

Scientific and Clinical Advances Advisory Committee Paper

Paper title	Preimplantation genetic screening
Paper number	SCAAC(02/15)07
Meeting date	04 February 2015
Agenda item	7
Author	Sarah Testori (Scientific and Clinical Policy Manager)
Information/decision	Decision
Resource implications	None
Implementation	Update to the patient information on the HFEA website, and to guidance on PGS in the Code of Practice. Any changes to the Code of Practice will need to be approved by the Authority and would come into effect in October 2015
Communication	Update to the HFEA website – Code of Practice changes will be communicated in Clinic Focus by July 2015
Organisational risk	Low
Committee recommendation	Members are asked to: <ul style="list-style-type: none"> • Review the recent literature in this area and consider the safety and efficacy issues that may arise from such techniques. • Review the HFEA website text (Annex A) and provide comments to the Executive, relating to possible updates and changes including any studies they feel should be added to the website text as highlighted articles.
Evaluation	Updates and further studies will be evaluated in annual horizon scanning
Annexes	Annex A: Current website information Annex B: Current Code of Practice guidance on PGS Annex C: Sequencing-by-synthesis NGS

1. Introduction

- 1.1. Preimplantation genetic screening (PGS) describes the process of checking the chromosomal composition of embryos. The rationale for this is based on the fact that human reproduction is highly inefficient, producing high percentages of aneuploid embryos even at young ages (Kuliev et al, 2005; Fragouli et al, 2011). These aneuploid embryos are frequently non-viable, leading to implantation failure, miscarriages, or congenital abnormalities (Hassold and Hunt, 2001). PGS is meant to identify aneuploid embryos prior to embryo transfer, allowing the choice of embryos free from aneuploidies and thereby increasing the likelihood of pregnancy and reducing miscarriage rates.
- 1.2. Based on this rationale, PGS was widely adopted in IVF treatment. However, several years after its initial introduction, a number of randomised controlled trials (RCTs) showed that far from leading to improved IVF outcomes, PGS significantly decreased chance of ongoing pregnancy in comparison with IVF without PGS (Mastenbroek et al, 2011). (Although a recent prospective RCT demonstrated an increase in the live birth rate in older women after PGS using FISH (Rubio et al, 2013)).
- 1.3. The common methodology employed for PGS in the first 15 years of its existence was blastomere aspiration of embryos on the third day after fertilization, followed by fluorescence in situ hybridization (FISH) analysis of the aspirated blastomere(s) (Mastenbroek and Repping, 2014). To a greater or lesser extent, the failure of PGS to improve IVF outcomes was attributed to, the technique of FISH itself, which is subject to considerable interpretation errors and only enables analysis of limited number of chromosomes (Gleicher and Barad, 2012), as well as different performance levels at different laboratories (Cohen et al, 2007),
- 1.4. In addition to this, there is some concern that other factors may diminish the accuracy with which PGS can operate. Mosaicism is the phenomenon whereby a single cell, or small group of cells, may not represent the chromosomal complement of the entire embryo (Taylor et al, 2014). Therefore by chance a biopsy taken for the purpose of PGS may give a result of more or less aneuploidy than is present in the embryo as a whole. It is also believed that embryos may have a repair and/or exclusion mechanism to deal with aneuploid blastomeres (Bazrgar et al, 2013).
- 1.5. This has led to the development of techniques such as comparative genomic hybridization arrays (aCGH) and single nucleotide polymorphisms (SNP) arrays, which allow the analysis of all 24 chromosomes with a greater accuracy than FISH (Wells et al, 2008). These are now the methods of choice for most clinics undertaking PGS.

2. Background

- 2.1. The HFEA publishes information for patients about PGS on its website. SCAAC last gave dedicated consideration to the safety and efficacy of PGS in 2009 and has continued to monitor research through its horizon scanning function on an annual basis.

- 2.2. Following on from SCAAC's meeting in 2009 HFEA guidance and licence conditions outlined in the Code of Practice was amended. (See Annex B for the current Code of Practice guidance note on PGS).
- 2.3. The new guidance states that, "Centres should ensure that they keep up to date with relevant literature and professional guidance in order to validate the use of PGS for each category of patient to whom they offer it. Validation should also be based on data from previously published studies and retrospective evaluation of the clinic's own data," and that, centres should provide information to patients considering PGS, about the risks associated with the procedure, and the unproven nature of the procedure.
- 2.4. There are conflicting views about the value of PGS in IVF treatment. While it is now widely acknowledged that PGS, using FISH on a limited number of chromosomes, confers no advantage and may even be detrimental to overall success in achieving a live birth, there is no consensus on the impact of the newer techniques of aCGH and SNP arrays on IVF outcomes (Gleicher and Barad, 2012; (Lee et al, 2015; (Fragouli and Wells, 2012; Wells et al, 2014).
- 2.5. A number of clinical trials, including RCTs, have been recently carried out to assess the effectiveness of these newer techniques. This paper presents the conclusions of these trials and subsequent critical reviews of their data. Also presented are developments from the recent literature regarding the application of next-generation sequencing in PGS. Further to this the Executive has recommended consideration to updating the patient information on the website and the guidance in the Code of Practice where appropriate.

3. Research developments

- 3.1. There is an ongoing debate as to the clinical utility of PGS. Its proponents (Wells et al, 2014; Fiorentino et al, 2014a) cite a growing number of RCTs which have produced clinical data supporting the hypothesis that screening of embryos for aneuploidy can improve IVF outcomes. While its detractors assert that significant shortcomings of the same RCTs significantly downgrade the level of evidence they provide, and point to concerns regarding safety and efficacy of PGS in general (Mastenbroek and Repping, 2014; Gleicher and Barad, 2012).
- 3.2. Clinical trials supporting the effectiveness of newer techniques for PGS
 - 3.2.1. In a recent study, Yang et al (2012) compared the effect of PGS via aCGH versus embryo selection on the basis of morphology on IVF outcomes. First-time IVF patients with a good prognosis (age <35, no prior miscarriage) and normal karyotype seeking elective single embryo transfer (SET) were prospectively randomized into two groups: In Group A (n=55), embryos were selected on the basis of morphology and comprehensive chromosomal screening via aCGH (from day 5 trophectoderm biopsy) while Group B embryos were assessed by morphology only. In Group A, a total of 425 blastocysts were biopsied and analysed via aCGH and aneuploidy was detected in 44.9% of blastocysts. A total of 389 blastocysts were microscopically examined from Group B. The authors found that embryos randomized to the aCGH group implanted with greater efficiency, resulted in ongoing

pregnancy more often (69.1% in Group A versus 41.7% in Group B), and yielded a lower miscarriage rate than those selected without aCGH.

- 3.2.2. A recent study (Forman et al, 2013) carried out a randomized trial aimed at determining whether performing PGS (via rapid, real-time PCR on trophectoderm biopsies of day 5 embryos) and transferring a single euploid blastocyst can result in an ongoing pregnancy rate that is equivalent to transferring two untested blastocysts while reducing the risk of multiple gestation. A total of 205 infertile couples (with a female partner less than 43 years old and with a serum anti-Müllerian hormone level ≥ 1.2 ng/mL and day 3 FSH < 12 IU/L and with at least two blastocysts on day 6) were randomised into two groups. From the study group (n=89) all viable blastocysts were biopsied for real-time, PCR-based PGS and single euploid blastocysts were transferred. Patients from the control group (n=86) had their two best-quality, untested blastocysts transferred. The ongoing pregnancy rate per randomized patient after the first ET was similar between the groups (60-65%), with singleton pregnancies in 100% of the study group, compared to 53.4% multiple pregnancies in the control group.
- 3.2.3. A recent study (Schoolcraft et al, 2012) carried out a RCT to evaluate the clinical efficacy of PGS (via SNP microarray on with trophectoderm biopsies, with all blastocysts subsequently vitrified) in IVF patients of advanced maternal age. Infertile patients of maternal age > 35 years were randomized at egg retrieval into two groups. In Group A (n=30) fresh blastocyst transfer was carried out on embryos selected by morphology alone. Patients in Group B (n=30) underwent frozen blastocyst transfer with only euploid embryos tested by PGS. Infertile advanced maternal age patients had higher ongoing implantation rates (A=40.9%, B=60.8%, $P < 0.05$) and fewer first trimester pregnancy losses (A=20%, B=0%, $P < 0.05$) following a frozen blastocyst transfer with screened euploid embryos, when compared to routine fresh blastocyst transfer based on embryo morphology alone.
- 3.2.4. In a recent study by Scott et al (2013) carried out a RCT to determine whether rapid quantitative real-time PCR (qPCR)-based PGS (on day 5 trophectoderm blastocyst biopsies) improves IVF implantation and delivery rates. Infertile couples (n=155), in whom the female partner (or egg donor) was between the ages of 21 and 42 years, were included in the trial. A total of 134 blastocysts were transferred to 72 patients in the study (PGS) group and 163 blastocysts to 83 patients in the control group. PGS resulted in statistically significantly improved IVF outcomes, as evidenced by meaningful increases in sustained implantation (PGS=79.8%, control=63.2%, $P = 0.002$) and delivery rates (PGS=66.4%, control=47.9%, $P = 0.001$).

3.3. Reviews criticising recent PGS trials

- 3.3.1. A number of recent reviews have questioned the extent to which these and other trials demonstrate the ability of PGS to improve IVF outcomes (Mastenbroek and Repping, 2014; Gleicher and Barad, 2012; Lee et al, 2015). The authors of these reviews point to a litany of shortcomings which include: small sample size, lack of blinding, power calculations, suitable controls and generalisability, suboptimal primary end-points (implantation rate, instead of ongoing pregnancy rate or live birth

rate) and a failure to consider subsequent frozen transfer cycle in control groups and the resulting cumulative delivery rates.

3.3.2. Despite this, Lee et al (2014) considered that data from clinical trials “did reveal potential benefits of using PGD-A [PGS] techniques over morphology-based selection of embryos” while Gleicher et al, (2012) were “convinced that PGS in properly selected patients...improves IVF pregnancy and, likely, also reduces miscarriage rates.”

3.3.3. Mastenbroek et al (2014) were far more scathing in their conclusions. They point to the financial aspects of PGS, which is “commercially very attractive as it can significantly increase the turnover of a clinic”, and suggest that, “the medical professionals offering PGS either are unaware of the true value of the available data or are driven by other motives.”

3.3.4. A number of other issues more general to PGS are also raised in these reviews:

- The exact prevalence of mosaicism between cells at the blastocyst stage using the new methods for analysis is as yet unknown. Any mosaicism would decrease the accuracy with which an embryo could be selected as euploid or aneuploidy, and could result in healthy embryos being destroyed and unhealthy embryos being transferred.
- It cannot be fully excluded that harm is caused to the embryo during the biopsy procedure. While follow-up studies to assess the impact of PGS have been undertaken, they have involved very small sample sizes. (One recent study found no statistically significant differences in major or minor anomalies between children conceived after IVF/ICSI with or without PGS (Beukers et al, 2013), while another found that the neurodevelopmental outcome of PGS children aged four was similar to that of controls (Schendelaar et al, 2013).
- These techniques favour day 5/6 transfer. However, there is some data to suggest that this results in less favourable live birth rates, compared with a day 2/3 transfer when frozen cycles are included (Blake et al, 2007).
- Aueuploidy increases with increased maternal age, and consequently PGS is sometimes recommended for patients of advanced maternal age. However, advanced age also results in diminished ovarian reserves, with only small egg and embryo numbers of poor quality. PGS could reduce the number of transferable embryos (potentially to zero), reducing the rate of live births per cycle. It might be more appropriate to use PGS in patients with recurrent implantation failure or recurrent miscarriages (or good prognosis patients) but this is questionable.
- There is accumulating evidence that freeze-all cycles can be used without impairing, and maybe even improving, the cumulative pregnancy rate of that IVF cycle. Therefore no selection method would ever lead to improved live birth rates. The purpose of embryo selection should therefore be restricted to determining the order in which the embryos will be transferred, but not to select out embryos (assuming embryo biopsy does no harm).

- It has not been determined whether PGS represents a cost-effective approach to IVF for patients.
- All the authors agreed that there was a need for more, well-designed RCTs to test the efficacy and cost-effectiveness of PGS, and that these are well overdue.

3.4. Next-generation sequencing for use in PGS

- 3.4.1. Advances in next generation sequencing (NGS) technology have provided new tools for detecting DNA mutations and/or chromosome aberrations for research and diagnosis purposes. Combining this technology with whole genome amplification (WGA), a technique whereby the entire genome is copied many times, has enabled the detection of copy number variations (CNV) in single cells (Navin et al, 2011). This has paved the way for the development of WGA and NGS protocols for use in PGS (See Annex C for details).
- 3.4.2. In a recent study Fiorentino et al (2014b) validated a NGS-based protocol for 24-chromosome screening of embryos. In their study, karyotypically defined single-cells derived from cultured amniotic fluids or products of conception, or single blastomeres biopsied from embryos produced in 68 clinical PGS cycles, were analysed by NGS. The results were compared either to conventional karyotyping of single cells or aCGH diagnoses of single blastomeres. The results demonstrated 100% consistency with conventional karyotyping and 99.8% chromosome copy number assignment consistency with aCGH. The authors noted that their protocol demonstrated the ability to accurately detect “segmental changes (as small as 14 megabases in size), indicating that diagnosis of partial aneuploidies is well within the ability of this technology.”
- 3.4.3. Another recent study (Wells et al, 2014) aimed to develop a rapid, scalable, cost-effective method for the genetic analysis of single cells (blastomeres) or trophoctoderm biopsies derived from human preimplantation embryos, using low-pass NGS (which provides less than 0.1% genomic coverage). Their data confirmed that highly accurate detection of aneuploidy could be achieved in single cells from embryos using their methodology. The authors assert that this technique can be carried out at a speed (potentially within 8 hours), throughput (at least 32 samples in one run) and cost (more than a third less than with the most widely used microarray-based approaches), appropriate for use in conjunction with standard embryo biopsy and transfer protocols. In addition this authors also demonstrate that NGS has the potential to carry out diagnosis of single gene mutations simultaneous to chromosomal analysis, and that it can be used to acquire quantitative data on mtDNA copy number and mutation load.
- 3.4.4. Following on from their previous work, Fiorentino et al (2014b) carried out a double blinded clinical study to determine whether NGS techniques can be used reliably for comprehensive aneuploidy screening of human embryos from patients undergoing IVF treatments, with the purpose of identifying and selecting chromosomally normal embryos for transfer. Fifty-five patients undergoing PGS were enrolled in the study, 192 blastocysts were obtained, and trophoctoderm biopsies were performed on day 5

or day 6/7 for slower growing embryos. The consistency of NGS-based aneuploidy detection was assessed by matching the results obtained with aCGH-based diagnoses. Their results demonstrated that NGS was able to determine aneuploidy with 99.98% specificity and with 100% sensitivity. Following transfer of 50 euploid embryos in 47 women, 34 women became pregnant (based on positive hCG levels, resulting in the birth of 31 healthy babies (with 3 biochemical pregnancies and 1 miscarriage) (Fiorentino et al, 2014a).

3.5. The future

- 3.5.1. Data from these and other studies suggests that it is technically feasible to extend NGS to allow whole genome sequencing of embryos. This coupled with the growing ease with which preconception carrier screening can be conducted (including commercially by companies such as 23andMe) may be leading us towards a future where IVF and PGS/D will be used not for the treatment of infertility or avoidance of disease, but to allow people to select to have the healthiest possible child (Hens et al, 2013). Although this would not be permitted under current HFEA regulation, it is likely technically possible already, and it seems plausible that some people might have an appetite for such innovations. It is important to be mindful of this and to make sure that the ethical and regulatory framework keeps pace with the science.

4. **Conclusions and recommendations**

- 4.1. Recent research and literature demonstrates that considerable progress has been made in the techniques available for use in PGS, but there is still considerable controversy surrounding its practice in IVF, and a continuing need for a greater number of well-designed RCTs.
- 4.2. The aim of the patient information is to provide a fair, balanced and accurate picture on current progress regarding PGS to assist patients who are seeking to make decisions about fertility treatment.
- 4.3. The Executive recommends that the current website information for patients is updated and consideration is given to whether guidance in the Code of Practice, particularly regarding information clinics should provide to patients about PGS, should be amended.
- 4.4. Members are asked to:
- Review the recent literature in this area and consider the safety and efficacy issues that may arise from such techniques.
 - Review the HFEA website text (at Annex A) and provide comments to the Executive, relating to possible updates and changes including any studies they feel should be added to the website text as highlighted articles.
 - Consider whether any points in the Code of Practice guidance regarding information to be provided to patients prior to PGS (9.1 at Annex B) should be amended and, if so, provide comments to the Executive regarding possible amendments.

5. References

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ANNEX A: Current HFEA website information

Pre-implantation genetic screening (PGS)

[On this page:](#)

- [What is PGS?](#)
 - [Is PGS for me?](#)
 - [How does PGS work?](#)
 - [What is my chance of having a baby with PGS?](#)
 - [What are the risks of PGS?](#)
 - [Where do I start?](#)
-

What is pre-implantation genetic screening (PGS)?

PGS (also known as aneuploidy screening) involves checking the chromosomes of embryos conceived by IVF or ICSI for common abnormalities. Chromosomal abnormalities are a major cause of the failure of embryos to implant, and of miscarriages. They can also cause conditions such as Down's syndrome.

- [In vitro fertilisation](#)
- [Intra-cytoplasmic sperm injection \(ICSI\)](#)

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Is PGS for me?

Your specialist may recommend PGS if:

- you are over 35 and have a higher risk of having a baby with a chromosome problem (such as Down's syndrome)
- you have a family history of chromosome problems
- you have a history of recurrent miscarriages
- you have had several unsuccessful cycles of IVF where embryos have been transferred, or
- your sperm are known to be at high risk of having chromosome problems.

However, various [studies have questioned whether or not PGS is effective](#) at increasing the chance of having a live birth.

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How does PGS work?

The procedure for PGS is usually as follows:

Step 1. You undergo normal IVF or ICSI treatment to collect and fertilise your eggs

Step 2. The embryo is grown in the laboratory for two to three days until the cells have divided and the embryo consists of about eight cells.

- Step 3.** A trained embryologist removes one or two of the cells (blastomeres) from the embryo.
- Step 4.** The chromosomes are examined to see how many there are and whether they are normal.
- Step 5.** One, two or three of the embryos without abnormal numbers of chromosomes are transferred to the womb so that they can develop. Any remaining unaffected embryos can be frozen for later use.
- Step 6.** Those embryos that had abnormal chromosomes are allowed to perish or may be used for research (with your consent).

Possible variations to this procedure

There are possible variations to this procedure and the trophectoderm biopsy technique can be used in some cases.

Testing at five to six days

It is possible that instead of removing and testing one or two cells from a two – three day old embryo, some centres may allow the embryo to develop to five - six days, when there are 100-150 cells.

More cells can be removed at this stage without compromising the viability of the embryo, possibly leading to a more accurate test.

Alternatively some centres may test eggs for chromosomal abnormalities before they are used to create embryos. Polar bodies (small cells extruded by eggs as they mature) can be extracted and tested.

Comparative Genomic Hybridisation (CGH)

A small number of clinics are now using a procedure called comparative genomic hybridisation (CGH) which allows centres to test for abnormalities in all 23 chromosomes.

These abnormalities may or may not be of biological significance, but their presence will lower the chance of finding suitable embryos for transfer.

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What is my chance of having a baby with PGS?

Because a large proportion of patients who receive PGS are older patients, patients with a history of miscarriages or other indications and also because many of the embryos produced are not suitable for transfer to the womb, the success rate varies considerably depending on the patient's individual circumstances.

The average success rate for PGS treatment in the UK for in the year from 01/01/2008 - 31/12/2008 is:

- ** (2/7) for women aged under 35
- ** (2/15) for women aged between 35-37
- ** (7/25) for women aged between 38-39
- ** (12/42) for women aged between 40-42
- ** (1/29) for women aged between 43-44
- ** (0/12) for women aged over 44

** Percentages are not calculated where there are less than 50 cycles. Figures given in brackets are (cycles resulting in a live birth / all cycles started).

Various studies have questioned whether or not PGS is effective at increasing the chance of having a live birth. There is a lack of evidence that having a treatment cycle with PGS will increase your chances of having a baby compared to having a treatment cycle without PGS.

More robust randomised controlled trials are needed before a decision can be made either way.

Centres are required to validate the use of PGS (i.e demonstrate there is evidence) for each category of patients they offer it to (e.g advanced maternal age, recurrent implantation failure, recurrent pregnancy loss and male factor infertility).

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What are the risks of PGS?

Some of the risks involved in PGS treatment are similar to those for conventional IVF. For more information, see:

[Risks of fertility treatment](#)

Other problems unique to PGS treatment include:

- some embryos may be damaged by the process of cell removal
- possibility that no embryos are suitable for transfer to the womb after PGS.

It is important to understand that there is no guarantee against a miscarriage occurring even though PGS has been carried out prior to embryo transfer.

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Where do I start?

To find clinics offering PGS, use the advanced search in our Find a clinic database:

- [Find a clinic - advanced search](#)

You can also access a list of Genetic Centres and Services in your area by visiting the Genetic Alliance UK.

- [Genetic Alliance UK](#)

If you are considering this treatment, you should talk to your GP to go through the options available. Your GP can also refer you to see a specialist at your local hospital or fertility clinic.

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Mosaic embryos

PGS relies on the theory that all the cells in a human embryo are chromosomally identical, so that if you examine one cell from an embryo, it will show whether or not all the other cells have a chromosomal abnormality.

However, research has shown that in some embryos (known as mosaic embryos), the cells are not chromosomally identical. As a result, many such embryos will be discarded that are in fact capable of producing a normal pregnancy.

ANNEX B: Current HFEA Code of Practice guidance note on PGS

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- Forms to use in your clinic

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Staff

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9. Preimplantation genetic screening (PGS)

Version 2.0

On this page:

Mandatory requirements:

- Extracts from the HFE Act
- Extracts from licence conditions

HFEA guidance:

- The use of PGS
- Prohibitions on embryo selection

Other legislation, professional guidelines and information

- Section includes interpretations of mandatory requirements

Refer to principles 5, 7 and 9

Expand

Download this guidance note

(148kb)

Please note: As of 1 October 2014 the downloadable Code of Practice is generated directly from online content, therefore the formatting may appear different to previous versions.

Download the full code (5412kb)

> Download all the directions

Search the Code

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Go



Mandatory requirements

Human Fertilisation and Embryology (HFE) Act 1990 (as amended)

Schedule 2

Licences for treatment

- 1 (1) A licence under this paragraph may authorise any of the following in the course of providing treatment services –
...(b) procuring, keeping, testing, processing or distributing embryos...

Embryo testing

- 1ZA (1) A licence under paragraph 1 cannot authorise the testing of an embryo, except for one or more of the following purposes –
- (a) establishing whether the embryo has a gene, chromosome or mitochondrion abnormality that may affect its capacity to result in a live birth,
 - (b) in a case where there is a particular risk that the embryo may have any gene, chromosome or mitochondrion abnormality, establishing whether it has that abnormality or any other gene, chromosome or mitochondrion abnormality,

Licence conditions

- T88 With respect to any embryo testing programme involving biopsy the centre must ensure that:
- a. no embryo is transferred to a woman where that embryo or any material removed from it or from the gametes that produced it, has been subject to a test that supplies genetic information about the embryo, unless the test has been expressly authorised by the Authority, and
 - b. any information derived from tests on an embryo, or any material removed from it or from the gametes that produced it, is not used to select embryos of a particular sex for social reasons.

T89 With respect to any embryo testing programme the centre must ensure that embryo testing is only being carried out for those genetic conditions that are expressly authorised by the Authority.

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HFEA guidance

The use of PGS



Interpretation of mandatory requirements

9A

An embryo may be tested to establish whether it has a particular chromosomal abnormality only if:

- a) that abnormality may affect its capacity to result in a live birth, or
- b) there is a particular risk that it has that abnormality, and where the Authority is satisfied that there is a significant risk that a person with that abnormality will have or develop a serious medical condition.

- 9.1 The centre should ensure that before people seeking treatment give consent to PGS for aneuploidy, they are given information explaining:
- (a) the risks associated with the procedure
 - (b) the unproven nature of the procedure, in particular that:
 - (i) more robust clinical and laboratory trials are needed to assess whether or not PGS can significantly increase live birth rates
 - (ii) the method of fluorescent in situ hybridisation (FISH) on embryos, using a limited number of chromosomes, is not effective at increasing live birth rates
 - (c) that embryos biopsied may not be available for cryopreservation and for use in subsequent treatment cycles
 - (d) the misdiagnosis rates associated with PGS for aneuploidy, including the fact that false results can be positive or negative
 - (e) that the more chromosome tests are carried out, the higher the possibility of the test not working and the lower the chance of finding suitable embryos for transfer
 - (f) that there is no guarantee against a miscarriage occurring, despite PGS for aneuploidy being performed, and
 - (g) the financial and emotional costs where treatment fails and there is no live birth following PGS for aneuploidy.
- 9.2 Embryos from which biopsies have been taken, or resulting from gametes from which biopsies have been taken, should not be transferred with any other (non-biopsied) embryos in the same treatment cycle.
- 9.3 Centres should ensure that they keep up to date with relevant literature and professional guidance in order to validate the use of PGS for each category of patient to which they offer it. Validation should also be based on data from previously published studies and retrospective evaluation of the clinic's own data.

Prohibitions on embryo selection



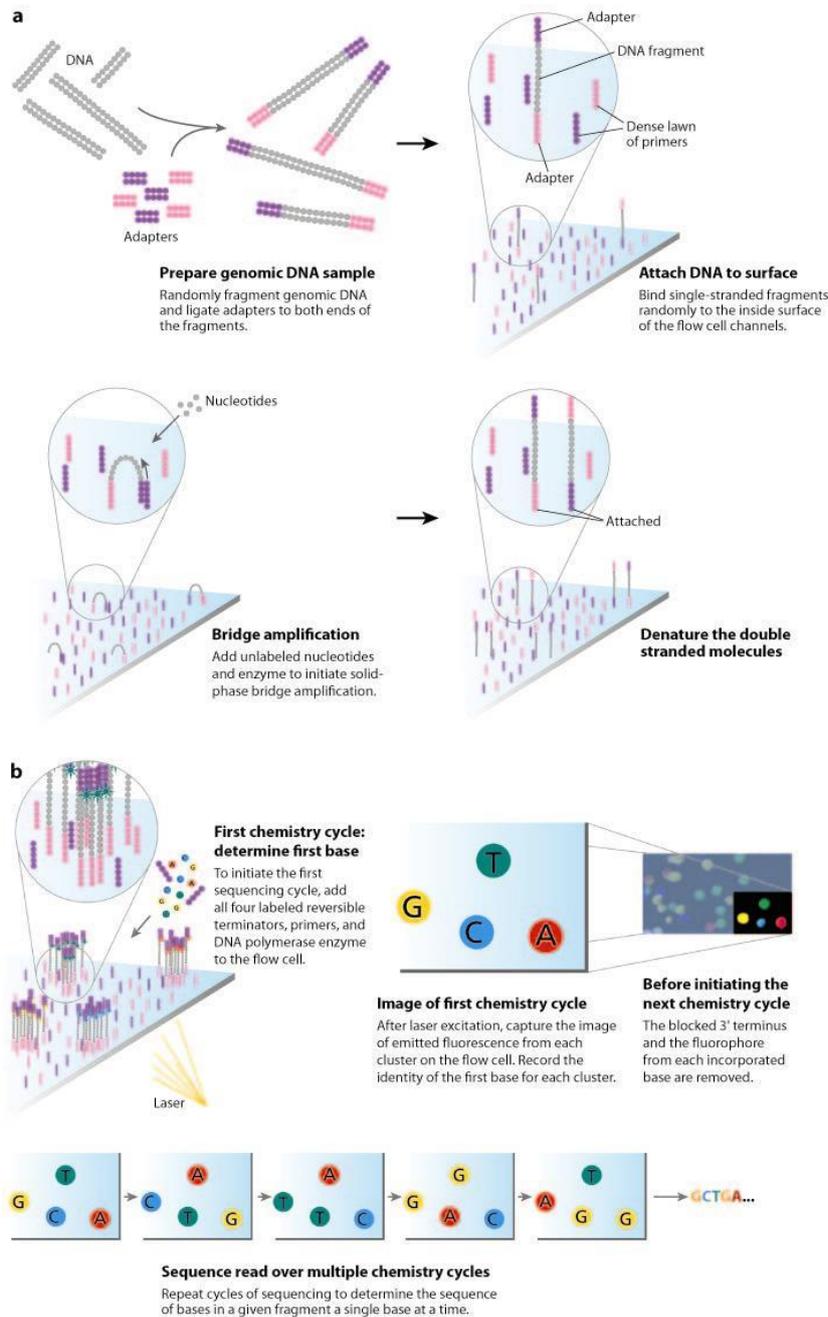
Interpretation of mandatory requirements

9B

The law requires that the centre should not select embryos of a particular sex for social reasons.

NOTE: Guidance note 10 (Embryo testing and sex selection) contains all the guidance and mandatory requirements relevant to embryo testing in general. Centres offering PGS should familiarise themselves with this guidance note as well.

ANNEX C: How next-generation sequencing enables analysis of copy number variation in single cells



1. Single-cells are lysed, subjected to WGA, fragmented, purified and barcoded libraries are assembled.

2. These are then sequencing by a NGS technology (paired-end sequencing is shown in the diagram), generating sequence reads of very short length.

3. These are aligned with a reference sequence of the human genome and the chromosomal origin of each fragment is identified.

4. This allows the proportion of DNA fragments from each chromosome to be determined, as the number of reads of a particular sequence is proportional to the number of chromosomes (or chromatids) present.

5. By adjusting the read-depth the resolution of the chromosomal analysis can be adjusted.

(Wells et al. 2014)(Fiorentino, Biricik, et al. 2014)(Mardis 2008)