Comparative European Approaches to Pre-implantation Genetic Diagnosis

GLOBAL PERSPECTIVES ON BIOPOLICY SYMPOSIUM SERIES 2007

Symposium Report

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Introduction

Pre-implantation Genetic Diagnosis (PGD) is a technique that has resulted from various developments in the fields of reproductive and genetic technologies. It involves the testing of embryos produced through *in vitro* fertilisation (IVF) for the presence of a range of genetic disorders. It may be considered as an early form of prenatal diagnosis. A single cell is removed from an embryo at the eight-cell stage of development (around three days old), leaving the rest of the embryo intact. The DNA from the removed cell may then be analysed to determine a range of genetic characteristics including the presence of sex chromosomes, extra genetic material (as in Down syndrome) or genetic variants such as the BCRA1 gene associated with familial forms of cancer. In practice a large number of embryos are usually created by IVF and each embryo is then tested by PGD. A decision can then be made to select one or more unaffected embryos for re-insertion into the mother's womb. This process is termed PGD with embryo selection.

On 1st May 2007, BioCentre: Centre for Bioethics & Public Policy hosted a symposium on 'Comparative European Approaches to PGD'. This was the second symposium in the centre's 'Global Perspectives on BioPolicy' symposium series, held at the Royal Society of Medicine, London.

Professor Nigel M. de. S. Cameron, Executive Chairman of BioCentre, opened the symposium with some introductory remarks before introducing Judge Christian Byk. In contrast to the first symposium of the series which focused on the more general issue of the UNESCO Declaration on Bioethics and Human Rights, Professor Cameron noted that the question of PGD is more highly complex and problematic. For example, the title of the first presentation clearly sets the issue in context through its focus on the ambiguity of law, medicine and social practice inherent in this application of artificial reproductive technology. By reviewing various European policies, Professor Cameron expressed his hope that the afternoon would provide opportunity to debate the UK policy situation more specifically.

Judge Christian Byk is involved in European biopolicy in various contexts, working with various international bodies including the Council of Europe, World Health Organisation and the European Union. He is Judge at the Court of Appeal, Paris, Deputy Chief Justice at the Paris North Superior Court as well as fulfilling the role of Secretary General of the International Association of Law, Ethics and Science. Judge Byk delivered the keynote address on 'Prenatal Genetic Diagnosis: An Ambiguous Legal Status for an Ambiguous Medical and Social Practice'. Responding to Judge Byk's speech with other European and UK perspectives were Prof. John Wyatt, a leading neonatologist at University College London and Dr. Chris O'Toole, Head of Research Regulation at the Human Fertilisation and Embryology Authority, London. Questions to the panel following the three presentations focused on the specifics of the ethics and regulation of PGD in the UK, and also drew attention to issues raised by the three presentations relative to one another. The symposium closed with a drinks reception.

Prenatal Genetic Diagnosis: An Ambiguous Legal Status for an Ambiguous Medical & Social Practice

- Judge Christian Byk, Court of Appeal, Paris and Secretary General, International Association of law, Ethics & Science

In an interview given to the daily newspaper "Le Monde" (4th Feb. 2007) and titled "France: the risk of eugenics", Prof. Didier Sicard, chairperson of the French National Bioethics Consultative Committee, considered that the practice of PGD is progressively leading to the idea that there is a right to give birth to a perfect child. He expressed the view that the insistence to test the future children for genetic abnormalities means that "the (children at risk) should be eradicated from humanity and that they are refused a right to life".

Replying to this opinion ("le Monde", 3rd march 2007), Prof. Pierre Leymarie and Dr Nathalie Leporrier, two specialists of PGD, rejected the view that this prenatal diagnosis is contributing to what Prof. Didier Sicard called " the terrible gap in the care of handicapped people". They insisted that the ethical principles on which the practice of medicine is based (the concepts of autonomy and the notions of non maleficence, beneficence and justice) are fully respected in the field of PGD which is furthermore governed by laws and the opinions of the National Bioethics Committee.

This controversy is particularly interesting because it stresses on a paradoxical point concerning PGD. Although this technique is strictly regulated in most European countries where it is regularly practised, the legal status of PGD may appear to some as unethical because it may be viewed as a facilitator for those who would like to select children for reason other than medical. The need to test human embryos before birth and the consequences that may occur to those detected with some abnormalities also revives the issue of the respect due to the human embryo.

I The respect due to the human embryo: an indirect thread to the legal status of PGD?

In medicine and clinical genetics, pre-implantation genetics diagnosis (PGD) is a considered alternative to prenatal diagnosis. Its main "advantage" is that it avoids selective pregnancy termination as the method ensures a pregnancy free of the disease under consideration. PGD thus is an adjunct to assisted reproductive technology, and requires in vitro fertilization to obtain oocytes or embryos for evaluation. This definition of PGD reveals how far PGD is related with the sensitive issue of how we should consider the human embryo. Indeed, PGD affects the human embryo in two ways.

- The technique used seriously affects the embryo because, as a form of genetic diagnosis performed prior to implantation, it demands that embryos be created and obtained by assisted reproductive technology, that biopsy procedures be performed on each, and that genetic analysis techniques be used to test the embryos concerned for specific diseases.

As such, PGD involves a manipulation of the embryos and may be considered as participating with all reproductive technologies in an approach that merely treats the human embryo as a means rather than an entity entitled to full protection.

- But, what is new with PGD is that, by its objectives of preventing the occurrence of some genetics characteristics in future children, it also has the power to previously exclude some genes from our common human genetic heritage. It is therefore viewed by some as a powerful tool that could lead to new forms of eugenics.

As a consequence, our ethical and legal opinion on PGD is certainly influenced by the already diverse national approaches to the consideration due to the human embryo.

We should wonder then if the ambiguous status that may result from this broad diversity may be clarified in some ways by the tentative attempts to harmonize European legislations.

A) The influence on the performance and regulation of PGD of existing national regulatory policies regarding the human embryo

Not all European countries have expressly faced the issue of what policy to adopt in the case of PGD. However, the approach- prohibitive to restricted admissibility and full admissibility- will often depend on the attitude adopted in each country regarding the status of the embryo.

1) The prohibitive approach

For historical and well known cultural reasons, prohibitive regulation is found mainly in Germany, Austria, and Italy

-In the first country, the Embryo Protection Act 1990 clearly prohibits using a human embryo for any reason other than ensuring its survival (art 2) while it defines the embryo as a fertilized human ovum capable of development as soon as fusion of the nuclei as taken place.

According to this article, every totipotent cell harvested from an embryo is also an embryo which should be protected. Although some medical associations are in favour of a modification of the law, both the Ministry of health and the parliamentary commission on "Law and Ethics in Modern Medicine" rejected this proposal. Consequently the discussion concerns only the possible acceptability of PGD using non totipotent cells.

In practice, PGD is not performed in Germany and, although the population in general has little knowledge about it, surveys show some potential public allowance of PGD in certain severe diseases that may result in an early death of the child concerned.

- In Austria, there is a widespread opinion that article 9 paragraph 1 of the Reproductive Medicine Act 1992, which states that viable cells may not be used for any other purpose than medically assisted reproduction, would conflict with the use of PGD because in this case the examination of the viable cells is not aimed at inducing a pregnancy as required by law. However, taking into account the question at what point in time an examination to induce the pregnancy is required, opinions greatly differ regarding the consequences of this conflict on the admissibility of PGD (full ban, extensive or exceptional admissibility).

In a 2004 report to the Federal Chancellery, the Austrian Bioethics Commission made a statement regarding limited regulatory approval of PGD but a strong minority of members shared the view that the present ban on PGD should not be waived.

- In Italy, the 2004 law on assisted reproduction technology put an end to the bewildering ART scene by imposing strict limits to reproductive technologies. In particular the law does not allow access to ART for couples who carry genetic diseases with a risk of transmission to the future child, makes it mandatory to implant all embryos at the same time, and bans PGD. Although a large majority of voters approved in a June 2005 referendum the repeal of the law, the results were invalidated due to a low percentage of voters (25,9% instead of the 50% required) following a strong intervention by the Vatican urging people to boycott the vote.

We may also mention Ireland and Malta (a very restrictive bill on reproductive technology is under discussion in Parliament since 2005) for their prohibitive attitude.

2) The restrictive regulatory approach

Most of the countries which have authorized PGD have adopted a strict regulatory approach.

- In Scandinavian countries, Sweden and Iceland have the most restrictive attitude (PGD is only permissible in case of hereditary and chromosomal disorders) while Norway and Denmark do also authorize tissue typing if sibling suffers from a serious and untreatable disease.

- As regard Spain and Portugal, PGD is permitted in Spain under the provisions of the Medically Assisted Reproduction Act 1988 which allows it only to detect hereditary diseases in order to treat them if possible or to prevent their transmission. Portugal is in the process of adopting a law that would require pre-implantation diagnosis tests to be performed only for the benefit of parents that could appreciate all their implications. In Greece the 2002 law on reproductive medicine makes it only accessible to avoid the transmission of a severe genetic disease to a child.

- In Belgium, the Embryo Research Act 2003 applies to pre-implantation genetic diagnosis and prohibits research or treatments with eugenic purposes including sex selection (with the exception of sex related diseases).

In France, since the Bioethics Act 2004, PGD, although it should be exceptionally used, covers not only hereditary disorders but also tissue typing for sibling. Switzerland approved in 2004 a Federal Law on Genetic Testing (into force since 1st April 2007) which applies to PGD but prohibits the determination of sex for other purposes than a diagnosis and bans genetic predispositions tests when they are used for reasons other than medical reasons.

3) The "moderate" liberal approach

- In the Netherlands, while the Health Council has approved in previous advisory reports of the acceptability of PGD, a 2006 report concentrated on certain applications including tissue typing. It reaffirms in particular that it has no weighty objections to letting the parents choose the sex of the future child if the sex is known as the result of a procedure carried out for medical reason and if this choice does not require further intervention.

- The UK approach is certainly the most liberal regarding PGD. After extending policy on tissue typing in 2004 –this being upheld by a decision of the Law Lords of April 8th 2005-, the Human Fertilisation Embryology Authority decided in 2006 to allow genetic tests for inherited cancer susceptibility with the precision that "the broad approach decided by the Authority...will not limit the discretion of an HFEA Licence Committee to consider the individual circumstances of each case".

In its role of advising the government on policy and regulation, the Human Genetic Commission (HGC) however suggested a prudential approach in its 2006 report "Making Babies: reproductive decisions and genetic technologies". The report recommended "that new screening programmes should not be introduced just because it has become possible" and that "studies of the development of children conceived by PGD should be set up". Although the Commission does not agree with arguments that the future development of PGD could be the beginning of a slippery slope leading to the creation of "designer babies", it considers that PGD, which is still at a very early stage, should not be practised as purely routine.

In conclusion of this overview, we may note that the national attitudes towards PGD vary considerably from country to country. While some countries have no rules yet, others prohibit such action and several impose strict conditions; only very few have a liberal approach based on a case - by -case assessment. If the influence of existing regulation on embryo protection is quite real, however we should remark that some countries prohibit PGD and permit abortion while others prohibit abortion but allow PGD.

It is difficult in such circumstances to expect great clarifications of European regulations in the field of PGD.

B) Do European regulations clarify the legal status of PGD?

Amongst the European institutions, it is certainly the Council of Europe - the Strasbourg based Human Rights institution - which has developed the most explicit and binding policy in this field.

1) The Council of Europe

The European Convention on Biomedicine and Human Rights, which came into force in 1999, clearly adopted a very positive approach to PGD and any kind of genetic testing.

- Article 12 asserts that "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 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".

In the future an additional protocol on genetics to the convention will give further details on the application of this provision.

- The only restriction posed by the Convention in its article 14 concerns the prohibition to use genetic testing to select the sex of the future child with the exception of sex-linked diseases.

Globally, the Convention may appear as adopting a liberal attitude. As the test is permitted for health or scientifically related purposes, it may be used not only to diagnose a disease but also to detect predispositions or susceptibility. No further condition of seriousness or treatability is required, the application of the scope of articles 12 and 14 being left to the appreciation of national legislation. But corrections and more limitations may result from the future protocol to the convention on genetic testing.

Therefore, at present the Convention does not really propose a policy to harmonise national regulations but merely made the choice to allow the full diversity of existing national regulations.

2) The European Union

The limited legislative competence of the European Union in the fields of medicine, research and human rights does not allow very powerful action by the EU institutions.

- However, article 3 of the European Charter of Fundamental Rights, which is not at the present time a binding instrument, prohibits "eugenic practices in particular those aiming at the selection of persons". Although opponents to PGD may use this statement to argue against PGD, the debate and comments concerning the elaboration of this article make it clear that it addresses only to State

coercitive measures and sex selection in the same way the Convention on biomedicine does.

- In a 20th February 1996 opinion on prenatal diagnosis (PND), the European Group of Ethics to the European Commission considered that "a framework, based on general ethical principles, is preferable (to a listing of illnesses or handicaps) to determine which PND and associated genetic counselling will be offered". As the HFEA in the U-K, the Group supported "a "case-by-case" approach (that) would have the advantage of minimizing reference explicitly to a model of normality, which would lead to stigmatization.

- A negative opinion on PGD was expressed in 2001 by the Temporary Committee on Human Genetics of the European Parliament but not adopted by the Assembly.

In conclusion, the European Union has certainly not adopted yet a clear opinion on the practice of PGD. It certainly explains why, following the adoption on 18th December 2006 of the 7th Framework Programme which allows stem cell research, the EU Science and Research Commissioner called on the EGE to provide an opinion on the implementing measures required during the ethical review.

Conversely to human reproductive cloning which resulted in the elaboration and adoption within 10 months from the birth of Dolly of a protocol to the European convention on biomedicine and human rights prohibiting this new technique, the extension of PGD is left to the complexity and uncertainty of national attitudes towards this ambiguous procedure.

II The evolving indications for PGD: a slippery slope to a new social eugenics?

In just a few years, applications of PGD-once strictly reserved for the prevention of severely debilitating or fatal conditions that strike in early childhood- have expanded in different directions which creates great ambiguities in the use of this technology.

A) From the prevention of severe diseases …

1) The evolving state of the art

PGD has been available since the 1990's for testing of aneuploidy in low prognosis infertility patients and for single gene and X-linked diseases in at-risk couples.

However several new developments for PGD have been reported since 2000.

- A first group mainly concerns improving the initial indications for PGD.

Testing for aneuploidy has been improved by introducing full karyotyping of single blastomeres or polar bodies.

Regarding couples with chromosomal translocations who have experienced repeated spontaneous abortions, methods of identifying unbalanced translocations have been developed.

Globally, the biopsy procedures and the genetic analysis techniques have also been improved making possible a much greater use of PGD, in particular for low prognosis patients asking for aneuploidy analysis.

Indeed those improvements do not really raise particular new ethical issues regarding the initial indications for which PGD is used with the exception it may slightly increase the number of couples that may benefit from the techniques.

- The second group of techniques is more ethically sensitive.

First comes as a logical extension of PGD for Mendelian disorders its use for susceptibility conditions to avoid the birth of children who are healthy at birth but face a higher risk of having cancer or other serious disease. For example, PGD has already been carried out to avoid the birth of a child with the Li-Fraumeni syndrome (P53 mutations) and may be sought for BCRA1 and 2 susceptibility for breast cancer.

PGD has also been used by a woman who carried a gene for early onset Alzheimer's disease and may be practiced for other late –onset conditions.

PGD for HLA matching for an existing child has been used to enable a family with a child with Fanconi anaemia to have another child who would serve as a source of haematopoietic stem cells.

Finally, the most controversial use of PGD is non-medical. It concerns non-medical gender selection to serve parental interest in having a healthy child in a particular gender.

The other controversial use- but still in perspective- is PGD for non-medical traits such as hearing, height, beauty or sexual orientation. Although only potential at the present time, this last indication may raise our awareness about the capacity of the existing public policy to face these new indications for PGD.

2) The moral and regulatory context in which PGD developed

In general, the existing legislations or recommendations that govern the practice of PGD in European countries, even when they have adopted a liberal approach, have always supported the idea that PGD should be used for medical purposes in an ethical and legal context that prohibits eugenic practices globally and sex selection in particular.

Although the regulatory approach is different in the two countries, it is remarkable to note that France and the UK have adopted a very careful analysis of the conditions in which the extension of PGD should be allowed.

- In its 22 November 2001 opinion on "ethical issues in the creation and selection of pre-implantation embryos to produce tissue donors", the Ethics Committee of the Human Fertilisation and Embryology Authority insisted on 3 main questions:
  - Is PGD with HLA typing compatible with the "welfare of the unborn child?
  - Is licensing PGD with HLA typing compatible with the public good?
  - Can morally significant criteria be found to demarcate "acceptable" and "unacceptable" reasons for the conception and selection of embryos?

-The principles highlighted in these questions – welfare of the unborn child, compatibility with the public good and the criteria to demarcate "acceptable" and "unacceptable" reasons – are not very far from the views expressed by the French National Bioethics Committee in its 4th July 2002 opinion on the extension of PGD.

Furthermore, the existence of a licensing system under the authority of the HFEA in the UK and the Biomedicine Agency in France is also an important bench mark in the regulatory policy of the two countries which may prevent any misuse of PGD

a) The prohibition of eugenic practices

In a November 2003 preliminary survey on national policies governing new technologies of human genetic modifications, the authors noted that already 67% of Western European countries adopted laws that prohibited reproductive human cloning (58% in Eastern European countries) while 54% (33% in Eastern countries) also prohibited research cloning . Since then the trend has moved on to further prohibitive legislations.

b) Accepting PGD as a tool to prevent severe diseases in offspring

Since PGD has been available in the 1990's, the main indications concerned couples with a high risk of transmitting a severe inherited condition to their offspring (either a monogenic disorder or a chromosomal aberration) and couples that undergo IVF treatment and whose embryos are screened for chromosome aneuploidies to increase the chances of an ongoing pregnancy.

If the number of diseases put on the list may be discussed regarding the application of the condition of severity, we may however observe that these two indications are generally accepted by the existing regulations applying to PGD.

The answer is different if we consider the development of the indications for PGD. The more they take into account the wishes of the parents and the less they may comply with the ethical principles that were mentioned both by the British and French ethics commissions in their above quoted opinions on an appropriate and effective framework to justify the social acceptance of PGD.

Is it however possible to conclude that the risk of a slippery slope to eugenics is real or that the limits some would like to put on new PGD indications are simply part of a precautionary syndrome, which is a way to cope with our fear of scientific and medical progress?

B) …To a new type of eugenics?

1) Are they good reasons for expanding the indications for PGD?

Before entering the ethical debate concerning the expanded uses of PGD, we should recall that its most common use, which is to screen embryos in assisted reproduction for chromosomal abnormalities, is still a controversial technique because it implies not to transfer the embryos detected positive. For those who believe that the human embryo demands an absolute protection, it certainly infringes the respect due to human life. Some ethical instances, such as the French National Bioethics Committee, although not going so far, considered that PGD procedure, compared to prenatal diagnosis, may encourage eugenic behaviour because it does not imply the physical and moral suffering of an abortion.

It is probably this kind of argument that may build a bridge between the common indications for PGD and the new ones. We slightly move from a controversy based on the status of the embryo to a controversy that focuses on selecting embryos for different indications.

a) Medical indications

- Some positive arguments for expanding PGD indications rely on the fact that they provide strong medical indications. Improving accuracy in selecting viable embryos for IVF transfer may generate a more reliable procedure than assessing the viability of in-vitro embryos by visual examination or morphology. Should we then prevent a greater use of PGD for low prognosis patients?

Personally, I don't think so, especially if the procedure is carried out professionally and the parents are carefully selected on a medical basis.

PGD may also be used more widely in selecting embryos not affected by Mendelian diseases and may become an important alternative for couples that are carriers of autosomal recessive, dominant or sex-linked diseases. Unless PGD were available, some at-risk couples might forego reproduction rather than risk an effected child or terminating an effected pregnancy.

- But the medical argument is not sufficient to justify the use of PGD. PGD should also respect a framework of ethical and legal principles that govern the biomedical procedures: the respect of human dignity, autonomy, justice… as we mentioned earlier.

In the following two examples, the respect of these principles is broadly questioned.

PGD for HLA matching for an existing child has a strong medical indication. It is used, for example, to allow a family with a child with Fanconi anaemia to have another child who would serve as a source of haematopoietic stem cells. The objective is legitimate because without a stem cell transplant, the first child is likely to die. Conversely to the use of PGD for Mendelian diseases, we may even say that PGD in this case is supporting life: it will save the life of the affected child by giving the birth to a new child. The ethical problem relies however in another point: the risk imposed on the new child as it becomes an instrument in an attempt to save the existing brother or sister. The psychological consequences may be great for the members of the family concerned and demand psychological support before and after the intervention. Consequently, the decision to use PGD for HLA matching should certainly be taken on a case by case basis.

The second example concerns PGD for late-onset conditions. Once again, the medical indication exists. A woman who carries a gene for early onset Alzheimer's disease may wish to have a child that would be free of that condition.

The ethical problem which makes this issue different from other risk of transmitting serious disease to a future child is that in this case PGD will lead to avoid the birth of a child who will be healthy for a number of years before experiencing Alzheimer's disease.

Therefore this ethical issue is very similar to the one raised for susceptibility conditions with one additional feature: the concern about the ability of the effected parents to raise the child.

Because late onset conditions are dominant, people would not be tested unless they knew that they carry (or are at risk of carrying) the disease gene themselves and faced a greatly shortened life span. Then the ethical issue is whether the physicians act properly when they enable a woman or a couple to have a child knowing that the child may soon lose one parent.

We may recall that in some countries- this is the case in France- assisted reproduction is only accessible to couples whose both members should be alive at the time of implantation of the embryo. But, we may also note that assisted reproduction is accessible –this is also the case in France- to couples affected by HIV.

b) Non-medical indications

The ethical twist is obviously clearer concerning the use of PGD for non-medical indications.

This does not mean that the request for PGD does not rely on intelligible and serious grounds. It means that these grounds are essentially based on cultural and individual choices.

- Requests for PGD for gender selection- an easy procedure which requires karyotyping only the sex chromosomes- is a good example of the role parental and societal choices.

Two groups of parents are concerned. One is from people who wish to select the sex of their **first born child** and we know that due to cultural mores, in almost all cases, the first born preference is for a male child. The second group is from people who already have a child of one gender and wish to have a child of the opposite gender. In many cases the request comes after a family had two or more children of the same gender.

Different arguments, ethical but also legal and social, are often opposed to those requests.

The interest of the coming child is either non-existent – he is merely the instrument of societal or parental wishes - or questionable – in societies where male children have better living conditions than female -

Moreover, if sex selection for first children were carried out on a large scale, it could lead to great disparities in the sex ratio of the population as it has occurred in China and India, although the use of PGD may only marginally likely to contribute to those disparities.

Should we consider that the use of PGD to select the sex of second or subsequent children is more acceptable because the parental desire is to introduce gender variety in the family? We may consider in this case that neither the intention nor the consequences of the practice are sexist.

- Other controversial uses may arise with the potential availability of PGD for non-medical traits such as hearing, sexual orientation, height, beauty, intelligence and other factors.

One potential would be tests for GJB2 mutations, which are the largest contributors to inherited deafness. We can then imagine, once the test will be available, that a couple with a history of deafness would like to have the test in order to increase their chances of having a hearing child or a deaf child if we suppose the deaf parents might prefer to educate their child in their own environment and culture. Similar issues would also arise if a genetic test for sexual orientation became available.

Although PGD acts negatively by screening out embryos, we may fear that expanding the use of PGD for the sole purpose of parental desires will reinforce the idea that parents may exercise the control over the genomes of offspring.

In order to secure the ban of such practices, we may hope that in the future States or the national health services will not consider PGD tests for" deafness" or other social handicap as part of a program of predictive medicine.

We may draw from this review of new PGD practices the following remarks. When the medical indication is dominant and the risk for the life of the coming child is high and immediate, the ethical acceptability for expanding the use of PGD will be great although it would always require a societal debate to make the future parents and the society aware of our individual and global responsibility.

When the medical indication disappears, the justification that PGD is in the interest of the child (preventing that he /she would be affected with a major disease) is also disappearing. Then cultural and individual choices become prevalent. Is it then ethical to allow PGD to contribute to those choices? Some would argue that the influence of PGD would be very marginal while others will

protest and consider that assisted reproductive technologies have not to be used to reinforce sexist attitudes or to satisfy the desire of the parents regarding the traits of their children. Finally the more pragmatic will observe that if PGD is not permitted for sex selection, pregnancy and abortion might occur instead.

A necessary way to solve or balance the complexity of the ethical debate is also to consider the following question:

2) Who decides? : is the respect of autonomy illusory?

- The conservative approach to PGD mainly focuses on the role of the State or the medical profession to control and limit the use of PGD. In this approach, PGD is regarded as a very specific technology that should be only available for a limited number of couples selected on medical and psychological criteria. The respect of autonomy then means that the couple or the woman concerned has the right to refuse the test but not the right to claim for it.

An approach fully based on individual autonomy would probably consider that PGD, as other techniques in the field of human reproduction should be available if required by the patient according to what he/ she thinks is his/her best interest. Ethical issues raised by the use of PGD would then have to be decided only by the couple or the woman concerned as far as they have obtained from the medical professionals the necessary information.

- If we are not satisfied by these two opposing approaches, we may remark that there is an ethical need for different levels of decisions.

The availability of PGD technology and the ethical and legal framework according to which it should be practiced is certainly an issue that concerns the whole society and that requires previous public discussion.

Although using PGD for medical indications should be left to the sole decision of the couple or woman concerned, the role of the doctors in selecting those couples is great.

While in some countries the availability of PGD technology opposed to limited alternatives to allow parents to educate a child handicapped by a serious genetic disease will obviously influence the parental decision, in other countries inequitable access to PGD may also create disparities.

Regarding non medical indications for PGD, the respect of the autonomy of parents may be seen as a slippery slope to soft eugenics while supporting traditional cultural attitudes may be viewed as a way to reinforce sexism. In all cases, a State or institutional intervention to encourage PGD for other reasons than medical may raise the risk of genetic discriminations.

Consequently, it seems that in the case of PGD for non-medical indications, State intervention should be used mainly to limit the role of autonomy and to protect future children of genetic discriminations. However, the autonomy of the parents should stay decisive in the final decision to use or not PGD in the situations for which PGD may be legally permitted and also in drawing the consequences of a positive test.

Conclusion:

As a screening method to sort out embryos, PGD will always be affected by the ambiguity of the practice consisting in selecting, even negatively, human embryos for procreation.

This ambiguity, which is attached to the moral value we give to the human embryo, also reflects our new ability to control genetically our offspring.

We then have to face questions such as: what is the most ethical choice between preventing the birth of a child that would die or be seriously handicapped if we don't use PGD, or letting the child be born with such a risk although the parents disagree?
Are we sure that we may in all circumstances solve this dilemma by explaining that the choice should be the choice of the parents offered the possibility of welcoming an handicapped child at home?

Are we sure that PGD does not portend future applications of predictive medicine which will aim at improving the quality of human beings by preventively selecting them in order to eliminate major diseases?

If we suppose that tomorrow human genetic selection will make us resistant to new viral pandemics such as HIV, SARS or avian flu, the temptation would be great to eliminate those risks. Whose voice could then legitimately oppose what the whole community would consider as a public health necessity?

This is certainly the reason why I do not believe in the prohibitive approach. If we would like to be in a capacity to face with the dilemmas I described, we better need to learn how to control and limit the use of PGD than to fully prohibit it now and have to authorize it broadly when we will face emotional situations.

But the strict regulatory approach, which I favour, means more than an administrative and sanitary supervision over the practice of PGD. It implies an ongoing state of ethical vigilance including interdisciplinary evaluation of the consequences of each extension of PGD and the consequent submission of the arguments to a public debate.

The standing ambiguity of PGD may then be transformed into an ethical virtue by generating an incentive to exercise our individual and collective responsibility.

PGD — Medical Developments and Social Perspectives

- Professor John Wyatt, Professor of Neonatal Paediatrics, University College London

Professor John Wyatt addressed the social and medical implications of PGD.

He began his presentation with a review of data from the European Society for Human Reproduction and Embryology (ESHRE) PGD registry. This data set has been generated by a consortium of healthcare professionals on a voluntary basis since 1999. 66 centres, mainly in Europe, contribute data to the registry. Referring to the most recently published data from 2003, Prof Wyatt explained that from 2984 cycles of oocyte retrieval, 20917 were embryos created, of which 14747 were subject to successful diagnostic testing. 3695 of these embryos were transferred and 714 frozen. 2039 episodes of embryos transfer resulted leading to 501 live pregnancies, which represents 18% success per cycle of oocyte retrieval. There were 128 cases of fetal loss (13 by selective reduction and 2 by TOP). In total 453 live babies were recorded, of which 295 were singletons, 152 twins and 6 triplets, and of which 164 were preterm. 4% of live babies had major malformations. Prof Wyatt pointed out that one of the reasons for this high incidence of malformation was the additional risk associated with multiple pregnancies. Reasons given for PGD referral in the 2002 data set were: age related aneuploidy (61%), genetic risk and subfertility (30%), genetic risk and objection to TOP (19.3%), genetic risk and previous TOP (8.4%); other reasons were cited in 24 % of cases. (Totals exceed 100% because multiple reasons could be given.) Regarding sex selection, Prof Wyatt explained that only 2 of the collaborating centres offered this service on social grounds. Approximately 3% of PGD cycles recorded involved sex selection; 644 embryos were created, 445 successfully tested and 92 transferred in 47 episodes of embryo transfer. 15 live pregnancies resulted. 76% of social sex selection cycles favored boys over girls.

Moving on to discuss PGD for inherited breast cancer and early onset Alzheimer's disease, Prof Wyatt reviewed the cumulative risk posed by variants of both conditions. He noted that for both BRCA 1 and 2 the cumulative risk to women from families with cancer-predisposing mutations reached 85% and 86% respectively by age 70; for early onset Alzheimer's disease, cumulative risk associated with PSEN1 or APP mutations approached 100% by age 70.

Prof Wyatt displayed to his audience advertising for sex selection and other reproductive health services in the USA; speed, ease, success, good prices and special bargains characterized the tone of adverts. Sex selection in the US was on offer for a fee of $18480; in the UK by contrast PGD costs £4000-6000 per cycle, and 50% of cycles are NHS funded. Drawing on BBC news coverage of the controversy around PGD, Prof Wyatt described the frustration of some PGD users that PGD is sometimes framed in terms of the pursuit of 'perfect children', but he noted with concern a tendency to justify PGD in terms of eliminating genes from future generations. A contributor to Radio 4's Today program, for example, spoke of the option to "eradicate this genetic transmission…from generation to generation," and a writer in the Times newspaper spoke positively of the possibility to "annihilate the gene from the family tree." Later in his presentation, Prof Wyatt questioned whether this framing of the issue might be used to call for elimination of unaffected genetic carriers of disease.

Prof Wyatt next reviewed some technical difficulties, concerning outcomes, and social issues raised by PGD in Europe. Technical difficulties associated with PGD included misdiagnosis due to mosaicism, the high failure of diagnostic procedure leads to significant rate of embryo wastage, diagnostic errors lead to pressure for prenatal screening, aneuploidy screening may not lead to higher live baby rate, and possible increased risk to embryo from the biopsy procedure. Concerning outcomes after PGD included an increased rate of prematurity and multiple births, an increased burden on neonatal intensive care resources, increased rate of perinatal brain injury leading to cerebral palsy and learning difficulties, and an increased risk by 25% of major congenital malformation. Social issues raised by the large variations in PGD availability and regulation across Europe included the existence and likely increase in reproductive tourism, and the preferential

selection of males over females in the small number of centres which offer sex selection for social reasons.

Prof Wyatt expressed a concern that parents are not always aware of the full range of issues and possible adverse consequences for themselves and for their babies. The "take home baby rate" is relatively low and levels of psychological stress are frequently high. Moreover, parents may feel implicit coercion to agree on prenatal screening and TOP if an abnormality is detected. The difference between framing PGD in terms of "reproductive autonomy" or terms of "social responsibility", can lead to a need to *justify* failure to use it. In terms of wider social consequences Prof Wyatt asked whether society will continue to provide resources for disabled children whose existence might have been avoided?

Returning to a comparative European perspective, Prof Wyatt noted that in the UK, PGD has frequently been framed as a simple balancing of "benefits" and "risks". Fundamental issues of human identity, dignity parent-child relationships and social responsibilities are invisible. In Germany, by contrast, debates have centred on "human dignity", "eugenics" and "instrumentalisation" of human beings.

To conclude, and drawing on his discussion of implicit social influences around PGD, Prof Wyatt raised the question of whether the rhetoric of choice is appropriate to parenthood. He quoted Mary Hubbard: "To the extent that prenatal interventions implement social prejudices against people with disabilities, they do not expand our reproductive choices. They constrict them." And he recalled the words of CS Lewis: "Man's power over nature turns out to be power exerted by some men over other men." Reflecting on the traditional distinction between creating and begetting children, Prof Wyatt noted that in his experience as a neonatal physician, children are regarded as gifts to be loved and accepted unconditionally, whereas PGD tends towards portraying children as created and conditionally chosen artifacts. In closing Prof Wyatt used the words of ethicist Gilbert Meilaender: "We are very reluctant to let the mystery of personhood - equal in dignity to our own - unfold in the lives of our children…. We need the realization that the children who come after us are not simply a product for us to mould."

Pre-implantation Genetic Testing: The Role of the HFEA

- Dr. Chris O'Toole, Head of Research Regulation, Human Fertilisation & Embryology Authority

Dr Chris O'Toole used her presentation to outline the purpose and activities of the HFEA. She reminded her audience that the HFEA was established as a result of the 1990 HFE act as a non-departmental public body, with a lay majority, responsible for taking licence and policy decisions. Its statutory responsibilities are to licence and monitor clinics carrying out treatment, to licence and monitor clinics carrying out human embryo research, to regulate storage of gametes and embryos, to maintain a Register of Information, to produce a Code of Practice, and to provide information**.**

The HFEA regulates PGD, Dr O'Toole explained, as part of its responsibilities over the bringing about the creation of an embryo *in vitro,* and keeping or using these embryos. Moreover, the HFEA may license "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."

Dr O'Toole next reviewed the PGD procedure. It begins with a genetic consultation, assessment and counselling. The IVF cycles consists of hormone stimulation, gamete collection, fertilisation (by IVF or ICSI), embryo culture, and blastomere biopsy 2-3 days after fertilisation. Genetic testing by FISH or PCR precedes the transfer of suitable embryos to the woman. After this the hope is that a pregnancy and birth will result. Applications of PGD include testing for single gene disorders such as Cystic Fibrosis and Spinal Muscular Atrophy, testing for sex-linked diseases such as Haemophilia and Duchenne Muscular Dystrophy, and testing for chromosomal rearrangements.

In the UK, Dr O'Toole explained, clinics carry out approximately 200 cycles a year (or 500 – 600 cycles since 2000). In the UK since 2000, less than 100 babies have been born following PGD. 10 clinics are licensed to carry out PGD, and PGD treatment accounts for 0.6% of all assisted reproduction treatment.

PGD licenses can be issued either by a license committee, or the HFEA executive. Licence committees issue licenses for new PGD centres, for new conditions, and for HLA tissue matching; the executive can add new approved conditions to centres already licensed for PGD. A licence committee is made up of 5 HFEA members and it makes decisions on applications for licences, variations to licences and can apply conditions to licences. All PGD applications require review of application documentation, review of current law and HFEA policy, an inspection report (if applicable), assessment of suitability of staff and facilities, and finally peer review. According to the HFEA's PGD code of practise, PGD should be licensed only where 'there is a significant risk of a serious genetic condition being present in the embryo,' where 'the perception of the seriousness of the condition by those seeking treatment is an important factor,' and 'the use of PGD should be consistent with current practice in the use of prenatal diagnosis.'

Dr O'Toole next proceeded to explain some HFEA policy decisions regarding PGD for HLA typing. In the first case, a couple, P, have a child with a diagnosed, heritable genetic disease; they want to have a second child. Under natural conception conditions the 2nd child faces significant risk of serious disease, no risk of iatrogenic harm, and there is a small chance that it should be a histocompatible donor. If PGD is conducted, there would be negligible risk of serious disease, small (theoretical) risk of iatrogenic harm, and a likelihood that the new child be a histocompatible donor. Because the significant risk of serious disease under natural conception conditions exceeds the small iatrogenic risk to the new child, in this case the HFEA would rule in favour of PGD. In contrast, Dr O'Toole discussed a second case where a couple, Q, have a child with a sporadic, non-heritable disease, and want to have a second child. In this case, under natural conception there is unknown risk of serious disease, no risk of iatrogenic harm, and a small chance that the new child be a histocompatible donor. Following PGD, there would be no reduction in risk of serious disease, small (theoretical) risk of

iatrogenic harm, and substantial likelihood of histocompatible donor. However, in this case the small risk to the new child of iatrogenic harm by PGD would outweigh the lack of such risk under conditions of natural conception. Therefore the HFEA's policy was to choose natural conception over PGD.

Reviewing this policy decision, the HFEA conducted research into the health risk associated with blastomere biopsy, the psychological implications for the welfare of any child born as a result of the treatment, the current state of the art in bone marrow and cord blood transplantation, the current legal provisions/relevant case law, the ethical issues and related scenarios, and into public opinion formation on this issue. Following this review the HFEA modified its position regarding couple Q who have a child with a sporadic, non-heritable disease, and want to have a second child. As before, with natural conception there is unknown risk of serious disease, no risk of iatrogenic harm and small chance of the second child being a histocompatible donor; following PGD, the HFEA believes that there would be no reduction in risk of serious disease, no significant risk of iatrogenic harm, and substantial likelihood of histocompatible donor. Following the reassessment of iatrogenic risk from 'small' to 'no significant risk', the HFEA would now rule in favour of PGD.

Dr O'Toole next discussed the HFEA's recent public consultation "Choices and Boundaries". Its aim was to gather the views of the public, medical profession and interested parties on the use of PGD for late consent inherited conditions like inherited breast cancer. The consultation sought to establish what is the lowest penetrance of a gene that may be considered to confer a 'significant risk' upon an embryo. The consultation further questioned whether age of onset of a condition, and availability of treatment impacted public assessment of the seriousness of a condition. What, the consultation sought to establish, should be the limits of the application of PGD, and how much emphasis should be placed on the individuals seeking treatment relative to the views of society? The consultation did not generate consensus; indeed the only areas of substantial agreement were that provision of PGD should not be determined by current practice in prenatal diagnosis, and that the penetrance of a condition should not be the only factor that should be taken into account in PGD licensing decisions. As an outcome following the consultation, the HFEA agreed that we should consider the use of PGD embryo-testing for conditions such as inherited breast, ovarian and bowel cancers, and that in each and every case we need to look at all the factors around a particular condition, age of onset, treatability, the average penetrance, and, importantly, the medical history of the individual family concerned before coming to a decision.

In closing, Dr O'Toole referred to the forthcoming draft Human Tissue and Embryos bill. In this bill, Dr O'Toole said, the Government will propose that the law is changed to include explicit criteria for the testing of embryos. In board terms, legitimate purposes will be to allow screening of genetic or chromosomal abnormalities which may lead to serious medical conditions or disabilities, or miscarriage, and to enable the identification of a tissue match for a sibling suffering from a life-threatening illness, where umbilical cord blood is to be used in the treatment of a sibling. Deliberately screening-in a disease or disorder will be prohibited.

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