

Human Fertilisation and Embryology Authority

SCAG and ELC Joint paper

Committee:	Scientific and Clinical Advances Group and Ethics and Law - Joint meeting
Meeting Date:	16 th June 2005
Agenda Item:	1
Paper Number:	SCAG/ELC(06/05)01
Paper Title:	Information gathering for emerging issues in PGD report
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For Information or Decision?	Information and Decision
Resource Implications:	Dependent on the scope of the review
Organisational Risk:	Medium
Recommendation to the Committee:	Members are asked to: <ul style="list-style-type: none"> • Discuss the issues raised in this paper; • Decide whether a policy review is needed; • If a decision is taken that a policy review <i>is</i> needed, have some preliminary discussion about the scope of the review.

1. Background

- 1.1 A paper was taken to the Authority in November to approve the plan to look at PGD and susceptibility genes. Following this paper a more detailed project initiation document was presented to SCAG and ELC for comment. At the SCAG and ELC meeting, it was decided that the project would be divided into two discrete stages; an initial information gathering stage and a review stage, the scope of which would be informed by the information gathering stage. The scope of the initial stage was; testing for genetic susceptibility genes, testing to avoid carrier status for recessive conditions and new methods for genetic testing.
- 1.2 This work was initiated because it is very likely that an application to carry out PGD for a susceptibility gene will be received in the near future. It is

therefore timely that work is carried out to consider the issues surrounding licensing conditions that are not fully penetrant.

- 1.3 The HFEA has already licensed some susceptibility gene conditions such as Familial Adenomatous Polyposis and Neurofibromatosis type 2. This work is not intended to fetter the discretion of a Licence Committee, instead it aims to help members think about some of the issues associated with late-onset, not fully penetrant conditions.
- 1.4 This paper aims to inform members of what genetic testing is already available for susceptibility conditions, the current status of prenatal testing for these conditions and the potential demand for preimplantation genetic diagnosis.
- 1.5 From the information gathering work we were able to divide the issues into two areas; those that will have an immediate demand and those that might have demand some time in the future. Issues with immediate demand are: PGD for susceptibility gene conditions and PGD for carrier status. The HFEA has been approached about both of these issues already. These will be discussed in sections 5 and 6 respectively. New techniques in genetic testing which are likely to be less immediate, will be discussed in section 7.
- 1.6 The next stage of the project is to decide if a policy review is needed and, if so, to discuss the scope of the review and what form it should take. SCAG and ELC's opinion will be included in a paper to the July Authority meeting.

2. Introduction

- 2.1 Susceptibility conditions are different from other inherited conditions because the faulty gene is not fully penetrant. A person who inherits a gene for a susceptibility condition such as breast cancer has an increased risk of developing the condition. This contrasts with conditions where the gene is fully penetrant, such as Huntington's where development of the condition is guaranteed.
- 2.2 Different susceptibility genes can confer different risks. For example, some conditions such as Neurofibromatosis type 1 (NF1) are very high risk. NF1 is almost 100% penetrant compared to breast cancer which can be up to 80% penetrant or as low as 30% penetrant.
- 2.3 In order to inform our work, we approached PGD centres, clinical geneticists and selected patient groups. We had meetings with representatives from the Genetic Interest Group (GIG), CancerBACUP and Breakthrough Breast Cancer. From the centres we contacted, we

spoke to three PGD clinicians. We also had meetings with three clinical geneticists including a cancer specialist and a group who are doing research on the demand for PND and PGD for susceptibility gene conditions.

3. Legal aspects of PGD licensing

A summary of the legal aspects of PGD licensing and international comparisons is available in Annex A.

4. Susceptibility gene and late-onset conditions

4.1 Some conditions that are not fully penetrant and may be late-onset have a faulty gene linked to the disease that could potentially be tested for using PGD. Most of the conditions that were identified as part of the information gathering work are cancers where a specific susceptibility gene has been linked to the condition (section 4.2). There were also several non-cancer conditions identified that could be tested for using PGD and/or sex selection (section 4.3). For the purposes of horizon scanning we also attempted to identify conditions where there is a familial inheritance pattern, and therefore there is likely to be a gene linked to the condition where the gene has not yet been identified (section 4.4). It should be noted that the penetrance of these conditions may not be as high as for the already identified susceptibility gene conditions.

4.2 **Cancer conditions** with identified susceptibility genes:

- Breast cancer - BRCA1, BRCA2 and TP53 genes;
- Ovarian Cancer - BRCA1 and BRCA2 genes;
- Hereditary non polyposis colon cancer (HNPCC) - MSH2/3/6, PMS1/2 and MLH1 genes;
- Retinoblastoma- Rb locus deletion;
- Neurofibromatosis 1 (NF1) - neurofibromin gene;
- Von Hippel Lindau (VHL) - VHL1 gene;
- Familial posterior fossa brain tumour - SMARCB1 gene;
- Ataxia Telangiectasia - ATM gene;
- Multiple endocrine neoplasia type1 (MEN1) - Menin gene;
- Multiple endocrine neoplasia type2 (MEN2) - RET gene.

4.3 **Non-cancer conditions** that were identified with the potential to be tested for using PGD are:

- Early-onset Alzheimer's - APP, PS1 and PS2 genes;
- Attention deficit hyperactivity disorder (ADHD) - sex selection;
- Y-chromosome deletion - sex selection.

4.4 Inherited conditions where there is **no gene linked to the condition**:

- Some types of brain tumours;
- Further types of breast cancers (BRCA);
- Prostate cancer;
- Hypertension;

Further details, including age of onset, treatment options and availability of PND and PGD, are available in Annex B.

Susceptibility gene conditions

- 4.5 Susceptibility gene conditions are complicated by the variability of the conditions both in terms of age of onset and penetrance. In some cases the susceptibility gene condition affects children and young adults (Neurofibromatosis 1 and retinoblastoma); with others *usually* not having an affect until adulthood, forties and fifties (breast cancer and Hereditary Non Polyposis Colon Cancer). There is also variability of the age of onset of symptoms with people affected by the same condition; for any given condition a mean age of onset is used.
- 4.6 The penetrance of a given condition can also vary from person to person meaning that it is difficult to predict absolute risk. There are several factors that can affect the penetrance of a specific condition; the specific gene that results in the condition (there is often more than one susceptibility gene for any condition), the mutation within the gene and also the effect of other genes on the susceptibility gene.
- 4.7 Some conditions will have a variable penetrance depending on age. For example, a faulty gene could confer a risk of 50% of developing the disease in early adulthood but by the time a patient is in their 50's the risk is significantly higher, perhaps close to 100%. This is the case for Multiple Endocrine Neoplasia type 1 which is 43% penetrant by age 20 and 94% penetrant by age 50.
- 4.8 From the work we have done, we have identified a group of conditions with varying susceptibility. Most of the conditions identified were highly penetrant (more than 90%) but mutations in either of the BRCA genes result in a much more varied penetrance but both can be up to 85% penetrant. We have not identified conditions where there are genes that always confer a very low susceptibility to a condition *i.e.* 10%. In all of the conditions that have been identified here, having a copy of the affected gene will significantly increase a patients chances of suffering from the condition.

Lower penetrance susceptibility conditions

- 4.9 In addition to the susceptibility genes discussed above where susceptibility is generally high (e.g. 90%), there are likely to be susceptibility genes

identified that increase the chance of developing a condition by a very small amount (e.g. 1 or 2%). There is no demand for PGD and PND for these very low-penetrance susceptibility genes and these should be distinguished from high-penetrance susceptibility genes.

- 4.10 The actual number of conditions where there is a susceptibility gene which significantly increases the chance of suffering from a given condition is relatively low. Although there is potential for more to be identified, these are likely to fall into the lower penetrance category of conditions where risk is only marginally increased.

Emerging issues in PGD with an immediate demand

5. PGD and susceptibility gene testing

- 5.1 In order to try to predict the demand for PGD for late-onset, incomplete-penetrance disorders, we examined the demand for prenatal diagnosis (PND) for the same conditions and this is discussed below. The demand and current status for carrier status testing is discussed in section 6.

Demand for PND and susceptibility gene testing

- 5.2 Clinical geneticists report that to date there has been very little demand for PND for susceptibility conditions. Of the people that we spoke to there had been no requests for PND for BRCA genes and only one request for FAP, but the patient then later changed her mind.
- 5.3 Conditions for which PND is available varies between different centres; there is not a central list of conditions for which tests can/cannot be offered. PND is available for late onset disorders although requests are rare in comparison with requests for other genetic conditions and are generally from families with very severe and untreatable disorders. It is recommended that PND for late onset disorders is only undertaken with full genetic counselling.¹
- 5.4 There are several factors that impact on patient demand for PND for susceptibility genes. One significant factor is that there are relatively few patients who know they are carriers and therefore are in a position to be tested. For example, in breast cancer there has to be a very strong family history and the patient has to be considered to be high risk before genetic testing is offered. If genetic testing is offered, and the patient decided to go for the test, there are very long waiting times for results and in 20% of cases the test is inconclusive because the entire BRCA gene is not always screened.

¹ Advisory Committee on Genetic Testing. Prenatal Genetic Testing Report for Consultation. February 2000

- 5.5 Patient information could also affect demand. Most patients are very dependent on the information provided by health care workers and if they are not informed of PND as an option then they are unlikely to ask for it independently. The information given to patients can vary from centre to centre and is often dependent on how colleagues within the unit feel about offering PND for conditions that are late-onset or not fully penetrant. Similarly, in some cases, there are concerns that if a fetus is tested and the patient opts for a termination, the obstetrician would not be willing to carry out the operation because of their own ethical concerns.

Potential demand for PGD for susceptibility gene conditions

- 5.6 We contacted the centres that offer PGD in order to inform our understanding of the potential demand of PGD for susceptibility genes. Since starting the work, one centre has applied for a licence to perform PGD for retinoblastoma. One centre has approached the HFEA about the possibility of a licence for BRCA testing and developed a questionnaire to send out to known carriers of the BRCA genes to find out about demand. This centre would like to become a specialist centre for PGD for cancer susceptibility disorders. Other conditions that they are considering are: NF1, VHL, HNPCC and MEN1. There was some interest from other clinics to do BRCA1/2 testing.
- 5.7 The potential demand for PGD is dependent on some of the same factors that apply to PND such as availability of genetic testing. The susceptibility gene that is affected needs to be known before PGD can be worked up for single cell analysis. The patient would also probably be referred to a PGD centre and would also be dependent on information provided by health care workers.
- 5.8 Differences in potential demand for PGD compared to PND may arise if medical staff feel that PGD is less ethically problematic for late-onset disorders than PND and therefore are more likely to suggest it as an option to patients. Some patients may also feel that they would prefer not to have a termination of an affected child but would be happy to select an unaffected child from a group of embryos. However, some patients may be deterred by the invasiveness, expense and low success rates of PGD.

Availability of PND and PGD for susceptibility gene conditions

- 5.9 Last year, genetic specialists and members of the RCOG scientific advisory committee were contacted to get their views on the availability of PGD for susceptibility gene conditions. Again the comments received were variable.
- 5.10 Those that were against offering PGD for these conditions commented on the possible availability of better management and treatment for these conditions in the future. One genetics specialist said that PGD would be

more appropriate than PND for these conditions but the uncertainty over penetrance should be an issue.

- 5.11 Some people thought that it should be a decision made by the family because they are in the best position to make the choice. A genetic counsellor said that no one on their team objected to PND or PGD for cancer susceptibility genes, but in the case of PND there would have to be consideration about whether the obstetricians would agree with them and be prepared to carry out the procedure.

Patient attitudes to testing for susceptibility conditions

- 5.12 Patient attitudes to testing were explored by some preliminary discussions with organisations representing patients (Genetic Interest Group, CancerBACUP and Breakthrough Breast Cancer). In general, there is not much patient awareness or information about PND or the potential use of PGD for susceptibility gene testing (this is likely to be due to the uncertain availability). According to the Genetic Interest Group there had been some consideration of PND/PGD for Multiple Endocrine Neoplasia and breast cancer.
- 5.13 A group of breast cancer patients and carers had previously been asked about the use of PGD to avoid passing on an affected BRCA gene to a child by Breakthrough Breast Cancer for the Human Genetics Commission consultation on reproductive decision making. The responses to this question were very varied.
- 5.14 People who have a faulty BRCA gene do not consider they have a disability and because of this some felt that it was not an appropriate use of technology. Other reasons for not supporting the use of PGD for BRCA were because it would have meant that members of their family who had led fulfilled lives would not have been born. It was also noted that, although extreme, there are preventative treatments for breast cancer and a hope that in the future there would be better management of the condition so that it was not as life-threatening.
- 5.15 Other people felt that they would have liked the choice to have been offered to them because they are worried about passing on the affected gene to their own daughters. Women are worried about the reproductive dilemma that they have passed on to their daughters and the burden of potentially having to go through 'disfiguring surgery'.

6. Carrier Status and PGD

- 6.1 There have been in principle requests from some clinics about the possibility of carrying out PGD for carrier status in recessive conditions where the embryo is unaffected by the condition but still has one faulty copy of the gene. This was requested for an X-linked condition in the context of removing the reproductive burden from the healthy child to be born so that they would not have to be concerned about the possibility of having affected children.
- 6.2 We asked the centres about replacing carrier embryos versus unaffected to see if there had been any demand for this already and what current practice was. All the centres that we spoke to said that they put back the best embryo regardless of whether it was unaffected or carrier. This is often because there are limited numbers of good quality embryos and so it would be unlikely that there would be an option to only replace unaffected embryos. There has not been much demand from patients for only the unaffected embryo to be replaced, except for the in principle requests.
- 6.3 One clinical geneticist raised a point that within certain populations, being a carrier could have more impact than in the general population. For example, the frequency of the Tay-Sachs mutation within the Ashkenazi Jewish population is very high. An estimated 1 in 31 people within this population are carriers. Therefore a carrier that wanted children with another person within the population would be at much higher risk of having a child that suffered from the condition. Although the chances of having an affected child is significantly higher, the principle remains that the patient requesting PGD in this situation is removing reproductive decision making burden from the child to be born.

7. Emerging issues in PGD that may impact on future demand

- 7.1 While the success rates for PGD remain low and the invasiveness of the technique is high, it is unlikely that people who do not require IVF for fertility problems or who are not at high risk of passing on an inherited genetic condition would choose to have PGD for very low penetrance susceptibility conditions. However, there are some techniques that were identified as part of the horizon scanning work that might make this possible. More details of these techniques are available in Annex C (this paper was included in the April SCAG papers but the meeting was cancelled so the paper was not discussed).
- 7.2 Three techniques are discussed in the paper; whole genome amplification, comparative genome hybridisation and microarray analysis. The significant development that these techniques allow is that it could be possible to test embryos for many different genes simultaneously.

- 7.3 This would be largely irrelevant for the rare disorders such as cystic fibrosis and muscular dystrophy because any one individual is unlikely to be affected by more than one of these conditions. But it might be possible to use a microarray to test embryos for the presence of many susceptibility genes that increase the chances of suffering from a condition by a very small amount. Potentially it would allow parents to choose between an embryo that is at a slightly higher risk of a type of cancer and one that has a small chance of suffering from a neurodegenerative disorder later in life.
- 7.4 As mentioned above there is likely to be little demand for this low-susceptibility testing while IVF remains invasive and with relatively low success rates. When more very low penetrance genes are found to be linked to certain conditions, it would be likely that an embryo would contain many of these genes and so selecting the perfect embryo would be impossible. This is likely to still be the case even if techniques such as *in vitro* maturation are available, allowing the production and testing of many embryos simultaneously.

8. Conclusions

- We have already received an application for one susceptibility gene condition (Retinoblastoma) and we are likely to receive an application for others, probably BRCA, in the very near future;
- The HFEA has already licensed FAP and Neurofibromatosis Type 2;
- From the horizon scanning work we have carried out, we identified several susceptibility conditions that people may request to do PGD for. Most of these conditions are relatively high-penetrance cancer conditions;
- Most conditions that we identified resulted in a penetrance of greater than 90% e.g. Neurofibromatosis has a penetrance greater than 95% and mean age of onset is 20;
- Some of these conditions are only this highly penetrant by late adulthood and it is likely that there is a lower penetrance at a younger age e.g. Multiple Endocrine Neoplasia type 1 is 43% penetrant by age 20 and 94% penetrant by age 50.
- There are conditions with lower penetrance are e.g. breast cancer (35-85%) and HNPCC (70-80%)
- There has been very little demand for PND for susceptibility conditions although for most of the conditions identified, PND is available either in the UK or abroad (see Annex B);
- There has not been huge demand (in terms of quantity) to date for PGD from patients for susceptibility conditions. There is an interest from centres to carry out testing for BRCA and for other conditions such as NF1, VHL, HNPCC and MEN1;
- If susceptibility conditions are licensed, there may be more demand as patients are referred from clinical geneticists;

- There is not likely to be much demand for PGD for carrier status although we have had an 'in principle' request for a specific case. The significant factor of PGD for carrier status is that it is removing the reproductive decision making dilemma from the healthy child to be born;
- There is unlikely to be demand for PGD for many different genes simultaneously using microarrays and whole genome amplification. However, the techniques are well-developed and are likely to be introduced into clinics in the near future.

9. Recommendations

Members are asked to:

- Discuss the issues raised in this paper;
- Decide whether a policy review is needed;
- If a decision is taken that a policy review *is* needed, provide advice on the scope of the review.