, both recommend follow-up confirmation of PGD and in most centres tests are validated by a clinical scientist. Only in one of the five IVF centres are tests also validated by a doctor, and in one genetics centre the genetic test may be validated by a laboratory technician as well.

4.9.2 Education and quality assurance

The 1988 law and the amendments made to it in 2003 lay down regulations on cryopreservation of germ cells and preembryos, diagnosis, treatment and the functions of centres and biomedical teams, which must be qualified to perform assisted reproduction techniques. These teams typically consist of gynaecologists with experience in human reproduction and biologists with experience in embryology. Moreover, IVF clinics must be accredited by the Ministry of Health. Nevertheless, formal training is still not regulated in Spain. The medical speciality is Obstetrics and Gynaecology which includes four years of training.

Medical or clinical genetics is not a recognised speciality and the Spanish legislation does not require any related scheme or accreditation system. Genetic testing is therefore performed mainly by doctors or biologists trained in specialities accredited by both the Ministry of Health and the Ministry of Education and Science (these include paediatrics, obstetrics and gynaecology, internal medicine, chemical pathology, biochemistry, haematology and immunology). Since 2000 unofficial accreditation in human genetics is provided by the Spanish Association of Human Genetics.

Since 1988 a National Committee on Assisted Human Reproduction has been in operation. This committee has to be consulted in specific cases of PGD, such as HLA-typing of embryos to treat a sib/relative condition.

At least five IVF and genetics centres report PGD and PGS data to ESHRE, following the Best Practice Guidelines for Clinical PGD/PGS Testing. While all the respondents (i.e. IVF centres performing PGD) consider participation in EQA important or very important, only one reported that it is participating in an EQA scheme. The data from the genetics centres are similar (only one out of three is participating in an EQA scheme). The schemes reported are EMQN, the cystic fibrosis network for molecular diagnosis and AEDP (the Spanish Association of Prenatal Diagnosis) for cytogenetic analysis. Some centres have, or are in the process of obtaining, external quality accreditation (ISO). A number of centres have standardised working protocols.

In general the mutation to be analysed in preembryos is confirmed prior to the PGD procedure. In six centres familial mutations are confirmed in all cases. In one IVF centre this is performed in under 50% of cases, and in one genetics centre in over 50%. Positive and negative controls are also performed in all but one of the centres. Moreover, six centres have dedicated rooms for PGD (although the number and quality vary). The number of cells per embryo per diagnosis also varies from one to two, and biopsy and transfer protocols differ between centres. Biopsy is always performed by an embryologist/biologist. As a whole, genetic testing is assessed quite well before the couple receives PGD and ART.

4.9.3 Trans-border flows and financial aspects

Spain treats couples from abroad mainly due to legal reasons and test availability. However, the flow varies between IVF and genetics centres. Only one of the five IVF centres receives samples from abroad, whereas all three genetics centres receive samples from other European countries. By contrast, four out of the five IVF centres treat couples from abroad. The three genetics centres also treat foreign couples. Patients come mainly from Italy, Germany, Portugal, the United Kingdom and Turkey.

In the past couples have also travelled from Spain to Belgium or the USA for HLA selection of embryos. However, this changed recently when the new Law on Assisted Reproduction Techniques approved this practice. According to PGD experts, this is the most relevant change achieved by the new law and could further influence the trans-border flow from other countries to Spain.

As regards reimbursement, only two (out of 17) regional health services (Andalusia and Murcia) cover the expenses of IVF and PGD tests, and only Andalusia offers PGD as a public service (but not including couples treated for PGD outside Spain). In the rest of Spain, PGD is currently offered only by private IVF clinics or genetics centres. Furthermore, most private insurance companies do not cover PGD costs (although this may also depend on the type of contract between client and company). As a result, the current reimbursement situation influences clinical practice, i.e. PGD is performed mainly in private IVF and genetics centres in Spain (some is also performed abroad).

4.9.4 Monitoring

Monitoring of couples and offspring is variable. Three IVF clinics offer monitoring during pregnancy and the neonatal period. By contrast, two extend follow-up until paediatric age, either short-term or long-term. One clinic has a project to follow up children in out-patient

clinics. No information is available about monitoring surveys by the Spanish centres. Some IVF clinics have a paediatrics unit which offers follow-up. One clinic is developing a distance follow-up programme.

4.10 Switzerland

4.10.1 PGD services

PGD by embryo biopsy is illegal in Switzerland and is not available in any centre. One university centre offers testing by polar body analysis, on an experimental basis, subject to prior Federal and local ethical authorisation. The centre is currently following couples requesting testing for familial translocations, CF, beta-thalassemia and familial Mediterranean fever. Both counselling and testing are shared between the university IVF and medical genetics services, with close collaboration and regular consultation between the IVF clinic, IVF laboratory and the medical genetics clinicians and laboratories. After specialised genetic counselling, signed consent is obtained from the couple.

Such close collaboration will be required in Switzerland from 2007, when the Law on Human Genetic Analysis will require the involvement of qualified specialists in medical genetic analysis (holders of an FAMH certificate) in the majority of genetic tests, especially for rare disorders.

Data on international exchanges for PGD were not available from the many private IVF centres in Switzerland.

4.10.2 Education and quality assurance

As stated above, if PGD is offered in Switzerland it will require close interaction between medical genetics and IVF laboratories.

For directors of medical genetics labs, there is three years' formal postgraduate training leading to a qualification ("FAMH specialist in medical genetic analyses"). The legal requirement for direction by a holder of an FAMH certificate in medical genetics is not very clearly defined nor is it yet common practice, but this is expected to change after the Law on Human Genetic Analysis enters into force. At present there are no formal requirements for directors of IVF laboratories, although the possibility of an FAMH certificate for reproductive medical laboratories has been raised.

There are clinical specialisations ("FMH") in both gynaecology/obstetrics and medical genetics. Neither specialisation has particular requirements for training in the other field, but there is a tradition of good communication and collaboration between the two disciplines, built around prenatal diagnosis and infertility treatment.

Medical laboratory quality is assured at three levels in Switzerland, which would be equally applicable to PGD:

- 1) Accreditation by the Swiss Accreditation Service to the ISO 17025 and/or 15189 standards is widespread, including in medical genetics laboratories – approximately 75% of labs offering medical genetic testing are either accredited or have an accreditation

process “underway”.

There are many university and private IVF laboratories, four of which are accredited (ISO 17025 and/or 15189).

- 2) External quality assessment (EQA) is required by Swiss law for all medical testing laboratories, applying the “QUALAB concept”. Participation is verified by the governmental organisation “H+”. EQA is typically performed by international schemes, notably UK NEQAS, EMQN and BVmedgen.
- 3) The Federal Law on Human Genetic Analysis due to enter into force in 2007 requires laboratories offering genetic testing to have a renewable Federal licence to practise. The licensing requirements are currently being defined but include training of laboratory directors and staff, various quality criteria related to the accreditation standards and site visits by Federal experts. ISO 17025 or 15189 accreditation meets all the criteria and obviates the need for site visits.

Apart from accreditation, at present there is no formal requirement to validate genetic tests before they are introduced (sensitivity, specificity and predictive value). By contrast, before a new disorder can be added to the “Federal Analysis List” (for reimbursement) exhaustive documentation on the analytical and clinical validity of the test is required.

4.10.3 Trans-border flows and financial aspects

Swiss centres perform no testing; however, medical genetic services (principally but not exclusively university services) frequently provide PGD-related genetic consultation and counselling for couples from Switzerland or many other countries, particularly from outside Europe (Switzerland has a very high proportion of residents of non-Swiss origin). Representatives of three university medical genetics services were interviewed about their practices related to PGD. Couples interested in PGD are informed that it is prohibited by law in Switzerland and are commonly put in touch with foreign centres able to offer testing. In some cases the genetics service is active in the referral, contacting the centres and working closely as intermediaries, particularly when there is a language barrier. More commonly, however, couples are provided with contact details (plus genetic counselling) but have to make contact themselves.

The three services interviewed inform 10 to 20 couples per year about the possibility of PGD, but have little reliable information about whether PGD was performed or even whether contact was made. Couples are most commonly informed about centres in Belgium and Spain. Attempts had also been made to work with the UK, but these “did not work well because they were very restrictive in terms of the tests offered”. The partner centres can be selected on the basis of language, pathology and/or perceived quality. At least one centre explicitly regretted the absence of objective quality criteria for choosing PGD centres. Couples may also contact foreign PGD centres directly, without going through local services. At least one couple obtained PGD for a monogenic disease combined with HLA-matching for bone-marrow donation for the affected sibling in this way; their story was told in a national television broadcast in 2006.

Interviewees indicated that, whether or not PGD becomes legal, Switzerland will certainly continue to receive patients from many countries for healthcare of all sorts and is likely to remain a gateway to PGD services in Europe.

The Federal Law on Health Insurance requires mandatory reimbursement by health insurance companies of diagnostic tests only for disorders specifically mentioned on the “Federal Analysis List”. If PGD were performed in Switzerland for tests on the Federal Analysis List, the costs of the test would probably be covered by the health insurance scheme. The costs of the IVF procedures would probably not be covered, however, as infertility treatment is not presently reimbursed.

The administrative procedures for adding a new disorder to the list are extremely cumbersome and were mentioned as a major barrier, not to offering tests but to reimbursing the costs to families; the probability of discrimination against families with genetic disorders which are not on the Analysis List was mentioned. This situation may prove to be in contradiction with the new Law on Human Genetic Analysis which states that: “Nobody shall be discriminated (against) because of his genetic constitution”.

4.10.4 Monitoring

This is not an issue at present in Switzerland. The consensus was that this is important and must be a joint effort by a multidisciplinary team, including paediatricians and medical geneticists.

4.11 United Kingdom

4.11.1 PGD services

Since PGD involves creation, storage and use of embryos outside the body, it requires a licence from the Human Fertilisation and Embryology Authority (HFEA), the UK regulatory body for this area. In its most recent published figures, the HFEA reports that ten UK centres are currently licensed to provide PGD. However, it does not follow from this that each of these clinics in fact provides PGD on a regular basis, if at all. Instead, the results of the survey confirm that at least one of these ten clinics does not currently provide PGD despite being licensed to do so.

Of the ten clinics licensed to provide PGD, six responded to the survey and interviews were conducted at five (including one which did not respond to the survey). Of these five, three are private clinics which also treat NHS patients and two are NHS clinics which also treat private patients. They are all IVF clinics which also offer PGD, and all offer PGD for chromosomal abnormalities, monogenic diseases and sex selection for X-linked disorders.

There is no published list of all conditions for which PGD has been licensed by the HFEA in the UK because of concern that publication could compromise patient confidentiality in the case of rare conditions. However, the HFEA states on its website that it has licensed PGD for over 50 conditions.

The clinics reported a variety of arrangements and interactions between the IVF clinics and genetics laboratories in the context of PGD provision. Two occupied different parts of the same building, one reported that they were on different campuses of the same institution, one reported that they were in separate but linked institutions and one sends all its samples to Chicago for genetic testing. However, all the clinics confirmed that they communicate regularly with their genetics laboratories and reported no technical barriers to communication.

It was suggested that the genetics laboratory did not need to be in the same building, provided there was good and frequent communication between them, with one clinic suggesting that “having the testing done in the US only makes a few hours difference overall to if we were in the same building.”

In terms of practice, one clinic said that relations between IVF and genetics laboratories in the UK were often strained because neither quite understands what the other does. It suggested that this could be addressed by educating embryologists and geneticists in the others’ discipline. Another clinic also emphasised the important distinction between IVF and PGD.

Genetic counselling is offered by all clinics. All the clinics confirmed that they obtain informed consent from patients and most suggested that the genetic counsellor plays a key role in the consent process.

Four of the five clinics interviewed expressed concern that regulation of PGD in the UK by the HFEA has a negative impact on clinical practice. All four suggested that the licensing process is bureaucratic and fraught with delays which have consequences for patients. Three clinics mentioned that the HFEA lacks expertise in PGD to enable it to license PGD effectively, and two said that the HFEA appears under-resourced to perform its licensing function in relation to PGD. Two clinics also indicated that they are put in a difficult position with patients at the early stages of treatment because they do not know the outcome of the application to the HFEA. As one clinic put it, “We don’t know if the HFEA will accept a particular disease which means we don’t know what to tell the patients until the HFEA report back which is not good for the patients”. However, clinics added that it appeared that no application had ever been refused by the HFEA which led one of them to question the efficacy of regulation, stating that “we have superficial regulation in the UK, more concerned with what appears on paper than making any real difference.”

By contrast, one clinic expressed support for the existing framework, stating that it is “good and beneficial to have the knowledge that what we are doing has been looked at independently by other people and it does provide a certain amount of reassurance. The legislation is clear and we know what we can and can’t do, which is good in terms of managing our work.”

4.11.2 Education and quality assurance

All UK clinics providing PGD are licensed and inspected by the HFEA. However, they each follow different approaches to further accreditation and quality assurance. All the clinics confirmed that they maintain their own quality management processes and follow best practice guidelines, with four out of five referring to the ESHRE Guidelines in this context. Two clinics are accredited under the UK Clinical Pathology Accreditation (CPA) standards, and a third is working towards this. Another clinic has obtained ISO 9001 certification.

In relation to external quality assurance, one clinic uses the UKNEQAS schemes for molecular genetics and cytogenetics. The others confirmed they do not use EQA schemes, although one referred to its ISO accreditation in this connection. Only one clinic indicated that it has no designated quality manager. It was also reported that ESHRE is currently working on a quality system for FISH imaging.

All the clinics were aware of the HFEA requirements on training and continuing education for staff involved in PGD, and all were making efforts to send staff to national and international conferences. However, views were mixed on the benefits of specific training for PGD, some suggesting that it is more important to have proper training in genetics.

4.11.3 Trans-border flows and financial aspects

Four of the five respondents confirmed that they refer patients abroad, though for different reasons. Two clinics have referred patients due to lack of the specific technical expertise required for a particular diagnosis. Another suggested manpower and financial resources had been the cause of referral in the past. One clinic also mentioned regulatory and HFEA policy as reasons to refer patients outside the UK. None of the respondents suggested that they refer people outside the UK for social sex selection. In the words of one interviewee, “we don’t do it and I don’t agree with it so I don’t refer people anywhere.”

All clinics confirmed that they receive patients for PGD from outside the UK, though such patients make up only 5 to 10% of the total. The countries of origin of such patients vary considerably: Europe, the Middle East, Africa, India and the USA were all mentioned during interviews. One clinic has established a formal link with an Italian clinic to take PGD referrals. Another suggested that one possible explanation for the limited number of patients coming to the UK was “...because the system is restricted and slow.”

All the clinics confirmed that a proportion of their patients received public funding through the NHS, though the proportion varies considerably. One clinic has a formal arrangement with local NHS funding bodies that refer their PGD patients to that clinic, resulting in a majority of patients receiving public funding. This arrangement was described as follows:

“We now have a consortium of PCTs (Primary Care Trusts) within London and the home counties which covers about 16 million people. Provided they do not have any children already, and provided they have been seen by one of the regional genetic centres, they can apply for state funding for their treatment and they have a very good chance of having it funded. For couples who live outside that region then it is a postcode lottery in that some Health Authorities will fund it and some will not. If you have a Health Authority that will not fund it then you have to self-fund it.”

Another clinic reported that a similar arrangement had previously led to between one third and a half of all patients benefiting from public funding, and a third clinic suggested that 40 to 50% of patients currently receive public funding. Another clinic said that it had treated only one couple funded by the NHS. None of the respondents was aware of any NHS funding available for patients who sought treatment outside the UK.

All the clinics agreed that the shortage of clinical funding has an impact on clinical practice, agreeing that more funding would mean more patients treated. As one commented, “There is a serious lack of funding in this country for all PGD programmes so we can only work on a few diseases.”

4.11.4 Monitoring

Only one clinic reported that it is taking part in a comprehensive monitoring programme. This clinic is involved in a well established paediatric follow-up programme up until the children reach two years of age, but not beyond. One other clinic is conducting its own follow-up of patients, using a tailored questionnaire completed by families, but without paediatric involvement. Another confirmed that it remains involved in monitoring patients during the prenatal stage but not beyond. The others are not involved in monitoring programmes but one clinic is looking to establish a collaborative programme through ESHRE.

5 REGULATORY FRAMEWORK

In addition to national legislation, certain international laws are relevant to PGD provision and regulation in Europe. EU law has the greatest impact, but the Council of Europe still plays a role, particularly through its human rights jurisdiction. This chapter considers each in turn.

5.1 European regulation

5.1.1 European Union law

Directive 2004/23/EC¹⁷

The most significant EU legislation affecting assisted reproduction and PGD is the recent Human Tissue and Cells Directive. It introduces a wide range of quality and safety requirements and a new accreditation system for European “tissue establishments” that fall within its remit.

The categories of tissue covered by the Directive explicitly include gametes, embryos and human embryonic stem-cell lines. However, it applies only to tissue intended for human applications.

Each Member State must designate a “competent authority” responsible for implementing the requirements of the Directive. Each competent authority must then accredit, designate, authorise or license tissue establishments and organise inspections to ensure compliance with the Directive.

The requirements particularly relevant to this study are Articles 8 and 9 relating to traceability, import and export. All tissues and cells must be traceable from donor to recipient and *vice versa*. The same traceability requirements apply to tissues and cells imported from non-EU countries. This poses significant challenges in relation to cross-border flows of patients, embryos and gametes, especially where such movements are intended to avoid national prohibitions and restrictions. Linked to Article 8, Article 25 introduces the need for a European coding system for tissues and cells. Again, it is not clear how this would operate and nothing along these lines exists at present for PGD.

The Directive also introduces a range of provisions on quality assurance and risk management. Article 11 requires MS to implement adverse incident reporting systems and Chapter IV creates a general quality assurance framework for all tissue establishments. This is spelt out in more detail in two additional Directives which serve as technical annexes to the main Directive and set out the specific technical requirements and accreditation standards for tissue establishments. The first relates to the technical requirements for the donation, procurement and testing of tissues and cells, the second to technical requirements for the coding, processing, preservation, storage and distribution of tissues and cells¹⁸. These annexes

¹⁷ Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

¹⁸ Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

are not tailored to IVF or PGD laboratories and have proved controversial, with some feeling that some of the standards are inappropriate. However, there is a general consensus that the introduction of mandatory quality and safety standards is a positive development. MS are of course free to impose more stringent requirements.

Charter of Fundamental Rights of the European Union

The Charter is a non-negotiable and legally binding attachment to the EU Constitution. Since the Constitution has been put on hold, the Charter is of limited significance and its long-term future is uncertain. However, it is mentioned here to give the full picture and because it includes provisions which may be relevant to PGD.

Article 3 (“Right to the integrity of the person”) states that:

- “1. Everyone has the right to respect for his or her physical and mental integrity.
2. In the fields of medicine and biology, the following must be respected in particular:
 - the free and informed consent of the person concerned, according to the procedures laid down by law,
 - the prohibition of eugenic practices, in particular those aiming at the selection of persons,
 - the prohibition on making the human body and its parts as such a source of financial gain,
 - the prohibition of the reproductive cloning of human beings.”

Depending on the interpretation of “eugenic” this may have restrictive implications for PGD and related techniques. However, even if ratified, the Charter would be binding on EU institutions and on MS only in so far as they are implementing EU law: regulation of medical ethical issues at national level is not a matter for which the EU has jurisdiction and, consequently, the Charter would not apply to it.

5.1.2 Council of Europe

Convention for the Protection of Human Rights and Fundamental Freedoms (1950)

This Convention came into force on 23 September 1953. To ensure effective protection of the rights enshrined in the Convention, a European Court and Commission of Human Rights were established and are still functioning.

The key Articles of relevance to PGD are set out below in order of importance:

Article 8:

“(1) Everyone has the right to respect for his private and family life, his home and his correspondence.

Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

(2) There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others.”

Of all the rights enshrined in the Convention this is the most relevant to reproductive and genetic technologies because it simultaneously embodies the rights of patients, children and donors. It protects rights to self-determination and procreation, and any intrusion by the state into this private sphere must be justified under Article 8(2). However, although routinely applied to questions of reproductive autonomy, Article 8 is not always easy to apply to new reproductive technologies such as PGD with its associated moral and ethical controversies.

Article 12:

“Men and women of marriageable age have the right to marry and to found a family, according to the national laws governing the exercise of this right.”

Article 12 is the only article in the Convention which specifically mentions procreation. However, it has been made clear by the courts that Article 12 does not create an absolute right to found a family or to be provided with the assistance necessary to do so.

Article 2:

“Everyone's right to life shall be protected by law. No one shall be deprived of his life intentionally save in the execution of a sentence of a court following his conviction of a crime for which this penalty is provided by law.”

The European Court of Human Rights has largely managed to avoid directly addressing the issue of the rights of the embryo under Article 2, considering it a matter for national courts to determine. However, case law suggests that the unborn child – and, by implication, the embryo *in vitro* - is not regarded as a “person” directly protected by Article 2 and that if the unborn do have any “right” to “life” it is implicitly limited by the mother’s rights and interests.

It is also possible that Articles 3 (freedom from torture or from inhuman or degrading treatment or punishment) and 5 (right to liberty and security of person) could apply in cases where patients are forced to undergo unsuitable or dangerous treatment by the state. For example, a patient might be able to invoke Articles 3 and 5 if national law required doctors to transfer embryos to women as a matter of course, regardless of their number or genetic disorder.

The European Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine 1997 (the “Oviedo Convention”).

This Convention is intended to provide a framework for the protection of human rights in relation to the application of biology and medicine. In particular it covers the following topics of relevance to PGD:

Article 12 - Predictive genetic tests:

“Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling.”

Article 13 - Interventions on the human genome:

“An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.”

Article 14 - Non-selection of sex:

“The use of techniques of medically assisted procreation shall not be allowed for the purpose of choosing a future child's sex, except where serious hereditary sex-related disease is to be avoided.”

Article 18 - Research on embryos *in vitro*:

“(1) Where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo.

(2) The creation of human embryos for research purposes is prohibited.”

The Explanatory Report on the Convention provides additional insight into how these Articles are intended to be applied. In particular, paragraph 83 of the Explanatory Report states that “Article 12 as such does not imply any limitation of the right to carry out diagnostic interventions at the embryonic stage to find out whether an embryo carries hereditary traits that will lead to serious diseases in the future child.” Furthermore, with regard to Article 14 (see above), paragraph 94 of the Explanatory Report provides that it is “...for internal law to determine, according to the procedures applied in each state, the seriousness of a hereditary sex-related disease.”

The Convention sets out only the most important principles. Additional standards and more detailed questions are dealt with in additional protocols. However, the Oviedo Convention has received a very mixed response within Europe and several notable countries have decided not

to ratify it (including the UK, France, Belgium, Norway, Finland, Sweden, Germany and Russia). It has been widely criticised for its methodology and political bias, and the usefulness of such minimalist pan-European legislation has repeatedly been called into question. If there is agreement on certain matters covered by the Convention, these can be incorporated into national law, but the broad regulation of contentious areas of medicine and science makes it difficult for certain countries to agree to all the provisions in the Convention.

Closing Declaration of the Eighth Meeting of the Conference of National Ethics Committees (COMETH), Dubrovnik (Croatia), 25-26 April 2005

COMETH is made up of representatives of national ethics committees (or equivalent bodies) from the Council of Europe states. This declaration was made at the end of a COMETH conference which considered PGD amongst other things. It recognises the Oviedo Convention as the “cornerstone” of European biomedical law and makes specific reference to the benefits of a pan-European debate relating to PGD.

5.1.3 Other international treaties

Numerous international treaties and documents could be relevant to PGD, reproductive rights and protection of health and welfare. For example, Article 23 of the UN International Covenant on Civil and Political Rights confers a right to found a family and may extend to the right to procreate and co-habit. Also Article 10(h) of the UN Convention on the Elimination of All Forms of Discrimination Against Women states that men and women should have equal access to “specific educational information to help to ensure the health and well-being of families, including information and advice on family planning.” A comprehensive analysis of all such documents is beyond the scope of this report but they are nonetheless relevant since they may be invoked by those affected within signatory states.

5.2 National regulation

5.2.1 Belgium

The Belgian Termination of Pregnancy Law changed on 3 April 1990. Termination of pregnancy remains within the penal code, but is not punishable provided certain conditions are met: the woman has to undergo at least two consultations with a wait in between and has to declare that she is in a “critical situation” (although the definition of that is left entirely to the woman). After 14 weeks the pregnancy can be terminated only if the mother’s life is in danger, or if it is clear that the unborn child will suffer from an incurable disease. In that case, the treatment has to be administered in a hospital and a second doctor has to give an opinion. In the case of prenatal diagnosis, this is tolerated and no doctors have ever been prosecuted for terminating a pregnancy in cases of genetic defects.

No specific regulation on PGD exists in Belgium. However, several regulations pertaining to fields touching on PGD (e.g. embryo research, IVF and genetic services) influence the practice.

Most notably, the Law on Embryo Research explicitly forbids social sexing, while the Law on Hospital Funding regulates the number of embryos that can be transferred after an IVF cycle. Genetics services are regulated at the level of the Ministry of Public Health. Eight genetics centres are regulated and subsidised by the Ministry and, as such, are solely entitled to provide genetics services. The plan is that PGD will also be regulated by a law, which would make it mandatory that PGD is offered within a B-centre for ART (i.e. a centre accredited for the whole IVF process) and one of the eight recognised genetics centres.

At the moment, there is an extensive range of possibilities for PGD in Belgium and only on the rare occasions where patients request social sexing do practitioners have to refer patients abroad.

5.2.2 Czech Republic

Until 1993, when the former Czech and Slovak Federal Republic split into two independent states, the regulatory frameworks for healthcare were almost the same in the Czech Republic and the Slovak Republic. However, since 1993, although the general direction of change has been similar in both countries, specific differences in the legislation have appeared. Nevertheless, both states still have similar regulations for healthcare in several areas, including termination of pregnancy.

In the Czech Republic termination of pregnancy is regulated by the 1986 Law on Artificial Interruption of Pregnancy. Voluntary termination is legal up to the 12th week of pregnancy. After the 12th week termination is allowed only where the mother's life is in danger or where there is a risk of serious damage to or "inviability" of the embryo. In the event of genetic indications pregnancy may be terminated up to the 24th week of intra-uterine life only. Genetic indications may be either of serious hereditary disease of the foetus diagnosed by a prenatal diagnosis or of a high risk of serious hereditary disease determined by genetic examination of the parents. Additional indications of genetic risk are exposure during pregnancy to factors with proven teratogenic or mutagenic effects.

Prenatal diagnostics, including preimplantation genetic diagnostic (PGD), were not regulated by law until recently. The new Health Care Law containing an article regulating assisted reproduction and PGD has not been submitted to the Czech Parliament yet. However, at the end of April 2006 the Czech Parliament passed the Law on Research on Human Embryonic Stem Cells which contains an article on regulating assisted reproduction, including PGD and amends the old (1966) Law on the Health of the People. This amendment has been in force since 1 June 2006. Prior to this, clinical practice was regulated by the ordinance of the Ministry of Health on "*Recommended procedure standards for providing assisted reproduction*" issued in 2001. This ordinance specifies the conditions necessary for covering IVF expenses from the national health insurance fund, limiting reimbursement to a maximum of three implantations for women aged from 18 to 39. The ordinance also specifies the minimum technical equipment and level of education necessary in IVF centres performing treatment with donated oocytes.

The new Law on Research on Human Embryonic Stem Cells approved at the end of April 2006 regulates performance of assisted reproduction and PGD, together with donation of reproductive tissues. It set up the new register of assisted reproduction and introduced obligatory licensing of IVF centres by the Ministry of Health. The law also requires the

Ministry of Health to compile an inventory of PGD indications, to list the specific education and training requirements for the personnel of IVF centres and to specify the equipment required at IVF clinics. Under the new law, preimplantation genetic testing of the embryo is allowed for specified indications only, in order to exclude the risk of serious genetic diseases. Sex selection for social reasons is not legal: it is allowed only to prevent serious gender-related genetic diseases which are either incompatible with postnatal life, considerably shorten life or cause early invalidity and are not curable with present knowledge. The law also limits the number of fertilised and implanted eggs. The resulting embryos may be used only for implantation in the woman treated. However, if not all the embryos are used for implantation and the couple declares that they do not plan to use them in the future, they may be donated for implantation in other women or used for research purposes. If the reproductive tissues are donated by persons other than the infertile couple treated, the donors have to undergo all necessary tests, including genetic tests. The age of donors is limited by the law to between 18 and 35; there is no limit on the age of the woman to receive the implant. Implantation may be performed only after written informed consent is signed. The law also specifies that assisted reproduction may be performed only in the clinics licensed by the Ministry of Health. The Ministry may grant a licence to clinics fulfilling the specified requirements on equipment and personnel. The Ministry is responsible for compiling the list of such requirements.

Prenatal genetic testing is not regulated by law in the Czech Republic. Current clinical practice follows the ministerial ordinance. It consists of multi-marker biochemical screening of blood, typically performed between the 15th and 18th weeks of pregnancy, plus sonography at the 12th, 20th and 33rd weeks. In cases of increased risk of chromosomal aberration of the foetus, amniocentesis with consequent karyotype determination is recommended. Postnatal screening methods are regulated by the 2002 directive of the Ministry of Health. It states that postnatal screening for phenylketonuria and congenital hypothyroidism has to be performed in all neonates. Therefore, at the age of four to five days neonates undergo biochemical tests for phenylalanine and TSH in their blood.

5.2.3 France

Voluntary termination is legal in France up to the 12th week of pregnancy. This law has been in place since 1974 and was amended in 2001 to increase the maximum from 10 weeks to 12.

Prenatal diagnosis is allowed within a strict legal framework: there must be a high probability of birth of a child suffering from a disease of particular severity and recognised as incurable at the time of diagnosis. This law has been in place since 1970 and has been amended twice - in 1994 and 2004. No further changes to either of these laws are envisaged.

In France PGD is regulated by the Law on Bioethics (1994). A recent amendment places ART under the remit of the new “Agence de Biomédecine”. Laws and regulations pertaining to PGD are linked to the practice of prenatal diagnosis rather than to laws on embryo research. This explains why the conditions under which PGD may be carried out are similar to those regulating PND: (1) centres offering PGD must be licensed and their activity must be monitored, (2) the couples seeking PGD must have a high probability of giving birth to a genetically affected child, (3) the genetic defect must be of a particular severity and recognised as incurable at the time of diagnosis, (4) the genetic defect must be fully characterised in the parents, (5) only the previously identified defect may be investigated and (6) the couple must give written consent for the diagnosis. To obtain a licence to perform

PGD, applicants must demonstrate expertise in PGD to the health authority. Licences will be granted to IVF centres for the biopsy procedures and to genetics centres for single-cell analysis. Three centres have obtained such licences so far.

No changes in the current legislation are imminent.

5.2.4 Germany

The German Embryo Protection Act of 1990 is a penal law (in order to vest the legislative power in the central state) and states that only as many embryos may be generated *in vitro* as will be transferred in the same cycle (up to a maximum of three). This leads to the following process: first, all follicles are punctured and all oocytes inseminated on day 0. On the morning of day 1, zygote selection is performed and one, two or three zygotes are cultivated until transfer (on day 2, 3 or even 4): the rest of the zygotes are discharged or frozen. This is legally permissible since, in the eyes of the law, an embryo does not start to exist until noon of day 1 after fusion of the pronuclei. This means that for PGD, the first and second polar bodies may be biopsied, analysed and used for zygote selection prior to noon on day 1. Blastomere biopsies of embryos are not allowed under the law as long as the blastomeres are totipotent. Thereafter, biopsy is legal but selection is forbidden as embryos must be transferred.

This stands in marked contrast to general penal law: the morning after pill or IUDs are allowed, as methods to hinder implantation are legal. Until week 14 *post menstruationem*, after consultations, interruption of pregnancy for social reasons is unlawful but not punishable. For criminological reasons it is legal, and for medical reasons for the mother there is no time limit at all. Many German lawyers and ethicists state that there is a strong contradiction of values and many believe that the Embryo Protection Act conflicts with the German constitution (liberty of action, of science and of conscience). No court rulings have been made to date on this point.

5.2.5 Greece

Voluntary termination up to the 12th week of pregnancy is legal in Greece. In addition, termination of pregnancy for medical reasons (i.e. when there are indications that the embryo is suffering from a serious abnormality that could result in a congenital defect in the child) has been legal since 1977 for pregnancies that have not progressed beyond 24 weeks.

Article 10 of the recent Law on Medically Assisted Reproduction allows PGD for diagnosis of genetic disorders in embryos, following appropriate genetic counselling and informed consent. However, one important point to note is that (as confirmed by the interviewee) this law does not distinguish between PGD (diagnosis for a defined genetic predisposition that can be transmitted by parents) and PGS (which screens for chromosomal aneuploidy in preimplantation embryos, often associated with advanced maternal age, repeated IVF failure or repeated early pregnancy loss).

5.2.6 Ireland

PGD is not specifically regulated in Ireland. Article 40(3)(3) of the Irish Constitution protects the right to life of the unborn. “Unborn” is undefined and uncertainty has therefore arisen as to the point at which the embryo becomes “unborn” and therefore requires protection under the Constitution. If Article 40(3)(3) applies then an embryo diagnosed with a genetic disorder following PGD would not be allowed to perish. In these circumstances, PGD is not currently provided in Ireland and all patients seeking PGD are referred to clinics outside Ireland. Article 40(3)(3) was amended in 1992 to provide that the subsection quoted above “...shall not limit freedom to travel between the State and another state. This subsection shall not limit freedom to obtain or make available, in the State, subject to such conditions as may be laid down by law, information relating to services lawfully available in another state.”

Notwithstanding this provision, one clinic suggested that the process of referring patients for PGD abroad may in itself constitute a breach of the Constitution and result in prosecution. This has been a matter of academic legal debate but the *Roche v Roche* case, currently before the Irish courts, will help clarify the status of the embryo in Irish law. The judgment is due later this year. One suggested alternative approach would be for patients to contact PGD clinics outside Ireland and for those clinics then to approach the Irish hospital which has been looking after the patients, requesting the relevant information. It has been suggested that this inverted referral system may comply with the constitutional framework. However, concerns have been raised that it would be difficult for patients to know which clinics were suitable, who they should approach and how they should be contacted. This is of particular concern since patients seeking PGD are often in a vulnerable position.

Changes may occur in the months ahead, following the Report of the Irish Commission on Assisted Human Reproduction. This Commission conducted a review of the current legislation and regulations in force in Ireland, the position of assisted human reproduction and research, and the social, ethical and legal considerations that these raise. The Commission’s Report was published in 2005 and, amongst other things, recommended that “PGD should be allowed, under regulation, to reduce the risk of serious genetic disorders. PGD should also be allowed for tissue typing only for serious diseases that cannot otherwise be treated. Each licence issued for PGD should specify the proposed procedure. The regulatory body should oversee and monitor developments in PGD.”

It remains to be seen what changes, if any, result from the Commission’s Report. It contained two dissenting opinions from academics whose concerns have considerable weight. Also, it has been suggested that the forthcoming election in Ireland may mean that nothing happens until after the election. However, there is a significant need for specific legislation and regulation in Ireland dealing with the status of the embryo and related issues, including PGD.

As PGD testing is not provided, Irish clinics do not work to specific education and training requirements for PGD. Quality management systems are used by some clinics but current schemes are undergoing review to meet the requirements of the EU Human Tissue and Cells Directive. There are also some brief guidelines produced by the Irish Medical Council.

As a result of the constitutional protection for the unborn, termination of pregnancy is illegal in Ireland except in very limited circumstances. It may be permissible where there is a real and substantial risk to the life (as distinct from the health) of the mother. This exception stems from a case concerning a 14-year-old rape victim who was initially prevented from leaving Ireland in order to undergo a termination in the UK. The Irish Supreme Court overturned this and recognised that termination was permissible because there was a real and substantial risk

of suicide if the pregnancy continued. Also, ethical guidance published by the Irish Medical Council states that termination "...is not unethical if a child *in utero* should suffer or lose its life as a side-effect of standard medical treatment of the mother".

In the light of the constitutional provisions quoted above, women may not be prevented from travelling abroad for terminations, and it is lawful to provide information in Ireland about termination services in other countries, subject to strict conditions. On the contrary, it is not lawful to encourage or advocate a termination of pregnancy in individual cases.

By contrast, prenatal diagnosis is not regulated in Ireland. It was suggested that approximately 300 prenatal diagnoses are carried out each year. Gestational age scans at around 18 weeks usually include screening for structural anomalies, but termination for foetal anomaly is not permissible.

5.2.7 Netherlands

In the Netherlands voluntary termination is allowed up to the 24th week of pregnancy. This law has been in place since 1 May 1981. Changes to this law are envisaged, but the interviewees were not certain to what extent and in what direction. Prenatal diagnosis is self-regulated by the clinical geneticists profession. In Europe the Netherlands was one of the pioneers in prenatal diagnosis, which has been offered there since the 1970s.

The Healthcare Board and the Ministry of Health regulate PGD and have allowed it in one centre (Maastricht), with a possible extension to a second centre in the future. The indications are similar to those for prenatal diagnosis. This regulation excludes PGS, which is allowed only as a research activity. Recently the Minister of Health declared that PGS was not a diagnostic tool.

One centre reported that no changes were planned in regulation of PGD, whereas the other expects a second PGD centre to be designated and PGS to fall under diagnostics rather than research, as such also obtaining public healthcare funding.

5.2.8 Slovak Republic

There is no law regulating assisted reproduction and PGD in Slovakia at present. Healthcare is regulated by the new (2004) Law on Healthcare, but this law does not contain regulations relating to IVF or PGD. A Law on Assisted Reproduction including PGD has been prepared, but its final version will depend on the political balance after the forthcoming elections.

Termination of pregnancy is regulated by the 1986 Law on Artificial Interruption of Pregnancy and by the subsequent ordinance of the Slovak Ministry of Health. Under this law, termination is allowed up to the 12th week of pregnancy. After this, termination is allowed only in cases where the mother's life is in danger or where there is a risk of serious damage to or "inviability" of the embryo. In the event of genetic indications pregnancy may be terminated up to the 24th week of intra-uterine life only. Genetic indications may be either serious hereditary disease of the foetus, diagnosed by a prenatal diagnosis, or a high risk of serious hereditary disease, determined by genetic examination of the parents, or exposure during pregnancy to factors with proven teratogenic or mutagenic effects. The legal

consequences of IVF are also mentioned in the new Law on Family adopted in 2005. This law does not regulate performance of IVF but prohibits the role of “hired mother”.

The IVF clinic interviewed prefers the present unregulated but liberal *status quo* to regulation of PGD by law. Concerns have been expressed about restrictive regulation inspired by the current Italian laws. Foreign couples are coming to Slovakia for IVF and PGD from countries with restrictive regulation of PGD, such as Italy and Austria. However, only a few foreign couples came to Slovakia for PGD in 2005.

Prenatal genetic testing is not regulated by law in the Slovak Republic. Current practice for genetic testing is regulated by the ordinance of the Ministry of Health. The recent ordinance establishes biochemical screening of levels of maternal serum alpha-fetoprotein (AFP). It is typically performed between the 14th and 16th weeks. Some clinics routinely perform the triple test (AFP, HCG and E3). Sonography is performed at the 12th, 20th and 33rd weeks. In cases of increased risk of chromosomal aberration in the foetus, amniocentesis with consequent karyotype determination is recommended. Postnatal screening methods are regulated by the 2004 directive of the Ministry of Health. It states that postnatal screening for phenylketonuria, congenital hypothyroidism and congenital adrenal hyperplasia has to be performed in neonates. Therefore, at the age of four to five days all neonates undergo biochemical tests for phenylalanine, TSH and 17-hydroxyprogesterone in their blood.

5.2.9 Spain

The necessity for regulation of assisted human reproduction dates back to the development of techniques to treat infertility in the 1970s and '80s. Spain was one of the first European countries to legislate on this topic and its first law was approved by the Spanish Parliament (Cortes Generales) on 22 November 1988 (Act 35/1988). This law regulated ART, including artificial insemination, *in vitro* fertilisation (IVF) and intratuberc transfer of gametes. At the same time the law stated that these techniques might be applied to prevent and treat genetic or hereditary diseases, and set limits for research and experimentation with human gametes or fertile oocytes. The law defined the preembryo or pre-implant embryo as the group of cells resulting from the progressive division of the oocyte after fertilisation until approximately 14 days later. This law made it possible to offer couples and individuals with fertility problems a wide range of clinical solutions and to develop reproductive medicine in Spain. As a result, the number of human reproductive clinics increased both in public hospitals under the National Health System and in private hospitals.

Following the scientific advances and clinical changes, a new law amending certain aspects of Law 35/1988 was approved by the Spanish Parliament in November 2005 (Act 45/2003). This authorised use of preembryos, as defined above, for research purposes. The law is restrictive in two ways: (i) only preembryos frozen before November 2003 may be used for research and (ii) the maximum number of fertilised oocytes per reproductive cycle is three. Point (ii) might create clinical problems for many women, considering the technical success rate.

Very recently, in May 2006, the Spanish Parliament approved a new law that improves these two points and also addresses several aspects related to clinical genetics in reproductive medicine. Preembryo is now defined as “the *in vitro* embryo formed by a group of cells as a result of the progressive division of the oocyte from the time it is fertilised until 14 days later”. This ART law allows genetic selection of embryos for therapeutic use for ill relatives,

which was forbidden by the previous law. The law prohibits the cloning of human beings with a reproductive aim. The main objectives of this new law are to help couples or women with fertility problems to have biological children and to regulate application of genetic testing for prevention of genetic diseases, increasing security for the individuals and couples at risk. Accordingly, the main points addressed by the new law are as follows: (i) the law abolishes the limit of fertilising a maximum of three oocytes in each reproductive cycle - the number is now left to the clinical discretion of the physician and the destination of the remaining preembryos is a decision for the couple or the woman; (ii) these preembryos may be used for research after informed consent is obtained from the couple; and (iii) preimplantation genetic diagnosis (PGD) will be possible to avoid severe genetic disorders and as a therapeutic tool for existing affected children, that is PGD will be applied both for diagnosis of a mutation in a preembryo and for histocompatibility of the HLA system with an ill child. This last point is intended to allow selection of embryos from an IVF process which will be compatible with an affected child (future brother or sister) for whom bone marrow transplantation is the only realistic treatment.

The law established a Register for the Activities of Centres for Assisted Reproduction. This register has to include techniques and success rates, the number of preembryos conserved and other aspects relating to quality schemes. The data should be published every year and one requisite will be to obtain authorisation and accreditation from the Ministry of Health.

The new law also expressly prohibits the role of “hired mother” and cloning of human beings with reproductive objectives. Human cloning for therapeutic reasons will be regulated by a law on biomedical research that is now being prepared.

On the other hand, the law lays down penalties if the identity of germ cell donors is revealed, in cases of malpractice in application of ART and manipulation of biological samples, if the interests of donors or patients are harmed or if hereditary or congenital disorders that could be avoided are transmitted to offspring.

Since its current liberal legislation, Spain has become one of the European countries receiving couples from other countries for ART, especially from Germany and Italy – two countries that have restrictive laws. As PGD was recently made available at some IVF clinics and genetics laboratories, the number of couples seeking PGD abroad (e.g. in Belgium) should decrease in the immediate future (the Spanish Ministry of Health estimates that approximately 150 families are waiting for PGD). However, it is likely that after approval of the new reproductive law, couples looking to PGD as a therapeutic tool for ill children with a genetic disease will generate new trans-border flows from European countries to Spain.

Termination of pregnancy has been legal in Spain since July 1985. Law 9/1985 amended Article 417 bis of the Penal Code and expressly declared that termination of pregnancy is not punishable in three cases: (1) severe risk to the life or physical or psychological health of the pregnant woman, (2) the woman’s distress and (3) presumption that the foetus could be born with severe physical or psychological defects.

Prenatal diagnosis has become common practice in clinical medicine. Both ultrasound and genetic testing are performed. Ultrasonography is applied in weeks 10 to 12 to define foetal health and detect early signs of chromosomal syndromes (e.g. Down's syndrome) and a 20-week scan is performed to screen for foetal anomalies. A first trimester combined test or second trimester biochemical test is performed on most women as antenatal screening for

Down's syndrome. Prenatal karyotype analysis (usually following amniocentesis at week 15 or 16, but also after chorionic biopsy at week 11 to 13) is offered to pregnant women with positive screening and, in many clinics, to those older than 35 to 38. Genetic testing for inherited disorders is usually applied in DNA from chorionic biopsy (sometimes from amniocytes or foetal blood leukocytes) in women at risk because of a previous ill child or familial antecedents.

5.2.10 Switzerland

Switzerland has amongst the most restrictive legislation in the world on medically assisted reproduction, and *preimplantation diagnosis* in most senses of the term is prohibited. The Federal Law on Medically Assisted Reproduction ("RPMA"), in force since 2001, was developed following acceptance by a referendum on assisted reproduction in 1992 and massive rejection, in 2000, of a referendum on "human dignity" aiming (among other subjects) to ban *in vitro* fertilisation. The law, which is closely based on Article 119 of the Federal Constitution, prohibits:

- development of more than three embryos outside the mother's body;
- cryoconservation of embryos at the cellular stage;
- preimplantation diagnosis;
- egg donation;
- embryo donation;
- carrier mothers;
- development of embryos for research purposes;
- creating embryos for reasons other than pregnancy;
- sex selection;
- modification of the genetic material of gametes or embryos;
- cloning or creation of chimeras or hybrids.

The law specifically addresses the situation of the embryo. Its wording permits preimplantation genetic diagnosis by polar body analysis, which only indirectly examines the genetic constitution of the embryo. Polar body testing is therefore legal in Switzerland.

As both prenatal diagnosis and termination of pregnancy are permitted, the prohibition of PGD has been opposed by many groups on ethical grounds and is generally seen as scandalous by the medical genetics and gynaecology-obstetrics professions. After several parliamentary initiatives, votes by the National Council and the Council of States gave the Government a mandate to submit a proposal authorising PGD and defining the conditions under which it may be performed. This process is unlikely to be completed within the next two years and the outcome is unclear, particularly as any proposal will potentially be subject to referendum.

In contrast to PGD, *prenatal diagnosis* is permitted and is subject to far fewer restrictions. It is regulated by the new Federal Law on Human Genetic Analysis ("LAGH") of 8 October 2004, which is expected to be applied from January 2007 on. The LAGH prohibits determination of characteristics that do not directly affect the health of the embryo or foetus (with the possible exception of prenatal paternity testing) and determination of sex except for diagnostic reasons. The Law does not otherwise provide any indications of situations in which prenatal diagnosis

is acceptable, but concentrates on defining the requirements for providing information to enable the woman to make a free and informed decision. These conditions include:

- genetic counselling by a qualified person and written informed consent;
- the woman must be informed about her right to auto-determination before and after testing, if there is no possibility of therapy and/or prophylaxis, and about the possibility of contacting a centre for prenatal information and counselling;
- if a severe, incurable anomaly is detected, the woman must be informed about solutions other than interruption and of the existence of self-help groups and of associations of parents of handicapped children.

Voluntary termination of pregnancy was not legalised in Switzerland until 2002, when 72% of voters chose to replace a restrictive law dating back to 1942. Termination is now available up to the 12th week of pregnancy, on written request and in case of “a state of distress”, which is left to the woman to define. After this period, a medical opinion from a single doctor is required, indicating that termination of pregnancy is necessary to avoid “the danger of a serious threat to the physical integrity or of a state of severe distress of the pregnant woman”. Neither prenatal diagnosis nor even the foetus is mentioned in this law.

5.2.11 United Kingdom

The key legislation relating to assisted reproductive technologies (ART) and preimplantation genetic diagnosis (PGD) in the UK is the Human Fertilisation and Embryology Act 1990. It regulates most ART procedures, including PGD and PGS, and research involving human embryos. The 1990 Act also created the Human Fertilisation and Embryology Authority (HFEA), the UK regulatory body responsible for implementation of the Act.

Following implementation of the 1990 Act it has always been assumed that regulation of PGD falls within the regulatory remit of the Human Fertilisation and Embryology Authority (HFEA). PGD is deemed to fall within this licensing framework since it involves the creation of embryos *in vitro*, biopsies of those embryos and the transfer of one or more to a woman. Certainly, the HFEA has always felt able to grant licences to centres for PGD, albeit in relatively small numbers. This authority was recently subject to a legal challenge, but the House of Lords (the highest appeal court in the UK) held that PGD could lawfully be authorised by the HFEA as an activity to determine the suitability of an embryo for implantation, and that Parliament had intended to leave it to the HFEA to decide whether activities such as PGD could be permitted. Once it was conceded that PGD was licensable to produce not just a viable foetus but also a genetically healthy child, there could be no logical basis for construing the HFEA's power to end at that point and PGD with HLA matching (and, in principle, sex selection) also came within its remit.

The 1990 Act makes no explicit reference to PGD but the technique is regulated through the broader licensing of the creation, storage and use of human embryos. The 1990 Act prohibits the creation, storage or use of embryos without a licence. Schedule 2 sets out the kinds of licence which may be granted by the HFEA, including licences for “practices designed to secure that embryos are in a suitable condition to be placed in a woman or to determine whether embryos are suitable for that purpose” and “placing any embryo in a woman” where these are done in the course of providing “treatment services”.

The HFEA has developed a tailored licensing procedure for PGD. The most recent version of its Code of Practice has a section dedicated to preimplantation testing, stating:

“Centres may only carry out preimplantation tests for those genetic conditions, chromosomes or traits (or combinations of these), and using those specific tests (or combinations of tests) listed in the preimplantation testing Annex to their licence or approved by a licence committee in any particular case.

Centres must submit an application to the HFEA for each new condition for which they wish to test and for each new test they wish to use.”

This policy was further developed in 2005. In a press release dated 19 January 2005 the HFEA highlighted an effort to “... streamline the system of dealing with applications for embryo screening, cut down bureaucracy and speed up the approval process.” In summary, the new policy provides that centres which are already licensed to perform PGD and subsequently seek to use PGD for another X-linked condition or single-gene disorder must submit an application which will be “fast-tracked” provided:

- the disorder has already been licensed by the HFEA (i.e. at another centre);
- the centre has proven expertise in performing embryo biopsies; and
- the laboratory where the genetic testing will take place has previously been recognised by the HFEA.

Also, clinics authorised to carry out PGD for a chromosomal rearrangement such as reciprocal or Robertsonian translocation do not have to seek further approval from the HFEA in order to carry out PGD for additional chromosomal rearrangements. However, the old “slow track” procedure remains in place for the following cases:

- initial applications from centres applying to perform PGD or PGS for the first time;
- where the disorder has not previously been licensed by the HFEA; and
- all cases of preimplantation HLA tissue typing, with or without PGD.

Following a review of regulatory and other non-governmental organisations it has been decided to merge the HFEA with another regulatory body, the Human Tissue Authority. This is due to take place in 2008-09 and will create the Regulatory Authority for Tissue and Embryos (RATE), which will also be the single competent authority for the purposes of the EU Human Tissue and Cells Directive. Establishment of RATE will require new legislation and the government has already begun the process of reviewing the 1990 Act. In August 2005 the Department of Health issued a consultation document which highlighted the areas it wishes to address in any legislative reform. These specifically included PGD.

The HFEA’s regulatory remit is limited to the UK. It cannot regulate movements of patients into and out of the UK, although imports and exports of gametes and embryos require permission from the HFEA. The main reason for patients leaving the UK for treatment is to receive treatment which is not available in the UK. Two well-publicised cases illustrated this trend: one couple sought sex selection in Italy after failing to find a clinic in the UK which would apply for a licence to treat them, and another travelled to the USA for PGD with tissue typing. It is possible that other families have adopted the same approach, travelling abroad for treatment which is not available in the UK as a result of HFEA policy. The extent of such movements is not known.

In terms of the relationship between PGD and other forms of testing and termination, they are regulated separately. Strictly speaking, termination of pregnancy is still a crime in the UK. Under the Offences Against the Person Act 1861, it is a criminal offence intentionally to procure a miscarriage in oneself or another and, under the Infant Life Preservation Act 1929, it is an offence to destroy the life of a child capable of being born alive unless it is done in good faith for the sole purpose of preserving the life of the mother. However, the Termination of Pregnancy Act 1967 created statutory defences against these crimes: since 1968 termination of pregnancy has therefore been lawful where two doctors believe in good faith that one of the statutory grounds has been satisfied. Most terminations of pregnancies (97%) in the UK are carried out on the first of these grounds, namely "... that the pregnancy has not exceeded its twenty-fourth week and the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman or any existing children of her family."

Prenatal diagnosis is not regulated in the UK. The Department of Health has published certain policies which practitioners are encouraged to follow, and almost all women are offered some form of screening during pregnancy. The apparent inconsistency between this relatively liberal attitude towards PND and case-by-case licensing of PGD is a source of frustration to some working in PGD.

The licensing and inspection framework implemented by the HFEA provides the most tangible form of quality assurance for PGD laboratories in the UK. However, laboratories are also encouraged to obtain Clinical Pathology Accreditation (CPA). Clinical Pathology Accreditation (UK) Limited is a not-for-profit organisation jointly owned by the Royal College of Pathologists, the Institute of Healthcare Management, the Institute of Biomedical Science, the Association of Clinical Pathologists, the Association for Clinical Biochemistry and an organisation representing the independent sector. As part of its "Modernisation of Pathology Strategy", the UK Department of Health requires all medical laboratories in England to enrol with an accreditation scheme. The CPA process involves external and self-assessment of each medical laboratory applying to assess its compliance with the published CPA standards. Applicants must conduct a self-assessment of their ability to comply with CPA standards, complete a quality manual (including specific documentation) and return these together with a completed application form. These documents are then checked, followed by a formal external assessment process based largely on the appropriate ISO standards.

Table 15: Summary of national regulations on reproductive technologies

Country	Termination of pregnancy	PND	PGD
Belgium	Allowed, subject to conditions. After 14 weeks, allowed only if mother's life is in danger or if it is clear that the child will suffer from an incurable disease.	Allowed.	No specific regulation, but existing regulations on ART influence PGD.
Czech Republic	Allowed, subject to conditions. After 12 weeks, allowed only if mother's life is in danger or where there is a risk of serious damage to or "inviability" of the embryo. In cases of genetic indications, allowed up to 24 weeks.	Allowed and not regulated.	Allowed for specified indications and only to exclude the risk of serious genetic diseases.
France	Allowed up to 12 weeks. Allowed after 12 weeks where high probability of birth of child with a severe disease recognised as incurable.	Allowed, subject to regulation.	Allowed in certain circumstances and subject to regulation and licensing.
Germany	Allowed. After 14 weeks, no time limit if for medical reasons.	Allowed and not regulated.	Not allowed except for polar body analysis.
Greece	Allowed up to 12 weeks. Allowed up to 24 weeks where high probability of birth of child with a severe congenital defect.	Allowed.	Allowed, subject to legislation which allows PGD for genetic disorders.
Ireland	Not allowed.	Allowed and not regulated.	Not allowed.
Netherlands	Allowed up to 24 weeks.	Allowed and self-regulated.	Allowed and regulated.
Country	Termination of pregnancy	PND	PGD

Slovakia	<p>Allowed up to 12 weeks.</p> <p>After 12 weeks, allowed only where there is a risk to the mother's life or a risk of serious damage or "inviability" of the embryo.</p>	Allowed and not currently regulated, but guidance through ordinance of the Ministry of Health.	Allowed and not currently regulated, but draft law prepared.
Spain	<p>Allowed where:</p> <ol style="list-style-type: none"> 1. severe risk to the life or physical or psychological health of the pregnant woman; 2. "distress" to the woman; and 3. presumption that foetus could be born with severe physical or mental defects. 	Allowed and not regulated.	Allowed, subject to legislation which allows PGD for severe genetic disorders or as a therapeutic tool for existing affected children.
Switzerland	<p>Allowed up to 12 weeks on written request and in cases of "a state of distress".</p> <p>After 12 weeks a medical opinion is required, indicating that termination of pregnancy is necessary to avoid a serious threat to the physical integrity or of a state of severe distress of the pregnant woman.</p>	<p>Allowed, subject to some regulation.</p> <p>Determination of characteristics that do not directly affect the health of the embryo or foetus, and social sex selection prohibited.</p>	Not allowed except for polar body analysis.
United Kingdom	Allowed in specific circumstances defined by legislation.	Allowed and not regulated.	Allowed, subject to regulation, licensing and inspection.

6 CONCLUSIONS

6.1 PGD services in Europe

PGD is an expanding activity in Europe with increasing social implications (e.g. trans-border flows of couples).

The study is a first attempt at providing a clearer picture of the current situation in Europe as regards PGD-related practices. The survey developed for this purpose identified nine centres across Europe offering PGD as their sole activity and 44 centres performing PGD in addition to a full IVF service. Most of them are located in Spain, Belgium, the Czech Republic, Greece and the United Kingdom, indicating that patients are potentially travelling abroad to seek PGD treatment. The survey showed that patients do indeed travel within Europe for PGD, mostly for legal and financial reasons but also because of availability of the test (or lack thereof). The main receiving countries are Spain, Belgium and the Czech Republic, but also Cyprus (although only one centre was identified by the survey). Several centres located in other countries indicated that they treat patients from abroad without, however, giving details of the numbers treated each year.

A wide range of tests are available with a general trend towards custom-made tests, most commonly for extremely rare disorders, but also for some indications which may be less acceptable in prenatal diagnosis.

The main types of test offered by laboratories performing PGD included tests for monogenic diseases, cytogenetic testing for chromosomal abnormalities and sex selection for X-linked monogenic diseases, whereas “social sex selection” was found to be performed by only one centre. Thirty-seven laboratories replied that they performed PGS for aneuploidy screening, but it is still unclear how many are performing only PGS. The majority of labs that offer PGD for monogenic diseases in the countries included in the survey tend to offer tests for many or all common monogenic diseases investigated, for which prenatal testing is also widely available. The most common of these are CF and DMD. Interestingly, testing for Huntington’s disease is also offered by 46% of the labs, in spite of the late onset of the disease. A number of other adult-onset diseases are also tested for, including several cancer predispositions, indicating a potential trend for PGD labs to practise a wide variety of tests, some of which are not relevant to prenatal diagnosis.

Genetic counselling and informed consent guidelines adapted to PGD may need to be developed.

Genetic counselling is offered by the majority of the centres that responded to the survey (94%), although it is not clear whether such counselling is actually given. Similarly, the informed consent of the patient is required by the majority of the centres (94%), although the survey did not investigate who was responsible for obtaining consent or whether it was always in writing. Formal reports (i.e. documents from the laboratory to the referring doctor reporting the outcome of genetic investigations on a patient) are issued by 94% of the respondents and are typically validated by more than one person. This indicates that the majority of centres comply with PGDIS Guidelines (2004). Nevertheless, it is a cause for concern that not all centres issue such reports. Surprisingly, a significant proportion of those centres that do issue reports make no mention of follow-up in them, in spite of the fact that it is recommended or

suggested in the informed consent in the majority of the centres that replied to the survey (88%). This finding could point to a potential need to improve implementation of the informed consent process.

6.1.1 Quality assurance and education

Respondents to the survey highlighted the importance of quality assurance. Development of PGD-specific quality assurance schemes (or adaptation of existing schemes) is therefore gaining importance.

Quality assurance of PGD testing was evaluated by several criteria, including the qualifications of staff and the degrees of laboratory directors (McGovern et al. 1999). One notable point is that, according to the survey, the majority of directors of genetics laboratories have a PhD in contrast to the directors of clinics, who were typically MDs. However, a significant portion of IVF labs (22%) were directed by holders of only a Masters or similar post-graduate degree. At the same time, only about half the clinics and laboratories had a designated quality manager, indicating a potential need for improvement and further education at these centres.

Another important criterion for quality assurance and management with regard to PGD practice is record-keeping, for example, on success rates. Almost all centres keep data on their success rate and 81% on accuracy. Nonetheless, the findings that 19% of the centres keep no data on accuracy and that 9% do not even follow up until birth is worrying and highlights a potential problem with quality assurance and patient safety. A further measure of quality assurance takes the form of external quality assessment (EQA). Although there are no specific EQA schemes for PGD, ESHRE (2005) has recommended that a voluntary EQA scheme be implemented. According to the survey, the majority of centres rated EQA as important or very important but only one third of them were actually participating in EQA schemes. This indicates a clear need for development of EQA schemes specific to PGD (or for adaptation of existing schemes) to ensure that related technical aspects, interpretation and reporting of the results are properly assessed and comparable.

The EU Human Tissue and Cells Directive will have a positive impact on quality standards since it requires all relevant clinics (including centres performing PGD) to implement and update a quality system.

While the majority of clinics clearly stated that they believe that quality assurance is important in this field, there seems to be a gap between recognising its role and actually implementing a quality system. This suggests that many EU clinics will have considerable work to do in order to meet the requirements of the EU Human Tissue and Cells Directive¹⁹. Although many clinics indicated that they maintain written protocols (particularly those in countries with some form of licensing or accreditation system), the more detailed data suggest that this seldom amounts to a comprehensive quality management system for PGD.

The EU Human Tissue and Cells Directive and the technical annexes to it introduce a broad range of quality management requirements for clinics which fall within its remit (which

¹⁹ http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/l_102/l_10220040407en00480058.pdf.

include IVF clinics and PGD laboratories). Although the specific requirements of the Directive were not all addressed in detail in the questionnaire and in the interviews, the general indication from the majority of respondents was that few clinics meet these criteria at present. Clinics will presumably be allowed a reasonable period of time to implement the new requirements and, on the basis of the evidence provided by the study, there appears to be a willingness to engage in quality management in principle. It therefore seems likely that much will turn on the practicality and affordability of compliance for individual centres.

The second supplementary technical Directive also sets out detailed training and education requirements for tissue establishments. Predictably, it states that all staff should have appropriate initial training to demonstrate competence in the relevant activities. More surprisingly, it then goes on to list general and specific topics which should be part of any ongoing training programme. The general topics include an overview of the quality management system, the quality and safety criteria for accredited or licensed activities and the legal aspects of their work. The specific topics should be tailored to particular clinics and staff and should include quality control procedures, equipment handling and management of the registers and data analysis tools. None of the respondents suggested that such a comprehensive programme of training is currently being offered. Like quality assurance, there was an evident willingness to engage in education and training (although one clinic suggested that tailored training for PGD was misguided and that the focus should be on genetics *per se* instead). The professional bodies or ESHRE would seem well placed to devise a suitable programme to address this new requirement.

6.1.2 Accreditation

A need for further improvement was also identified as regards accreditation. Official recognition of the quality management system in the form of accreditation (including process management and technical competence) or certification (process management only) is an important step because it demonstrates in a clear, objective and independent fashion the competence of the laboratory and its personnel. Accreditation (based on international standards such as ISO 15189) is the single most effective way of assuring the quality of a medical laboratory. According to the survey, penetration of formal recognition of quality management is low in PGD centres. Thirty-three percent of labs and clinics have or are preparing some form of recognition, and only 17% are either accredited or working towards accreditation. One third of the genetics laboratories have, or are preparing, some form of recognition and 23% are accredited or working towards accreditation.

For the time being, the results from the questionnaire suggest that formal EQA schemes have yet to be implemented in the majority of centres, with only 24 accredited or working towards accreditation. Presumably these statistics will change over the months and years ahead as the EU Directive is implemented in Member States. However, as in the case of quality assurance, the initial and ongoing costs of obtaining and maintaining accreditation will inevitably influence its popularity. Where accreditation is combined with or incorporated into a regulatory framework there are further implications, which are considered below.

Nonetheless, another expected consequence of the EU Human Tissue and Cells Directive is a pan-European shift towards mandatory accreditation of clinics. Article 4 of the Directive requires each EU MS to designate a “competent authority” (or authorities) responsible for

implementing the other requirements of the Directive. Article 6 then requires MS to ensure that all relevant tissue establishments (which include PGD and IVF laboratories) are accredited, designated, authorised or licensed by the national competent authority once it has verified that the establishment complies with the requirements set out in the technical annexes.

Beyond the competent authority's role of implementing the requirements of the Directive and the technical annexes to it, its design and nature are not specified. MS therefore have some flexibility in how they fulfil this requirement. Those that have an existing regulatory or licensing body are likely to expand its role and remit to meet the requirements. In the UK, for example, the Human Fertilisation and Embryology Authority, which licenses IVF and PGD, is one of two competent authorities for the purposes of the Directive and its role will no doubt change accordingly. Other countries, such as the Czech Republic and Spain, have recently introduced new licensing bodies which appear to have been shaped by the requirements of the Directive, for example they assess equipment, personnel, techniques, registers and quality management schemes.

6.1.3 Monitoring and follow-up

There is a need to support monitoring of PGD treatment, with increased public funding and international cooperation.

The data collected on monitoring and follow-up suggest a very varied pattern across Europe. Monitoring of data on the outcome of treatment, not only during pregnancy but also at the neonatal stage and in the medium and long term, provides a wealth of information about safety and efficacy, in terms of both clinical- and cost-effectiveness. It can help to improve understanding of the impact that PGD treatment has on families and their children. The quality and safety of the technology should be assessed together with the benefits. Together, such data can be used to shape clinical, scientific and counselling practices, but also policy and legislation in this field.

This study suggests that whilst prenatal follow-up is routine in most clinics, neonatal and short-term follow-up are far less common, and systematic long-term follow-up for PGD is limited to one centre in Belgium. There may also be some limited long-term follow-up in Spain. A significant minority of clinics report that they provide no follow-up at all. By contrast, it was suggested that at least one clinic in Ireland, where PGD is prohibited, still makes an effort to follow up families treated abroad. Another shortcoming appears to be that few of the follow-up studies that are carried out are linked or share data. Some clinics reported that they run their own studies in isolation, and the ESHRE PGD Consortium study is the only reported international data collection looking at neonatal data from clinics within Europe and some outside.

There are a number of possible reasons why follow-up of PGD is not more common, but the two main factors put forward as reasons for this scenario are lack of expertise and expense. Follow-up requires input from suitably experienced paediatricians, paediatric nurses and counsellors, working in collaboration with the treating clinic. Without their awareness and enthusiasm, follow-up in this field is unlikely to take place. Linked to this, a worthwhile follow-up study over the medium to long term requires a significant investment of time and other resources, which in turn cost a considerable amount of money. This cost is higher still

for a multi-centre international study collecting data from across Europe and beyond. Given the relatively small number of children born following PGD, an international study is necessary but this would require significant sponsorship. As mentioned above, the ESHRE PGD Consortium is hoping to extend its current follow-up with those centres which have the infrastructure and financial means to participate. Ideally, further funding would facilitate wider participation, thereby adding to the value of the data.

6.1.4 Trans-border flows and financial aspects

To further elaborate the findings of the survey, the interviews also investigated the trans-border flows in ten European countries (including those identified as the principal receivers of patients from abroad, except Cyprus). In line with the survey, the main reasons for travelling abroad are legal (i.e. PGD not allowed in the country of residence, e.g. Germany, Switzerland and Ireland). Additional reasons for travelling to a specific country include the quality of the treatment (e.g. Czech Republic), test availability (e.g. Belgium and Spain), financial resources and manpower (e.g. UK). Spain, Belgium and the Czech Republic were also confirmed as the main receivers. However, the number of couples received from abroad is not entirely clear. Interestingly, most patients travelling abroad for PGD services come from various European countries, but also from the USA (e.g. to the Czech Republic, UK and Belgium), Lebanon (to France), Israel (to Belgium), etc.

As regards referrals, the survey indicates that most countries referring only provide information, whereas some directly refer couples abroad due to legal reasons. Although it is not entirely clear how referrals are made, several ways and sources were mentioned in the interviews. For example, most of the foreign couples treated in the Czech Republic obtain information from the websites of IVF clinics or receive recommendations from other couples who have been previously treated, whereas in Switzerland information is frequently provided by medical genetics services (principally but not exclusively university services). The same is true in the case of Ireland, where most referrals are made by the National Centre for Medical Genetics. One interesting point to note is that in certain countries (e.g. Germany) formal referral is prohibited.

In financial terms, the survey revealed that 20 of the 22 centres responding reimburse the cost of IVF and/or the cost of treatment and 19 also reimburse the cost of genetic testing (see Figure 18). Moreover, in the majority of cases the procedure (i.e. cost of IVF and treatment plus cost of genetic testing) is reimbursed either completely (e.g. Spain) or partly (ranging between 80% and 90%). This variability was confirmed by the interviews in the countries covered by the study (see Chapter 4).

6.2 Regulatory framework

Reproductive and genetic technologies are regulated in a wide variety of ways across Europe. The different perspectives of the countries analysed in detail are set out in Chapter 5 and summarised in Table 14. Although loosely grouped into those where procedures are “allowed” and “not allowed”, this detailed analysis of national regulation demonstrates the remarkable diversity of rules, restrictions and prohibitions.

This is perhaps to be expected in a field which seldom fails to generate moral and ethical debate. National governments must therefore decide whether to legislate in tune with majority opinion – be it the church, patient groups, researchers or doctors – or to find a compromise between diverging views. Examples of both approaches can be seen in this study. The UK and Belgium, for example, have adopted a compromise position allowing IVF, PGD and related research but in a regulated environment. By contrast, Ireland has a blanket prohibition on PGD, following the influential views of one majority group with a particular ethical position. Germany and Switzerland have adopted similar positions, prohibiting PGD with the limited exception of polar body biopsies. Whilst the option of regulation and licensing is not always perfect (see below), this study highlights one immediate consequence of adopting blanket policies prohibiting procedures such as PGD which are sought by families within each country: they go somewhere else for treatment.

Cross-border movements of patients are virtually impossible to prevent, and previous instances of countries attempting to prevent people seeking prohibited treatment abroad, or punishing them upon return, have generally proved unsuccessful in the long term. In broad terms, the relatively free movement of people and goods around the EU is a welcome development. However, there are disadvantages to such cross-border flows in relation to PGD if such treatment is prohibited in the family's country of origin.

To begin with, the evidence provided in this study suggests that doctors in Ireland, Switzerland and Germany are anxious about providing information to patients about suitable PGD clinics in other countries. Referral is said to be prohibited in Germany, and at least one Swiss clinic feared that even informing a couple about PGD was illegal. Similar fears about potential prosecution for referring patients abroad appear to exist in Ireland where doctors may be required to pursue a bizarre “inverted referral” process to avoid culpability. As a result, patients are left to identify clinics themselves, using only the information which is accessible and which they can understand. They are deprived of the benefit of medical advice, counselling and support at a vulnerable time. They are left to navigate a particularly complex area of medicine and science within a foreign healthcare system in what is likely to be a different language.

Secondly, even if patients are able to receive treatment abroad, the prohibition of PGD in their country of origin may complicate monitoring and follow-up. Where patients have been self-referred, the fact that PGD has been practised abroad may go unnoticed. Clinics could also be reluctant to get involved in following up families and children born as a result of a prohibited treatment. The evidence gathered paints a contrasting picture on this point: some clinics are clearly not deterred whilst others do not see it as their responsibility.

These potential disadvantages and problems are more difficult to come to terms with in the light of the apparent inconsistency in Germany, Switzerland and Ireland between, on the one hand, the prohibition of PGD and, on the other, the acceptance of prenatal testing and termination of pregnancy (although the latter is not allowed in Ireland). Germany and Switzerland both impose restrictions on the circumstances in which termination of pregnancy is allowed but both permit termination to avoid a serious genetic disorder. It is difficult to identify clear distinctions between this and provision of PGD for serious genetic disorders. By regulation, PGD is restricted to such conditions in certain countries in the same way that termination of pregnancy is restricted in the majority.

This is not to say that regulation is the best solution. Indeed, some of the evidence gathered was critical of regulation in this field. The majority of UK clinics expressed the view that the current regulatory model in the UK is inappropriate for PGD. Four out of five of those interviewed advocated an alternative, less onerous approach: as one clinic put it, “...the decision to perform PGD should be made by the physicians and the patients. The role of the state should be kept to a minimum. Obtaining individual licences for PGD practice is restrictive for research and clinical practice. The best people to decide are the potential parents.” However, as the fifth clinic commented more positively, a regulatory framework does at least give clarity for clinics and staff. It is this certainty which the Irish respondents are hoping for if new legislation is passed. No changes are imminent in Germany or Switzerland.

A degree of harmonisation has been achieved in regulation of this field thanks to the recent EU Human Tissue and Cells Directive. This introduces minimum quality and safety standards for tissues and cells intended for human application. This will include embryos for transfer following PGD. However, the standards are a minimum requirement and MS are free to impose more stringent restrictions – or indeed prohibitions. On the positive side, the Directive will mean that, in time, patients who travel abroad for PGD will know that they can expect certain quality and safety standards if they are treated in an accredited centre.

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ANNEX 1

Survey

In order to prepare and carry out the survey the following steps were taken:

1. Identification of different centres or units that perform PGD;
2. Development of the survey.

Identification of PGD centres

The European Society for Human Reproduction and Embryology (ESHRE) runs a very active PGD consortium. The mailing list of the members of this consortium was used to target those known to be actively in providing PGD within the EU. Some medical genetics laboratories offering PGD were identified by EuroGentest's quality assurance survey and database (2005). This listed 169 centres.

A second mailing list was then compiled using the ESHRE membership database of some 3 993 members. Those from outside the EU, those not working for IVF or PGD clinics and other inappropriate targets for the questionnaire were removed. Duplications and overlaps with the PGD consortium list were then identified. This left 1 515 recipients.

Development of the survey

The aim of the survey was to obtain a clear picture of current PGD practices in Europe.

To obtain a high response rate, an on-line questionnaire was developed in English based mostly on closed questions (yes/no answers or drop-down lists). The questionnaire could be answered in about thirty minutes, and users could save their replies and return to it at a later date. On submission, the replies were automatically fed into a database to simplify analysis.

The questions were devised by the authors and asked about:

- (1) laboratory environment,
- (2) personnel qualifications,
- (3) PGD services provided at the centre,
- (4) genetic counselling,
- (5) reporting practices and informed consent,
- (6) QA practices and monitoring details for the laboratory,
- (7) participation in EQA schemes,
- (8) accreditation/certification and licensing status,
- (9) transborder flows, and
- (10) reimbursement issues.

To make it easier to answer the questionnaire, different lists of conditions were provided. The first question on the survey asked about the activity of the centre (IVF + PGD, PGD only, IVF only or IVF + PGD referred) in order to allow a breakdown of results by activity for later analyses. Once a laboratory had chosen, say, PGD only, just questions relevant to genetics laboratories and not those on IVF clinics/laboratories were asked. Laboratories that perform only IVF activities were asked to give reasons why they did not perform PGD and what the likelihood was of them offering it in the near future.

In order to give respondents guidance about the meaning of some of the terminology used in the survey, a glossary was embedded in the information page of the on-line questionnaire.

An initial version of the questionnaire was drafted and sent to the expert group for validation. An introductory e-mail explaining the objectives and specifying the institutions involved in this study was sent to 169 PGD centres in approximately 20 countries. The e-mail invitation contained a specific URL link to the website hosting the survey. Embedded within the URL was a unique identifier that made it possible to track respondents for the purposes of calculating the response rate. Respondents could start the survey on the website, save their answers and return to the survey later if necessary. After submitting the data, respondents received a confirmation e-mail including a summary of their answers.

In addition, an invitation was sent by e-mail to 1 515 IVF contacts giving them an opportunity (1) actively to participate in the study or (2) to express their interest in the project and ask to be informed about the final report.

A first reminder was sent two weeks after the questionnaire. Centres were contacted again by e-mail in their mother tongue to encourage them to participate in the study. A final reminder was sent three weeks before the deadline (2 June 2006).

In the case of Germany, in spring 2006 the English invitation with a unique link to an English online questionnaire was e-mailed twice to 120 German IVF centres, followed by several reminders. Seven centres completed the English questionnaire. A German questionnaire was designed, based on the questions agreed for the interviews (see section 2.3), with 30 multiple-choice questions and a blank space for every question. This German questionnaire was e-mailed to all 120 centres with an invitation explaining the campaign and a request to complete the English questionnaire and to be prepared for an additional interview in German from the German team, based on the German questionnaire. The German cover letter and the German questionnaire were sent again by fax to 30 IVF centres which are members of the German PGD interest group.

Regulatory framework

In order to obtain a full understanding of how PGD is provided in Europe, the survey examined how it is regulated in those countries assessed in detail. It also looked at EU regulations which have an impact on provision of PGD, and other relevant European legislation. The report comments on how this regulation has an impact on clinical practice and the correlation with movements of patients between MS (and outside the EU) for treatment.

The analysis of the regulatory landscape is based on a review of the national legislation in each of the countries covered, the information published by national regulatory bodies, parliamentary publications and articles from relevant journals.

Current practice

To complete the information on current practice gathered by the survey and to obtain a more detailed picture of the situation, expert knowledge was sought by means of interviews conducted with genetics labs and IVF clinics offering PGD in specific countries, i.e. Belgium, the Czech Republic, France, Germany, Greece, Ireland, the Netherlands, the Slovak Republic, Spain, Switzerland and the UK.

ANNEX 2

PGD interviews

Interviews were modelled on the questionnaire set out below. Further information was added by desk research and from the team's expert knowledge.

1. What is the current legislation regarding PGD?

- How does it have an impact on current clinical practice?
- If not allowed, what action is taken?
- Are couples referred to/received from elsewhere (e.g. abroad) as a result? Where to/from and what percentage?
- To your knowledge, are any changes anticipated in the legislation in the next 18 months?
- If so, which?

2. What is the current reimbursement situation for PGD testing?

- Is it covered by the national healthcare system or by private companies (or both)?
- If so, are couples that go abroad also reimbursed?
- How does the current reimbursement situation have an impact on current clinical practice?

3. To your knowledge, what is the communication and interaction between IVF clinics and genetic labs?

- Are the two usually located in the same building? Are they part of the same institution?
- Is communication frequent?
- In your clinic, do you typically contact different labs or not?
- Are there any technical barriers?
- Of the two, which is typically responsible for genetic counselling?
- Who is responsible for informed consent? How is it provided?
- Is offspring monitoring provided? If so, who is responsible?

4. Do any specific quality assurance schemes exist? If so, which?

- Are there specific education and training requirements? If so, what kind (e.g. specific training programmes)?
- How is the quality of the centre improved?
- Are any specific guidelines followed?

ANNEX 3

PGD survey questionnaire

Introduction

Welcome to the “Preimplantation genetic diagnosis (PGD)” questionnaire. We invite you to fill in this web form, which covers the:

- Laboratory and/or clinical environment and contact persons;
- Information about PGD services;
- International flows and financial aspects;
- Quality assurance (accreditation-certification-licensing-external quality assessment);
- Information concerning PGD procedures.

You can save, check and modify data at any time before you submit the form. In addition, you can forward the unique url, which you received via e-mail, to one of your colleagues to complete the survey, if necessary.

Results of the survey will be posted on the [JRC-IPTS website](#) and will be published anonymously. Your confidentiality will be respected. All labs which participate will receive a report.

Please go through the questionnaire and submit after completion. Completing the survey will take you less than 30 minutes.

For further information [click here](#). If you have any further questions, please do not hesitate to contact us at esto@eurogentest.org

Survey

What kind of activity do you perform?

- IVF only
- PGD only
- IVF, PGD is referred
- IVF and PGD

1. IVF and PGD

Where do you work?

- In the IVF clinic
- In the IVF laboratory
- In the genetics laboratory

Indicate which structure is applicable to your situation:

- 1 IVF clinic <--> 1 genetics laboratory
- 1 IVF clinic --> multiple genetics laboratories
- 1 genetics laboratory --> multiple IVF clinics

Addresses of partner clinics

Addresses of partner laboratories

.....

.....

IVF clinic

IVF clinic's full name
Hospital/Service/Institute
Address
City
Postcode
Country
Secretariat phone number
Fax number
Affiliation

Clinical director

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

Quality manager

Does your IVF clinic have a quality manager?
 Yes
 No

If yes, please specify:

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail



IVF laboratory

Laboratory's full name
Department/Service/Institute.....
Address
City
Postcode
Country
Secretariat phone number
Fax number
Affiliation

Laboratory director

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

Quality manager

Does your IVF laboratory have a quality manager?

- Yes
- No

If yes, please specify:

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

Genetics laboratory

Laboratory's full name
Department/Service/Institute.....
Address
City
Postcode
Country
Secretariat phone number
Fax number
Affiliation

Laboratory director

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

Quality manager

Does your genetics laboratory have a quality manager?

- Yes
- No

If yes, please specify:

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

PGD services

1. Do you perform PGD for monogenic diseases?
 - Yes
 - NoFor which pathologies do you offer testing?
 - CF
 - β -thal
 - HbS
 - SMA
 - DM1
 - HD
 - CMT
 - FRAXA
 - A/B
 - DMD
 - Other
2. Do you perform PGD for chromosomal abnormalities?
 - Yes
 - No
3. Do you perform sex selection for X-linked disorders?
 - Yes
 - NoDo you perform social sex selection?
 - Yes
 - No
4. Do you offer mutation detection in probands/parents?
 - Yes
 - No
5. Do you offer PGD to families seeking to:
 - Avoid an adult-onset genetic disease (Huntington's, BRCA, Alzheimer)
 - Select HLA match for ailing sibling in combination with testing
 - Select HLA match for ailing sibling in the absence of heritable mutation
6. Do you freeze embryos for later use?
 - Yes
 - No
7. How many PGD cycles did you perform in 2005? (monogenic diseases, chromosomal abnormalities, sex selection - confidential data, for anonymous research only)
 - 1-10
 - 11-20
 - 21-50
 - 21-100
 - > 100
8. Do you perform PGS
 - Yes
 - No
9. Do you offer genetic counselling?
 - Yes
 - NoIf yes, please specify:
 - Available at the IVF centre
 - Available at the genetics centre

- Available from partners
10. Do you require informed consent?
- Yes
 - No

In the informed consent, follow-up confirmation by amniocentesis/choriocentesis is:

- Recommended
- Suggested
- Varies according to situation
- Not mentioned

11. Does your laboratory issue formal reports?
- Yes
 - No

Test results are signed/validated by:

- Medical doctor
- Clinical scientist
- Laboratory technician
- Other

In the reports, follow-up by amniocentesis/choriocentesis is:

- Recommended
- Suggested
- Varies according to situation
- Not mentioned

International flows and financial aspects

1. Do you receive samples from other countries?

- Yes
- No

2. Do you treat patients from other countries?

- Yes
- No

Approximately how many each year come from other countries?

From which countries do you receive patients?

What are the reasons for patients travelling to your clinic?

- Legal reasons
- Test availability
- Financial reasons
- Other

3. Do couples receive any public funding or reimbursement for PGD?

- Yes
- No

If yes, please specify approximately what percentage of the cost of each treatment is publicly funded or reimbursed.

Cost of clinical treatment (e.g. consultations, drugs) (%)

Laboratory costs (e.g. IVF, embryo culture, embryo biopsy)..... (%)

Genetics testing (%)

Quality assurance

1. Do you participate in External Quality Assessment (EQA) schemes?

- Yes
- No

Please list all schemes you perform for each provider; only participation and not success or failure is requested.

Year:

Organisation/Provider:

Disorders/Techniques/Schemes:

2. How do you rate the importance of EQA?

- Very important
- Important
- Irrelevant

3. Your laboratory keeps data on:

- Success rate
- Accuracy

4. Your laboratory follows up:

- During pregnancy
- Neonatal
- Short-term pediatric
- Long-term pediatric

5. Analytical data are kept for:

- < 9 months
- 9–12 months
- 1–2 years
- > 2 years

6. Does your laboratory contribute data to ESHRE?

- Yes
- No

7. Do you have written protocols/policies for:

- Validating tests before application
- Training staff

Quality assurance

1. Is your centre/laboratory accredited?

Yes/Underway

No

Centre/Laboratory

State

Norm

Organisation

Year

Accreditation No

2. Is your centre/laboratory certified/licensed?

Yes/Underway

No

Centre/Laboratory

State

Norm

Organisation

Year

Certification No

PGD procedures

1. Does your laboratory confirm the nature of familial mutations and/or chromosomal anomalies?
 - In all cases
 - > 50% of cases
 - < 50% of cases
 - Always trust external report
2. Number of cells analysed per embryo per diagnosis?
 - 1 blastomere
 - 2 blastomeres
 - 1 polar body
 - 2 polar bodies

On which day do you usually perform blastomere biopsy?

 - Day 2
 - Day 3
 - Day 4
 - Day 5

Which embryos do you biopsy?

 - ≥ 5 cells
 - ≥ 6 cells
 - ≥ 7 cells
 - Blastocysts

Who performs the biopsy of the embryo for your PGD patients?

 - Embryologist/Biologist
 - Lab Technician
 - Other

On which day do you usually transfer fresh embryos following PGD?

 - Day 3
 - Day 4
 - Day 5
 - Day 6
3. Do you perform positive/negative controls?
 - Yes
 - No
4. Do you have dedicated rooms for?
 - Pre-PCR (DNA-free)
 - PCR
 - Post-PCR
5. How close is the PGD lab to the IVF clinic?
 - same building
 - same institution
 - same city
 - same country
 - different country
 - other

2. PGD ONLY

Genetics laboratory

Laboratory's full name
Department/Service/Institute.....
Address
City
Postcode
Country
Secretariat phone number
Fax number
Affiliation

Laboratory director

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

Quality manager

Does your genetics laboratory have a quality manager?

- Yes
- No

If yes, please specify:

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

PGD services

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 - Yes
 - NoFor which pathologies do you offer testing?
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 - No
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 - > 100
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 - No

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- No

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- No

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- Legal reasons
- Test availability
- Financial reasons
- Other

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- Yes
- No

If yes, please specify approximately what percentage of the cost of each treatment is publicly funded or reimbursed.

Cost of clinical treatment (e.g. consultations, drugs) (%)

Laboratory costs (e.g. IVF, embryo culture, embryo biopsy) (%)

Genetics testing (%)

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- No

Please list all schemes you perform for each provider; only participation and not success or failure is requested.

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- Important
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- Accuracy

4. Your laboratory follows up:

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- Neonatal
- Short-term pediatric
- Long-term pediatric

5. Analytical data are kept for:

- < 9 months
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- 1–2 years
- > 2 years

6. Does your laboratory contribute data to ESHRE?

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- No

7. Do you have written protocols/policies for:

- Validating tests before application
- Training staff

Quality assurance

1. Is your centre/laboratory accredited?

Yes/Underway

No

Centre/Laboratory

State

Norm

Organisation

Year

Accreditation No

2. Is your centre/laboratory certified/licensed?

Yes/Underway

No

Centre/Laboratory

State

Norm

Organisation

Year

Certification No

PGD procedures

1. Does your laboratory confirm the nature of familial mutations and/or chromosomal anomalies?
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 - Always trust external report
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 - 2 blastomeres
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 - 2 polar bodies

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 - Day 3
 - Day 4
 - Day 5

Which embryos do you biopsy?

 - ≥ 5 cells
 - ≥ 6 cells
 - ≥ 7 cells
 - Blastocysts

Who performs the biopsy of the embryo for your PGD patients?

 - Embryologist/Biologist
 - Lab Technician
 - Other

On which day do you usually transfer fresh embryos following PGD?

 - Day 3
 - Day 4
 - Day 5
 - Day 6
3. Do you perform positive/negative controls?
 - Yes
 - No
4. Do you have dedicated rooms for?
 - Pre-PCR (DNA-free)
 - PCR
 - Post-PCR
5. How close is the PGD lab to the IVF clinic?
 - same building
 - same institution
 - same city
 - same country
 - different country
 - other

3. IVF ONLY

IVF clinic

IVF clinic's full name

Hospital/Service/Institute

Address

City

Postcode

Country

Secretariat phone number

Fax number

Affiliation

Clinical director

Last name

First name

Title

Dr

Prof

Other

Professional degree

MD

PhD

Other

Phone number

Personal e-mail

Quality manager

Does your IVF clinic have a quality manager?

- Yes
- No

If yes, please specify:

Last name

First name

Title

Dr

Prof

Other

Professional degree

MD

PhD

Other

Phone number

Personal e-mail



IVF laboratory

Laboratory's full name
Department/Service/Institute.....
Address
City
Postcode
Country
Secretariat phone number
Fax number
Affiliation

Laboratory director

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

Quality manager

Does your IVF laboratory have a quality manager?
 Yes
 No

If yes, please specify:

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

International flows and services

1. Do you send samples abroad?
 - Yes
 - No
2. Do you refer couples abroad?
 - Yes
 - No
3. Approximately how many couples do you refer each year?
- To which countries do you refer couples?
- What are the reasons to refer couples abroad?
 - Legal reasons
 - Test availability
 - Financial reasons
 - Other
4. Do you provide information to couples about the possibilities of treatment abroad?
 - Yes
 - No
- To approximately how many couples do you provide information on this each year?
- Which countries do you recommend?
- What are the reasons?
 - Legal reasons
 - Test availability
 - Financial reasons
 - Other
5. Why do you not offer PGD?
 - Unfamiliar with it
 - No patient has requested it (no market demand)
 - We would like to offer it but do not have the resources/staff/money/expertise to make it available
 - PGD is considered experimental
 - Not convinced it does not harm the embryo
 - Not convinced it yields accurate diagnosis
 - Ethical/moral concerns about its use
 - Concerned about liability
 - Legal reasons
 - Other
6. What is the likelihood you will offer PGD in the future?
 - Certain we will offer – process is underway
 - Very likely
 - Fairly likely
 - Unlikely
 - Certain we will not offer

4. IVF, PGD IS REFERRED

IVF clinic

IVF clinic's full name
Hospital/Service/Institute
Address
City
Postcode
Country
Secretariat phone number
Fax number
Affiliation

Clinical director

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

Quality manager

Does your IVF clinic have a quality manager?

- Yes
- No

If yes, please specify:

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

IVF laboratory

Laboratory's full name
Department/Service/Institute.....
Address
City
Postcode
Country
Secretariat phone number
Fax number
Affiliation

Laboratory director

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

Quality manager

Does your IVF laboratory have a quality manager?
 Yes
 No

If yes, please specify:

Last name
First name
Title
 Dr
 Prof
 Other
Professional degree
 MD
 PhD
 Other
Phone number
Personal e-mail

International flows and services

1. Do you send samples abroad?
 - Yes
 - No
2. Do you refer couples abroad?
 - Yes
 - No
3. Approximately how many couples do you refer each year?
- To which countries do you refer couples?
- What are the reasons to refer couples abroad?
 - Legal reasons
 - Test availability
 - Financial reasons
 - Other
4. Do you provide information to couples about the possibilities of treatment abroad?
 - Yes
 - No
- To approximately how many couples do you provide information on this each year?
- Which countries do you recommend?
- What are the reasons?
 - Legal reasons
 - Test availability
 - Financial reasons
 - Other
5. Why do you not offer PGD?
 - Unfamiliar with it
 - No patient has requested it (no market demand)
 - We would like to offer it but do not have the resources/staff/money/expertise to make it available
 - PGD is considered experimental
 - Not convinced it does not harm the embryo
 - Not convinced it yields accurate diagnosis
 - Ethical/moral concerns about its use
 - Concerned about liability
 - Legal reasons
 - Other
6. What is the likelihood you will offer PGD in the future?
 - Certain we will offer – process is underway
 - Very likely
 - Fairly likely
 - Unlikely
 - Certain we will not offer

Quality assurance

1. Your clinic keeps data on:
 - Success rate
 - Accuracy
2. Your clinic follows up:
 - During pregnancy
 - Neonatal
 - Short-term pediatric
 - Long-term pediatric
3. Analytical data are kept for:
 - < 9 months
 - 9–12 months
 - 1-2 years
 - > 2 years
4. Do you have written protocols/policies for:
 - Validating tests before application
 - Training staff
5. Do you get formal reports from the genetics laboratory?
 - Yes
 - No

European Commission

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Title: Preimplantation Genetic Diagnosis in Europe

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Abstract

Preimplantation genetic diagnosis (PGD) is now well-established and provided in many European countries. However, regulations, professional standards and accreditation requirements can differ notably. Furthermore, no comprehensive independent data exist about practice and provision in Europe, nor about the quality assurance practices and procedures designed to optimize the quality of the results. Consequently, IPTS launched a study to obtain a currently lacking knowledge of the provision and quality assurance of PGD services and cross-border activities in Europe. The present report sets out the findings of the study.

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