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CLINICAL REVIEW

Preimplantation genetic testing

Paul R Brezina *coordinator of reproductive genetics*[1], Dawn S Brezina *assistant consulting professor*[2], William G Kearns *associate professor and director* [3 4]

[1]Fertility Associates of Memphis, Memphis, TN 38120, USA; [2]Department of Medicine, Duke University School of Medicine, Durham, NC, USA; [3]Department of Gynecology and Obstetrics, Division of Reproductive Endocrinology and Infertility, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Center for Preimplantation Genetics, LabCorp, Rockville, MD

Preimplantation genetic (PG) testing is the practice of obtaining a cellular biopsy sample from a developing human oocyte or embryo, acquired via a cycle of in vitro fertilisation (IVF); evaluating the genetic composition of this sample; and using this information to determine which embryos will be optimal for subsequent uterine transfer. PG testing was first described in 1990 when the sex of cleavage stage embryos in two couples, both with X linked diseases, was determined.[1] The applications and use of various types of PG testing have continued to increase. However, the benefits and limitations of PG testing, both in popular culture and the medical community, are often misunderstood. This article reviews the technologies available in PG testing, and discusses the risks, ethical considerations, appropriateness, and controversy surrounding its use in different clinical situations.

Who benefits from PG testing?

PG testing is a term used to encompass all types of genetic testing conducted on oocytes or embryos after an IVF cycle.[2 3 4] The results of this genetic analysis allow decisions to be made regarding which embryos are optimal for transfer into the maternal uterus. PG testing has two broad categories: diagnosis and screening (box 1).[2 3 5 6]

What is PG diagnosis?

PG diagnosis is the testing of embryos for specific genetic abnormalities known to exist in one or both parents.[3 6] It cannot be performed in conditions where a definitive genetic cause has not been identified. Since the 1990s, improvements in the techniques used have allowed for an increasing number of disorders to be tested by PG diagnosis, including Huntington's disease, haemophilia, and cystic fibrosis.[1 7 8 9 10] PG diagnosis identifies specific genetic abnormalities by direct DNA sequencing or by determining structural chromosomal imbalances, using a variety of methods including microarrays and fluorescence in situ hybridisation (FISH).[11 12] Furthermore, diagnostic technology might be able to identify phenotypic traits, such as hair colour, but this practice is considered inappropriate and unethical.[13 14] PG diagnosis can also allow sex to be determined for family balancing purposes, but again this is controversial.[15 16] Although many clinics worldwide do offer PG diagnosis for family balancing, ethical concerns surrounding the practice have resulted in a substantial number of infertility clinics choosing not to offer this service.[15 16] In addition, PG diagnosis for family balancing is not a legal practice in all countries.[15 16]

PG diagnosis can be used to determine which embryos will be a human leucocyte antigen (HLA) match for the purpose of tissue donation for an existing sibling with medical conditions such as leukaemia.[17 18] Use of PG diagnosis for HLA matching is also controversial, because this preferentially chooses embryos that will be optimal tissue donors for existing siblings.[15 16] The ethical and legal issues surrounding this practice are complex, and include informed consent and possible exploitation. Again, the legality of using PG diagnosis for HLA matching varies in different countries.[15 16] Of 27 630 IVF cycles for PG testing reported over the past 10 years to the European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium, collecting data from around the world, 39% (n=10 824) were performed for PG diagnosis.[11] The vast majority of these cases, 94% (n=10 153), were performed to prevent the transmission of known parental genetic abnormalities.[11] Box 2 summarises which patients are appropriate candidates for PG diagnosis.

What is PG screening?

PG screening, unlike diagnosis, is a screening test for numerical chromosome abnormalities (aneuploidy) within embryos resulting from parents with a chromosomal composition presumed to be normal (normal karyotype). Prospective trials evaluating the chromosomal composition of tissue obtained from spontaneous miscarriages have shown that chromosomal

Correspondence to: P Brezina pbrezina@fertilitymemphis.com

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Web appendix: Web references

Summary points

- Preimplantation genetic (PG) testing is the practice of obtaining a cellular biopsy sample from a developing human oocyte or embryo, obtained via a cycle of in vitro fertilisation (IVF); evaluating the sample's genetic composition; and using this information to determine which embryos will be optimal for subsequent uterine transfer
- PG testing is divided into two broad categories: diagnosis and screening
- The purpose of PG diagnosis is to prevent the birth of affected children from parents with a known genetic abnormality, and is widely acknowledged as acceptable for routine clinical application
- The purpose of PG screening is to identify optimal embryos for uterine transfer in an IVF cycle and, in so doing, improve pregnancy success in certain patient populations; its routine clinical application remains controversial
- PG testing, especially with PG screening, might not always indicate the ultimate genetic status of the fetus
- As genetic diagnostic technology continues to advance, PG testing must be used in an ethical and equitable manner

Sources and selection criteria

The information sources used to compile this review were committee opinions regarding PG testing from major professional societies, published research and review articles, and several recent abstracts presented at international meetings. Articles were identified by a literature search using PubMed, Scopus, and Science Direct with no time limit; and keywords including "preimplantation genetic testing," "preimplantation genetic diagnosis," and "preimplantation genetic screening." When possible, published research articles were used. However, for some emerging data, it was necessary to cite data published currently only as meeting abstracts.

Box 1: PG testing

PG diagnosis

- Tests embryos for specific genetic abnormalities that have been shown to exist in one or both parents
- Purpose is to prevent the birth of affected children from parents with a known genetic abnormality
- Widely acknowledged as acceptable for routine clinical application

PG screening

- Tests for aneuploidy in embryos; parents have no diagnosed genetic abnormality
- Purpose is to identify optimal embryos for uterine transfer in an IVF cycle and, in so doing, improve pregnancy success in certain patient populations
- Its routine clinical application remains controversial

Box 2: Appropriate candidates for PG diagnosis

- Diagnosis is appropriate for:
- Autosomal recessive diseases in which both parents are known genetic carriers, such as cystic fibrosis or sickle cell disease
- Autosomal dominant diseases in one or both parents, such as Huntington's disease
- X linked diseases (such as haemophilia)
- Any parent who harbours certain balanced chromosomal translocations or inversions
- Diagnosis is not appropriate for:
- Medical conditions in parents in whom a definitive genetic cause has not been identified
- Testing for non-medical phenotypic traits, such as eye or hair colour
- Diagnosis is controversial for:
- Sex selection for the purposes of family balancing
- HLA matching for the purposes of creating a tissue donor for an existing diseased sibling

aneuploidy is the greatest causal factor in pregnancy failure.[19] Traditionally, PG screening was performed using FISH, for five to 14 chromosomes, on embryonic cells obtained at the cleavage stage (approximately three days after fertilisation).[12] Technical limitations of FISH makes the evaluation of more than 14 chromosomes difficult. However, several prospective randomised studies have shown that PG screening using FISH fails to improve pregnancy rates, and could actually worsen them.[12 20 21 22 23 24 25] This effect suggests that the act of embryo biopsy confers a deleterious effect on the developing embryo and that too few chromosomes were tested.

Recent retrospective cohort studies suggest that PG screening using new technologies that test for all 23 chromosome pairs, compared with FISH, could confer a pregnancy benefit in certain patient populations.[23 26] Additionally, other retrospective cohort studies have reported a further improvement in pregnancy rates using a recently introduced embryo biopsy technique that obtains cells of the trophectoderm (precursor to the placenta) from embryos five or six days after fertilisation.[23 27 28 29]

PG screening is currently a widely used tool. Of 27 630 IVF cycles for PG testing that were reported to the ESHRE PGD Consortium over the past 10 years, 16 806 (61%) were performed for PG screening.[11] Despite this high rate of use, however, large and well conducted randomised controlled trials are necessary to establish the efficacy of PG screening and define which patient populations might benefit from these technologies. Although a randomised controlled trial does exist that supports the use of PG screening to improve pregnancy outcomes with the transfer of single embryos, this single and relatively small study is insufficient to establish the widespread use of PG screening.[30] The need for these trials is highlighted

by previous studies showing the lack of efficacy associated with FISH PG screening.

There is disagreement even within the community of PG testing as to which patients are ideal candidates for PG screening. According to the ESHRE PGD Consortium review of 10 years of data collection, the most common reason for screening was advanced maternal age; other common indications included repeat implantation failure and recurrent pregnancy loss.[11] However, this dataset primarily included reporting centres from Europe, the Middle East, Asia, and South America. Only two centres reported data from the United States. The dataset also reported a decrease in the numbers of patients undergoing PG screening, and suggested that this effect might be due to embryo mosaicism at day 3, and the fact that most centres only tested for eight to 10 chromosomes and did not screen for all 23 pairs of chromosomes.

Most clinics conducting PG screening in the US primarily recommend it for older patients.[31] Recent US data have suggested that screening for all 23 pairs of chromosomes reduces first trimester miscarriages in women older than 35 years with a history of repeat pregnancy loss.[32] Prospective trials have suggested that such screening in women of advanced maternal age could confer some benefit, including a decreased rate of miscarriage.[33 34] Some centres use more liberal criteria, such as a previous aneuploid pregnancy, unexplained infertility, unsuccessful IVF cycles (repeat implantation failure), severe male factor, or patient request.

The most common indications for PG screening worldwide appear to be advanced maternal age, recurrent pregnancy loss, unsuccessful IVF cycles (repeat implantation failure), and severe male factor (box 3).[16 11] Prospective randomised trials have not yet definitively shown a benefit of such screening in any patient group. Therefore, professional societies do not currently recommend the procedure's routine use. However, PG screening is used worldwide in many patient groups to improve pregnancy rates or reduce miscarriage rates. The benefit within these groups is yet to be definitively determined. Screening could be offered concurrently to patients undergoing PG diagnosis with no need for repeated biopsy of another cell.[4 w1]

What techniques are used for IVF and PG testing?

IVF involves the stimulation of female ovaries to produce an unusually high number of mature follicles within a single menstrual cycle through the use of exogenous hormone preparations. The oocytes within these follicles are then retrieved by follicular fluid aspiration (guided by ultrasonography), and fertilised with sperm. Embryos result from successfully fertilised oocytes. Embryos that achieve certain developmental milestones are then either transferred into the maternal uterus or cryopreserved. Traditionally, this transfer and cryopreservation process was performed at the cleavage stage of development, approximately three days after fertilisation. Recently, for various reasons, this process is increasingly performed at the blastocyst stage of development, approximately five days after fertilisation.[w2]

How are embryo biopsies taken?

Three types of biopsies may be used for PG testing: polar body biopsy, cleavage stage biopsy, and blastocyst stage biopsy. The biopsy itself is accomplished by first weakening the outer layer of the oocyte or embryo, generally with a laser, followed by mechanical extraction of cell(s).[w3 w4]

Polar body biopsy

The process of oocyte development includes a series of meiotic divisions resulting in two sets of haploid maternal DNA that is extruded from the maternal oocyte. These sets of haploid maternal DNA are called polar bodies and are accessible for biopsy. Although some researchers advocate using polar body biopsy for PG testing, others point to considerable limitations such as the ability of the biopsy to test only for maternal genetic abnormalities.[5 10 12] In some countries such as Germany and Italy, ethical concerns have led to legislation that substantially restricts the performance of a biopsy on developing embryos.[5 12 15 w5] However, because polar body biopsy may be performed on the oocyte before fertilisation, this technique is widely used in countries where such restrictions on embryo biopsy exist.[5 12 15 w5]

Cleavage stage biopsy

After fertilisation of the oocyte with paternal sperm, the resulting embryo undergoes a series of developmental milestones. By the third day after fertilisation, most normally developed embryos achieve the cleavage stage, in which the embryo consists of about six to eight cells. Cleavage stage biopsy refers to the removal of one of these cells for PG testing (fig 1⇓), and is currently the most widely used method of biopsy for all forms of PG testing.[5 w6 w7 w8] However, there are concerns surrounding the procedure, such as possible embryo damage and embryo misdiagnosis risk secondary to known cellular mosaicism—a condition in which a single embryo has a mixture of normal and abnormal cells—and have led to the recent use of blastocyst stage biopsy in many centres.[5]

Blastocyst stage biopsy

By about the fifth day after fertilisation, the embryo develops into two distinct types of cells: the inner cell mass, which develops into the fetus, and the trophectoderm, which develops into the placenta. PG testing at the blastocyst stage is performed by taking cells from the trophectoderm rather than the inner cell mass (fig 2⇓). Retrospective and prospective cohort studies suggest better results with blastocyst stage biopsy than with cleavage stage biopsy at this point in.[5 23 28 29 w6 w7 w8 w9 w10] This trend will probably result in blastocyst stage biopsy becoming the most used biopsy method for PG testing in the near future.[5]

How is genetic analysis performed in PG diagnosis and screening?

Numerous techniques are used to perform genetic analysis in PG testing. In general, single gene PG diagnosis relies on sequencing technology that is able to identify specific known DNA mutations. In PG diagnosis for known parental balanced chromosomal translocations or inversions, various other methods (including FISH (fig 3⇓) or microarrays) are used to determine unbalanced chromosomal errors in embryos.[w11 w12] By contrast, PG screening attempts to broadly evaluate the numerical chromosomal composition of the entire embryo.[4 5 6] FISH testing for aneuploidy in five to 14 pairs of chromosomes has been the traditional method for performing PG screening.[21] FISH for PG screening cannot diagnose chromosomes not tested in this limited evaluation.

Most new technologies for PG screening are able to detect aneuploidies in all 23 pairs of chromosomes.[21 26] Although a variety of technologies are currently available for screening 23 chromosomes, microarrays, using either single nucleotide polymorphism or comparative genomic hybridisation, are

Box 3: Most common indications for PG screening

While the routine clinical application of PG screening remains controversial, clinics currently offering this service often recommend its use in the following patient populations:

Recurrent pregnancy loss

Advanced maternal age

Unsuccessful IVF cycles (repeat implantation failure)

Severe male factor

currently the most commonly used methods.[w10 w13] These modalities can identify gains or losses of all 23 chromosome pairs.[w13] Figures 4⇓ and 5⇓ show examples of normal and abnormal embryos by PG screening, using arrays of comparative genomic hybridisation and single nucleotide polymorphism, respectively. Recent data from multiple centres suggest that the optimal approach for PG screening is to use trophectoderm biopsy in conjunction with some form of evaluation for 23 chromosome pairs.[23 28 29 w10] However, there is a lack of large, prospective randomised trials that show the definitive superiority of a single method of genetic testing or biopsy technique.

What are the risks associated with PG testing?

Some reports suggest that IVF in general could be associated with a small increase in infants born with certain medical conditions.[w14 w15 w16 w17 w18] When embryo biopsy is performed at the cleavage stage, all of the cells comprising the embryo are totipotent, meaning that there has been no cellular differentiation at this point.[w19] Therefore, in theory, removing one of these cells may reduce the growth rate of the embryo but should not result in an anatomical defect. Biopsy at the blastocyst stage only removes trophectoderm cells destined to form the placenta, leaving the inner cell mass (the cells destined to form the fetus) untouched.[w19] We are unaware of any studies that link embryo biopsy and PG testing to birth defects. However, because embryo biopsy and PG testing are recently developed procedures, the possibility of unknown deleterious effects in the long term can only be excluded by evaluating the health of children born after embryo biopsy and PG testing, well into the future.

PG testing has a risk of misdiagnosis, either by a spurious result obtained through the genetic testing process or by human error.[w20] A number of technological limitations are inherent to many genetic diagnostic methods. Current methods of DNA analysis, such as improved DNA amplification protocols and the use of microarrays, have been introduced to minimise these limitations.[23 27 w21] As is true for all medical diagnostic testing, human error has the potential to introduce inaccuracies at many points in the PG testing process that can result in a misdiagnosis. To minimise this risk, all laboratories conducting PG testing must have multiple layers of confirmatory information checks.[5]

Perhaps the greatest risk of misdiagnosis in PG testing is from cellular mosaicism within the developing embryo. PG screening studies have shown that as many as 50% of cleavage stage embryos possess a mixture of normal (euploid) and abnormal (aneuploid) cells.[5 w22] Consequently, a biopsied cell from a cleavage stage embryo might not represent the ultimate chromosomal status of the fetus.[5 w23] Recent work indicates that this mosaicism is greatly reduced by the fifth day after fertilisation at the blastocyst stage.[w23] However, even at the blastocyst stage, there are documented low levels of discordance between the inner cell mass, destined to form the fetus, and the cells obtained for biopsy in the trophectoderm, destined to form the placenta.[w23 w24] Therefore, even with the best techniques available, the risk of embryo misdiagnosis stemming from embryonic mosaicism exists.

Owing to the risks of misdiagnosis and cellular mosaicism, in all forms of PG testing, professional societies recommend offering chorionic villus sampling or amniocentesis to confirm the genetic diagnosis of a fetus once a pregnancy is achieved.[6] Box 4 summarises the risks associated with PG testing. Although such testing could confer a benefit to selected patients, patients must understand that the risk of misdiagnosis cannot be eliminated regardless of the method used.

What are legal challenges associated with PG testing?

The legal status of infertility services in general varies greatly between countries.[w25 w26 w27] Many countries have legislation in place that limits the use of certain types of PG testing.[w25 w27 w28] For example, in Germany and Italy, ethical concerns have led to legislation that substantially restricts the performance of a biopsy on developing embryos.[5 12 15 w5] But the status of these laws is in a constant state of flux. For example, Germany has recently relaxed some of its strict restrictions regarding PG diagnosis after fertilisation.[w5 w27] By contrast, however, the US has no current legislation limiting the time that embryo biopsy can be performed or the types of testing that can be performed.[w29]

PG testing for the purpose of sex selection (family balancing) is particularly controversial.[w29 w30] Advocates of this practice argue that the practice offers couples more autonomy and decreases the incidence of elective fetal termination in couples desiring a child of a certain sex.[w29 w30] Opponents of the practice maintain that choosing an embryo for uterine transfer on the basis of sex is not appropriate.[w29 w30] Furthermore, opponents point out that in some cultures where a male child is perceived to be preferable, PG testing for family balancing could exacerbate or create sex imbalances on a societal scale.[w29 w30] This practice is explicitly prohibited in many countries such as Australia, China, India, and Thailand.[w29 w30 w31] However, in other nations, such as the US, no legislation exists limiting the practice.[w29 w30] Monitoring of clinics providing PG testing also varies internationally. In the US, there is no specific monitoring of PG testing laboratories above that required by other highly complex human laboratories.

The inconsistencies with which PG testing is dealt with legally has led to some patients desiring services not permitted in their home country to travel abroad to obtain such services. This practice is known as “reproductive tourism” and is an increasingly common global phenomenon.[w32 w33]

What does the future hold for PG testing?

As genetic diagnostic technology advances, ever more detailed genetic evaluation of human embryos seems likely. The ethical and moral concerns that accompany such detailed testing are considerable.[21 w34] In addition, such testing, if not universally

Box 4: Risks associated with PG testing

Physical damage to embryo from biopsy

No current evidence for resulting anatomical deformities

Misdiagnosis

Technological limitations

Human error

Embryo misdiagnosis

Possible discordance of chromosomal composition of biopsied cell and remainder of embryo

May occur with mosaicism of aneuploid and euploid cell lines in the same embryo

Unknown risks

Because PG testing is a relatively new and emerging technology, possible deleterious effects of this procedure (embryo biopsy)—especially since it relates to possible disorders with a late onset—may not be evident for many years when children born via this technology become older

accessible, will inherently create serious inequities between those with and without means on both a national and international scale. Furthermore, the efficacy of PG screening has not been conclusively shown in large, multicentre, randomised controlled trials. In view of previous disappointments from using FISH for PG screening, such trials are essential to show the role of PG screening and other forms of preimplantation testing going forward.

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Tips for non-specialists

- PG testing is a field that is constantly evolving in relation to the technology available and the types of patients who may benefit from testing
- Reproductive endocrinologists and geneticists are best placed to advise couples on PG testing
- Non-specialist physicians should be aware of the general benefits and risks of PG testing

Additional educational resources

Resources for generalist healthcare professionals

- Royal College of Obstetricians and Gynaecologists (www.rcog.org.uk)—provides general information regarding PG testing as it pertains to general practice of obstetrics and gynaecology
- American Congress of Obstetricians and Gynecologists (www.acog.org)—provides general information regarding PG testing as it pertains to general practice of obstetrics and gynaecology

Resources for patients

- Royal College of Obstetricians and Gynaecologists (www.rcog.org.uk)—provides general information regarding PG testing
- American Congress of Obstetricians and Gynecologists (www.acog.org)—provides general information regarding PG testing
- Human Fertilisation and Embryology Authority (www.hfea.gov.uk)—provides general information regarding PG testing

Ongoing research

- Need for large, prospective, randomised trials evaluating the efficacy of PG screening
- Need for large, prospective, randomised trials comparing various approaches to testing modalities, biopsy methods, among other factors
- Improve existing and developing new technologies for genetic diagnosis
- Evaluate the natural history of aneuploid-euploid mosaicism in developing human embryos
- Determine the ideal patient population for many types of PG testing

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Figures

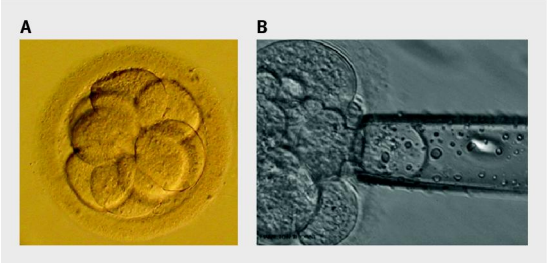

Fig 1 Cleavage stage embryo. (A) Embryo at the cleavage stage. (B) Cleavage stage embryo biopsy

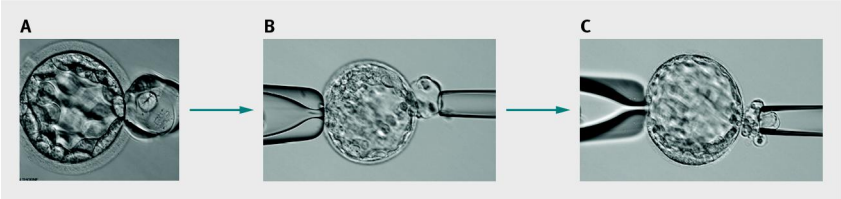

Fig 2 Blastocyst stage embryo. (A) Herniation of trophectoderm cells after application of a laser to breach the zona pellucida. (B and C) Process of obtaining a sheet of trophectoderm cells that will be analysed for PG diagnosis or screening

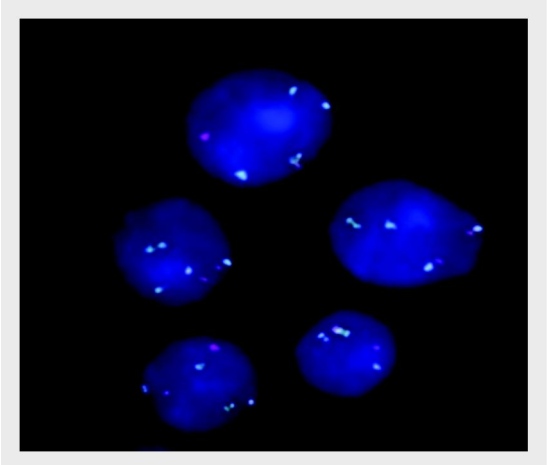

Fig 3 Photograph of chromosomes tagged with fluorochromes after DNA hybridisation using FISH. In this sample, chromosomes 13, 18, 21, X, and Y are evaluated with fluorophores of different colours. Two signals are identified for chromosomes 13, 18, and 21; one signal for the X chromosome; and no signal for the Y chromosome

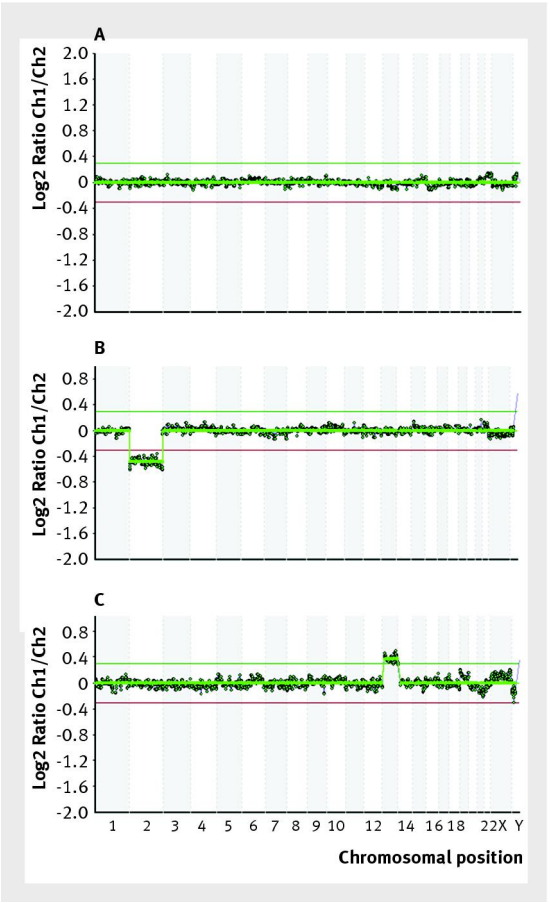

Fig 4 Samples evaluated by comparative genomic hybridisation arrays, for PG screening. (A) Diploid, with a relatively equal ratio of green:red fluorescence in all 23 pairs of chromosomes. (B) Monosomy for chromosome 2, with a clear downward deviation of the plotted line, indicating a relative reduction of green, compared with red, signal intensity. (C) Trisomy for chromosome 13, with a clear upward deviation of the plotted line, indicating a relative increase of green, compared with red, signal intensity.

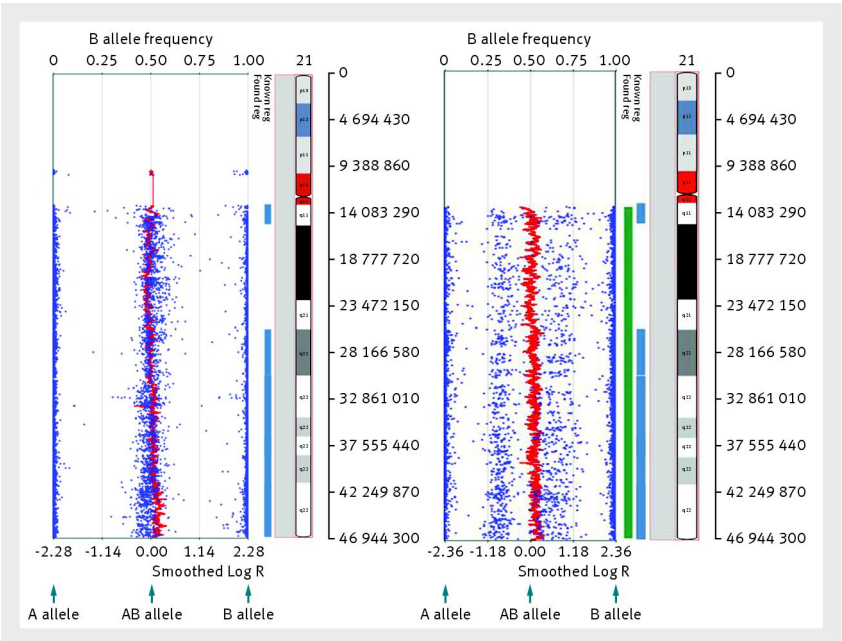

Fig 5 Samples evaluated by single nucleotide polymorphism arrays, for PG screening. (A) Diploid chromosome 21. (B) Trisomy chromosome 21. Note the presence of heterozygote bands (AB in the diploid sample, AAB and ABB in the trisomy sample)