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Preimplantation Genetic Diagnosis in Europe

(Executive Summary)

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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-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

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

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.