Preimplantation genetic testing for aneuploidy (PGT-A) has become a routine add-on for in vitro fertilization (IVF) to determine whether human embryos are to be clinically utilized or disposed of. Studies claiming IVF outcome improvements following PGT-A, however, used highly selected patient populations or inappropriate statistical methodologies. PGT-A was never clinically validated in its ability to define a human embryo as chromosomal normal, mosaic, or aneuploid, nor certified by a regulatory body, or an authoritative professional organization. Because of a high false-positive rate, PGT-A, actually reduces live IVF birth chances for many patients. Furthermore, in recent studies the PGT-A hypothesis was demonstrated to be mistaken for biological, mathematical and technical reasons. PGT-A, therefore, should clinically only be offered within experimental study frameworks.

Introduction to Preimplantation Genetic Testing

Based on a hypothesis, first formulated by Verlinsky et al. in the 1990s [1], preimplantation genetic testing for aneuploidy (PGT-A; see Glossary) is the latest iteration of a diagnostic procedure applied to preimplantation-stage embryos. Prior to embryo transfer into the uterus, the purpose is elimination of aneuploid embryos to improve implantation rates and time to pregnancy for the remaining embryo cohort in a given in vitro fertilization (IVF) cycle. Underlying assumptions for the hypothesis, have, however, been largely rejected (Box 1). In the USA, PGT-A by 2020 has become the most widely utilized add-on to IVF practice, greatly outpacing other developed countries, like the UK [2].

Despite quickly increasing clinical utilization, PGT-A has become a highly controversial procedure/test [3,4] (see Clinician’s Corner). We here summarize current knowledge regarding PGT-A, concluding that, as the diagnostic test that determines whether a human embryo can be transferred or should be disposed of, PGT-A does not fulfill even minimal criteria for ethical clinical use in routine IVF practice. Its clinical application, therefore, should be restricted to experimental investigations.

History of PGT-A

The concept of embryo biopsy for diagnostics evolved out of preimplantation genetic diagnosis (PGD) for single gene diseases and expanded to detecting and eliminating aneuploid embryos prior to transfer in order to improve IVF outcomes (Figure 1).

PGS 1.0

Verlinsky et al., originally proposed first and second polar body biopsies at the zygote stage [1] as material for genetic testing. Because technically difficult, clinicians, with few exceptions, never accepted polar body biopsy as a method of choice and, instead, moved toward cleavage-stage biopsy (biopsy of one or two blastomeres) at 6-8-cell stage on day 3 after fertilization (IVF).
Box 1. Underlying Assumptions for PGT-A and Their Respective Rebuttals

This box describes assumptions that support PGT-A in association with IVF since the late 1990s. The rebuttals attempt to demonstrate why these assumptions are incorrect.

Assumption 1: Embryo aneuploidy is a principal cause for failed embryo implantation. Studies of miscarriages suggested aneuploidy as a principal cause [6,1], supporting the expectation that PGS/PGT-A and deselection of aneuploid embryos would reduce miscarriage rates [32].

Rebuttal: Although aneuploidy contributes to failure to implant and to miscarriages, associations are weaker than assumed for several reasons. Mosaicism is frequently found in preimplantation-stage embryos [7,34]. Chromosomal abnormal embryos may self-correct downstream [28]. More recently, mitotic aneuploidy was not only recognized to represent most diagnosed aneuploidies at preimplantation stages [26,27] but was also determined in human embryos to represent a normal physiological finding at those stages [25–27].

Assumption 2: A single embryo biopsy at preimplantation stage reliably reflects the complete chromosomal complement of the embryo.

Rebuttal: At cleavage as well as blastocyst stages, existence of significant mosaicism, alone, negates this assumption [7,25–27]. The move from cleavage- to blastocyst-stage biopsies was partially motivated by a desire to reduce effects of mosaicism on the accuracy of what then was called PGS [53]. At the blastocyst stage, mathematical modeling, however, demonstrates indisputably that an average five or six-cell trophectoderm biopsy, even at hypothetical best assumptions of even distribution of aneuploid cells, cannot reliably define an embryo as either aneuploid or not aneuploid [28].

Assumption 3: An embryo’s ploidy status at blastocyst stage reflects a fetuses’ ultimate ploidy fate.

Rebuttal: Chromosomal-normal pregnancies may have placentas that contain islands of aneuploid cells [46,47]. Recent studies convincingly demonstrated an efficient self-correction mechanism in the embryonic, but not to the same degree in the extraembryonic cell lineage in a mouse model [23,24] and in human blastocyst stage embryos as well as human self-organizing gastruloids [25]. This explains persistent island of chromosomal-abnormal cells in even mature placentas [46,47] since the placenta is a product of the extraembryonic cell lineage. Downstream self-correction renders upstream biopsy results irrelevant.

Assumption 4: Percentage of aneuploid DNA within a single trophectoderm biopsy reliably determines degree of an embryo’s mosaicism and, consequently, implantation, pregnancy and live birth chances [12,43,54].

Rebuttal: (i) PGT-A incorrectly defines presence of mosaicism in an embryo by detection of aneuploid DNA in a single trophectoderm biopsy [4]. The correct definition of mosaicism is, presence of aneuploid cells (DNA) anywhere in an embryo [53]. (ii) PGT-A, moreover, associates clinical significance of mosaicism with increasing percentage of aneuploid DNA in a single biopsy [43,54]; a finding clearly refuted by two independent studies [29,56]. The study by Munné et al. [43] was refuted using the study’s own data set [56]. (iii) PGT-A’s cut-off values defining euploid (<20% aneuploid DNA) from mosaic (20–80%) and aneuploid (>80%) have neither a biological, experimental, nor logical basis [4,11]. (iv) Determinations of percentages of aneuploid DNA require accurate nominators and denominators. How many trophectoderm cells have been biopsied and/or have lost their DNA content during biopsy is, however, impossible to assess during embryo biopsy. A correct denominator, therefore, can never be determined. Consequently, reported percentages of aneuploid DNA in PGT-A must be spurious.

Assumption 5: Embryo biopsy results at cleavage stage (PGS 1.0) and blastocyst stage (PGS 2.0) are innocuous to embryos, not significantly affecting pregnancy and live birth chances in IVF.

Rebuttal: It is well understood that human embryos are extremely sensitive to manipulation and biopsy. Recently, a mathematical model suggested that damage to embryos caused by biopsy, may be a principal reason for disappointing IVF outcomes following PGT-A [28]. This model was recently challenged on mathematical grounds [57]. Excessive biopsy damage as a principal cause for why PGT-A has failed to improve IVF, already for biological reasons, appears unlikely. Both notions, that there comes no harm at all from an invasive embryo biopsy, and that biopsy damage may serve as an explanation why PGT-A has failed to improve IVF, therefore, appear equally unlikely.

fertilization; called preimplantation genetic screening, (PGS) [5]. The American Society for Reproductive Medicine (ASRM), however characterized what now is frequently called PGS 1.0 as having failed to demonstrate outcome benefits [6]. Moreover, investigators recognized that mosaicism at the cleavage stage could result in false-positive diagnoses [7].
PGS 2.0
Around 2008, the field moved from cleavage-stage to blastocyst-stage biopsy on day 5 after fertilization (PGS 2.0) [8]. This step allowed for removal of more cells (on average five or six) and, therefore, offered larger amounts of DNA for examination (Box 1). Newly available diagnostic technologies also for the first-time permitted testing of the complete chromosome complement of embryos, while PGS 1.0 had, at most, only allowed testing of up to nine of the most frequent aneuploid chromosomes. PGS 2.0 was formally challenged when in 2015 two reports appeared in the literature, claiming normal euploid births following transfer of embryos by PGS/PGT-A diagnosed as chromosomal abnormal [9,10]. Both publications represented a watershed moment because births of chromosomal-normal offspring following transfer of, by PGS 2.0 determined to be chromosomal-abnormal embryos, questioned the clinical validity of PGS/PGT-A at a most basic level.

PGS 3.0
However, rather than diminishing utilization, this time period also defined when the clinical utilization of PGS/PGT-A initiated an exponential expansion in the USA. The reason was easy to recognize. As in 2008, when an earlier credibility crisis had arisen for PGS 1.0 that led to introduction of PGS 2.0, the genetic testing industry was again ready with a solution; here described as PGS 3.0 [11]. In July 2016 The Preimplantation Genetic Diagnosis International Society (PGDIS), mostly representing the genetic testing industry, published (on its website only) a first ever practice guidance for PGS. At the same time, the society also announced a name change for the procedure/test from PGS to PGT-A. Remarkably, the new guidelines were unsigned, did not contain any references, and had not undergone peer review. Indeed, they offered no explanation what thought process had led to their guidelines and who had authored them. Yet, surprisingly, these guidelines radically changed how laboratories conducted the analyses of trophectoderm biopsies worldwide and how those results were reported to IVF centers. Most importantly, and in order to explain delivery of healthy offspring following transfer of embryos with allegedly aneuploid biopsy results, embryos no longer were only classified in binary fashion as euploid or aneuploid. The guidelines for the first time added a new third category of mosaic embryos [11].

Except for next-generation sequencing (NGS), most diagnostic platforms used for PGS/PGT-A to that point, could not differentiate a second DNA within a single trophectoderm biopsy and, therefore, were unable to diagnose mosaicism. Going forward, the new PGDIS guidelines, therefore, disqualified other platforms besides NGS. Shortly thereafter, and included in the 2016 PGDIS guidelines, the so-called threshold concept of PGT-A diagnosis proposed by Scott and Galliano [12], (re-)defined mosaicism (Box 2). However, this concept cannot reliably assess whether an embryo is normal euploid, mosaic, or abnormal aneuploid. That this threshold concept still determines whether human embryos are utilized in IVF or disposed of, is difficult to understand. It not only raises serious ethical concerns but also questions about the worldwide regulatory environment that pretends to extend special considerations to human embryos [13]. Going forward, after 2016, PGT-A went at many IVF centers from selective add-on, when PGDIS guidelines were first published, to an integral part of the IVF cycle. It even found utilization in third-party donor egg cycles [14]. Because egg donors are young and highly selected against potential fertility problems, they, even without PGT-A, historically offer the highest pregnancy and live birth rates in IVF and, therefore, are the least in need of add-ons to IVF.

PGS 4.0
The genetic testing industry, is already working on what could be called PGS 4.0, involving so-called noninvasive chromosomal analyses of human embryos via cell-free DNA obtained from the media used to culture embryos in IVF [15]. Under the argument that by avoiding the
damages caused by embryo biopsies (by some believed to be a principal reason for poor IVF outcomes following PGT-A), several IVF centers, once again, have prematurely and without proper prior validation studies introduced noninvasive PGT-A into routine clinical practice.

Impact of PGT-A on IVF Outcomes

Since the birth of Louise Joy Brown, the first offspring conceived through IVF on July 25, 1978 in Manchester, UK [16], IVF has proven itself to be a revolutionary treatment option for most female and male infertility. So far, close to 10 million births have been reported worldwide. Its success was recognized by biologist Robert Edwards being awarded the 2010 Nobel Prize in Physiology or Medicine (his co-investigator, gynecologist Patrick Steptoe, was deceased and, therefore, not eligible) [17]. Pregnancy and delivery rates from IVF consistently increased worldwide between
1978 and 2010. After 2010, they, however, plateaued and in more recent years have actually declined. Since 2010 they reached low levels in the USA not seen since the mid-1990s. Some have attributed those declines to the many add-ons to IVF that have entered clinical practice since 2010, often based on unverified claims of improving IVF outcomes [18]. PGT-A for several reasons represents the most consequential among those add-ons (Box 3).

Two recent editorials [19,20] following publication of the long-awaited STAR trial (Single Embryo Transfer of Euploid Embryo, NCT02268786), which failed to demonstrate outcome benefits from PGT-A [21], suggested serious reconsiderations of how PGT-A is clinically utilized. Barring intervention by the FDA or from professional organizations like ASRM, a reversal of current practice patterns appears unlikely, considering the strong combined economic incentives for IVF centers and genetic testing laboratories that basically share in the fees the PGT-A procedure generates. Economic incentives are strengthened since fees for the procedure are in the USA not covered by insurance. Insurance companies, correctly, consider PGT-A an unvalidated procedure/test. Consequently, patients must pay for PGT-A out of pocket at undiscounted rates, even if their IVF cycle is covered by a medical insurance which pays IVF centers only at discounted rates.

Independent of economic interests, for biological reasons alone, PGT-A does not add outcome benefits for patients in association with IVF since it does not meet the goals of its underlying hypothesis — to improve IVF outcomes.

**Biology of Preimplantation-Stage Embryos**

Advances in single cell analyses have improved the study of preimplantation and early postimplantation embryology and contributed to major recent breakthroughs. Notably, studies have at times revealed unexpected results. For example, a totally unexpected finding was that human embryos can, pre- and postimplantation, *in vitro*, maintain normal self-organization up to at least day 14 after fertilization without any kind of maternal contributions, and probably longer (current ethical guidelines do not permit longer experimentation with human embryos) [22].

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**Box 2. The Threshold Concept**

Current worldwide PGT-A practice based on 2016 PGDIS guidelines is faulty: PGT-A currently defines embryos as either chromosomal normal (if aneuploid DNA in a single biopsy <20%), as mosaic (if aneuploid DNA is at 20–80%) or as aneuploid (if aneuploid DNA >80%). The following five reasons explain why such an approach must be invalid. (i) Findings in trophoderm and inner cell mass may diverge (arrows in Figure IA and C). The figure also demonstrates that five-cell biopsies within the trophoderm may diverge in aneuploid DNA content (arrow in Figure IB). (ii) The exact number of cells in a trophoderm biopsy is never known. Therefore, the denominator (representing 100% of DNA in a biopsy) can never be ascertained, making it impossible to determine percentages. (iii) Every trophoderm biopsy damages individual cells, resulting in spillage of DNA and contamination of neighboring cells, further demonstrating that percentages of aneuploid DNA can never be accurately determined. (iv) Biological evidence for the thresholds of 20% and 80% does not exist. The 20% threshold between normal euploid and mosaic is only based on the current sensitivity of NGS which is limited to 20% of total DNA. Lower levels are not detected. It is for this technical reason that any mosaicism up to 20% is considered euploid normal. (v) Within the mosaic range, defined as 20–80% aneuploid DNA, outcomes are similar [29,56]. To assume that thresholds of aneuploid DNA in a biopsy are predictive of IVF outcomes, therefore, is incorrect. Such an assumption is, however, especially harmful to IVF outcomes when it comes to the threshold of 80%, which unequivocally determines embryos that, based on PGDIS guidelines [54], must be disposed of.
It has been known for decades that the fetus is the product of the embryonic **inner cell mass** (representing the embryonic cell lineage), while the trophectoderm that forms the placenta is a product of the extraembryonic cell lineage. That these two cell lineages, however, process aneuploidy differently, was only recently discovered, first in the mouse \[23,24\] and, more recently, also in human embryos and gastruloids \[25\]. Those data in mice and humans act in unison, suggesting that early-stage embryos are dynamic entities and possess a self-correcting mechanism that selectively eliminates aneuploid cells, more efficiently in the embryonic than extraembryonic cell lineage.

![Diagram](https://example.com/diagram.png)

**Figure 1.** (A) Potential incongruity between a hypothetical 20% biopsy (1/5 aneuploid cells circled) and potential adjacent trophectoderm five-cell patches. Also demonstrates the difference between the trophectoderm biopsy (20%) and a hypothetical inner cell mass biopsy (arrow), where aneuploidy is 40% (4/10 cells). (B) Hypothetical mosaic trophectoderm biopsy by PGDIS guidelines with 3/5 cells aneuploid (60%), while adjacent areas in trophectoderm show a different distribution. (C) A hypothetically 100% aneuploid trophectoderm biopsy (circle), while adjacent areas demonstrate clear mosaicism, as does the inner cell mass with only 40% mosaicism (4/10 cells). Mouse \[23,24\] as well as human data \[25\] have demonstrated that up to 50% aneuploidy in inner cell mass can undergo complete self-correction.
It now appears established that aneuploid cells in a human preimplantation-stage embryo are so prevalent that their presence must be considered a physiologically normal phenomenon, with single cell studies suggesting a prevalence of aneuploidy in the low 80% [25–27]. Furthermore, it was shown that among embryos with aneuploid cells, 31% demonstrated meiotic but 74% mitotic aneuploidies [27]. Since aneuploidy in human embryos is dependent on maternal age, these percentages are likely age dependent. By days 4–5 after fertilization, maximum aneuploidy within embryos, however, starts declining, rapidly falling to 5–6% by day 7. In mice, a p-53-dependent autophagy-mediated apoptotic process eliminates aneuploid cells [24], while in human gastruloids, a cell-lineage-specific bone-morphogenetic-protein-4-dependent apoptotic process offers self-correction downstream [25]. This suggests apoptosis as an active process in eliminating aneuploidy and acting as a self-correcting mechanism and weakening the assumption that all aneuploid embryos need to be eliminated.

PGT-A Is Built on Misconceptions

A Single Biopsy Cannot Represent the Whole Embryo

The previously-noted observations that most aneuploidy at preimplantation stages is mitotic in origin are relevant for the better understanding of currently existing conflicts over PGT-A and IVF practice. If most aneuploid cells in a preimplantation-stage embryo undergoing trophectoderm biopsy are of mitotic rather than meiotic origin, for biological reasons alone, a five or six cell trophectoderm biopsy cannot represent the whole embryo or even the whole trophectoderm [28]. While meiotic aneuploidies are present in all cells and, therefore, even in a small trophectoderm biopsy result in 100% aneuploid DNA, mitotic aneuploidies are clonal and, therefore, in such a small biopsy may at random lead to a result of 0–100% aneuploid DNA (Box 2).

Mosaic biopsy results according to PGDIS guidelines [54], therefore, must be differentiated from what biologically represents a mosaic embryo. In other words, the PGDIS definition of mosaicism
is misleading. By PGDIS criteria, a truly mosaic embryo may under two circumstances actually have a completely normal PGT-A biopsy: (i) if the amount of aneuploid DNA in the biopsy is between 1 and 19% and, therefore, below detection levels for current NGS platforms; (ii) if the embryo may have no aneuploid cells (DNA) among biopsied cells but does have clonal aneuploidy elsewhere in the trophoderm or even inner cell mass. In contrast, any amount of aneuploid DNA in a single five or six cell trophectoderm biopsy must represent a mitotic–mosaic embryo. Moreover, the possibility that an embryo is meiotic–aneuploid only exists if 100% of the biopsy’s DNA is aneuploid and, even then, as mathematical modeling demonstrates, there is no certainty that the whole embryo is aneuploid \[28\]. Even under the most favorable assumption of even distribution of aneuploid cells, reaching such certainty would require an excess of 28 trophectoderm cells in a single trophectoderm biopsy. This is a thought experiment, but not an option if the embryo is to survive. Thus, for most basic biological reasons, a single trophectoderm biopsy can never with certainty determine whether a human embryo is euploid, mosaic or fully aneuploid. Consequently, PGT-A should not be permitted to determine whether an embryo is transferrable into a uterus or must be disposed of.

Self-Correction Could Eliminate Aneuploidy
That fact that human embryos can to significant degrees self-correct downstream from blastocyst stage offers further reason to question the utility of PGT-A. Even assuming a biopsy result at blastocyst stage is technically correct in reporting aneuploidy, one can still not be certain that this represents the final fate of the embryo as a fetus. First, a trophectoderm biopsy may not reflect ploidy of the inner cell mass (embryonic cell lineage). Second, even assuming that to be the case, one cannot be certain that the embryonic cell lineage will not self-correct downstream \[25\]. In other words, after receiving a diagnosis from PGT-A suggesting mosaicism or aneuploidy, the likelihood of a false-positive diagnosis is high. Support comes from excellent pregnancy and live birth rates and low miscarriage risk following transfers of such chromosomal abnormal embryos \[9,10,28,30\]. As noted, disposals of false-positive embryos after PGT-A is especially harmful in women who produce only a few embryos. PGT-A, therefore, adversely affects IVF outcomes especially in older women and women with low functional ovarian reserve, an observation reported already in 2007 during the PGS 1.0 period \[31\].

False Claims of Low Mosaicism Rates
How prevalent a feature mosaicism is in preimplantation-stage embryos has been a hotly debated subject, with some proponents of PGT-A to this date claiming the rate to be as low as 5% \[32\]. A worldwide survey of IVF providers revealed that 46% believed the mosaicism rate at blastocyst-stage to be <10% \[33\]. False claims of low mosaicism rates have in principle three causes. (i) The wrong belief that most aneuploidy in preimplantation-stage embryos is meiotic rather than mitotic. (ii) The reliance on single trophectoderm biopsies in attempting to quantitate mosaicism in preimplantation embryos. Only meiotic aneuploidies will always be diagnosed in a single trophectoderm biopsy. How many clonal island of mitotic aneuploidies are diagnosed, of course, will increase with number of biopsies obtained. (iii) A misunderstanding of the physiological relevance of chromosome instability as an essential evolutionary feature during early developmental stages of human embryos \[34\]. Likely also stemming from oversimplified explanations of chromosomal miscarriage data, the detection of aneuploid cells was perceived as poor. From there, to the conclusion that IVF failure must be primarily a chromosomal event, was only a relative short step.

Is There a Physiological Purpose to Embryo Aneuploidy at Preimplantation Stages?
From this point on, Verlinsky’s original PGS/PGT-A hypothesis \[1\] attempted to unsuccessfully prove it for over 25 years. It failed because it, in so many aspects, contradicted most basic
biology. Although the degree of chromosomal instability in human embryos in the 1990s was not well understood, cancer genetics quickly brought chromosomal instability into focus in conjunction with invasiveness [34-36]. In the late 1970s, scientists were already intrigued by the common denominators of tumor invasiveness and tolerance versus trophoblast invasiveness and embryo tolerance by mothers, allowing invasion of an aggressive paternal semi-allograft. This was demonstrated by an early paper by Gleicher in 1979, entitled, Common Denominators of Pregnancy and Malignancy [37].

It is now increasingly obvious that such common denominators exist. Based on the suggestion that, among mammals, degree of placental invasiveness correlates to vulnerability to malignancies, evolution of placental invasiveness, and metastatic cancer growth have been recently causally linked [38]. Both may be aneuploidy dependent, as aneuploidy helps in circumventing host immune responses [39]. Aneuploid cells in human embryos were recently also shown to upregulate immune response genes [27].

Acquisition of aneuploidy apparently is a typical stage in the differentiation of human cytotrophoblasts to an invasive phenotype [40]. Although a potential connection between trophectoderm aneuploidy and embryo implantation requires further confirmation, it would also explain why aneuploidy is so prevalent in preimplantation-stage embryos but, then after implantation, rapidly almost completely disappears [25,27]. It is intriguing to speculate that selection of favorable aneuploidies could be established as helping the implantation process.

Late Breaking News
While this manuscript was under review, two papers have been published addressing the subject of PGT-A that deserve notice. An Opinion article by two prominent experts in the PGT-A arena appeared as a pre-proof posting that advocated abandonment of the term mosaicism in association with the PGT-A procedure because of questions about its clinical significance. Yet, interestingly, their conclusion was not to abandon the utilization of PGT-A but to change terminology and replace the term mosaic with intermediate copy number [41]. How, if a test lacks clinical significance, simply changing a name would change anything in clinical practice remains unclear.

Another manuscript still in press also deserves mention. It claimed that transfers of blastocyst-stage embryos before their PGT-A status was known resulted in 0% sustained pregnancy or delivery for embryos later determined by PGT-A to have been completely aneuploid. Euploid embryos achieved the usual high pregnancy rate reported by this group of investigators [42]. High sustained implantation/live birth rates (68%) were reported for embryos found to be mosaic.

This study is noted for three reasons. (i) It contradicts a considerable number of studies that knowingly transferred embryos, by PGT-A found to be chromosomal abnormal and reported excellent pregnancy and live birth rates [9,10,25,29,30,43]. (ii) Like many PGT-A studies before, it selected out favorable patients by mandating that IVF cycles produced blastocyst-stage embryos. Outcome data from favorably selected patients cannot be automatically transferred to general populations. (iii) Achieving 100% specificity for a method of embryo selection has never before been reported in IVF. Finally, the blastocysts selected for transfer in this study were chosen based purely on morphological grading. When the sustained implantation rates were compared between patient in the study group (biopsy) versus an age-matched control (no biopsy), there were no differences (48% vs 46%, respectively).

Concluding Remarks
Because of patient demand and financial incentives for IVF centers (and testing industry), widespread utilization of PGT-A will likely continue, unless a regulatory agency, like the FDA, or a

Outstanding Questions
Are there alternatives to PGT-A in testing embryos chromosomally via trophectoderm biopsy at blastocyst-stage? Yes, there are but their utility must also be questioned. Polar body biopsies at zygote stage are accurate for mosaic aneuploidies but they only represent a minority of aneuploidies [8]. Noninvasive PGT-A at blastocyst stage has been suggested [19] and is already being clinically marketed but, like prior versions of the procedure, has never been validated. Neither option, however, considers the embryos’ ability to self-correct downstream, rendering a diagnosis upstream mute.

Is there any purpose left for testing embryos genetically prior to embryo transfer? Yes, there is. For example, if a chromosomal determination is solely made for sex selection, a trophectoderm biopsy involving five or six cells will likely be accurate, although differences in sex between multiple embryo biopsies have been reported [49,50]. Similarly, embryo biopsies to diagnose single gene diseases are accurate. Improvements in IVF cycle outcomes can, however, not be achieved through PGT-A.

What is the ultimate physiological purpose of mosaicism (aneuploidy) in preimplantation-stage embryos? With almost all embryos between cleavage and blastocyst stages being mosaic or outright aneuploid (i.e., containing aneuploid cells), it appears likely that aneuploidy at these developmental stages may have a physiological purpose. Considering that aneuploidy has been established as a crucial component in tumor invasiveness, it has been suggested that aneuploidy may enhance embryo implantation.

What would be the purpose of further exploration of potential benefits of embryo mosaicism at preimplantation stages? Potential benefits would be twofold. First, for infertility treatment, a better understanding may allow embryo selection but, paradoxically, not for the current purpose of PGT-A, the exclusion of embryos from transfers, but for exactly the opposite, selection of preferred embryos for transfer. Second, for cancer therapy, under the assumption that aneuploidy...
professional organization, like ASRM, chooses to intervene demanding transparency and disclosure to patients as required by the UK Human Fertilisation and Embryology Authority. Considering the negative clinical consequences of PGT-A on IVF described previously, and ethical concerns about disposal of large numbers of human embryos with normal pregnancy potential, it is surprising that no such intervention has taken place so far.

Patient demand is produced by information that they receive from various sources, but most importantly, from their own physicians. Due to biased and often inaccurate information from the laboratory testing industry, other economically interested parties and the PGDIS, and the societal appendix of all financially invested groups in utilization of PGT-A, many physicians in the IVF field are themselves misinformed. They, therefore, unwittingly pass incorrect information on to their patients. As this incorrect information is increasingly counterbalanced in the literature [19,20] and in the media, patient demand can be expected to recede.

As noted (Box 1), embryo biopsy only unlikely causes enough damage to embryos to invalidate potential outcome advantages of PGT-A, as has been suggested by a prominent voice in the debate [44]. As described here in detail, principal causes for the failure of PGT-A over at least three generations of PGS/PGT-A to improve IVF outcomes are likely the incompatibility of the PGS/PGT-A hypothesis with biological realities in preimplantation-stage human embryos. The realities of mosaicism and self-correction of embryos downstream are not changed by avoiding potential damage from embryo biopsies. Moreover, noninvasive diagnoses, by themselves, create new technical problems, as noted elsewhere [45]. We, therefore, concur with recently expressed opinions that PGT-A, at minimum, should be restricted to women who produce good embryo numbers [19] and, more likely, only to experimental protocols [20]. ASRM’s Practice Committee also again reaffirmed PGT-A’s lack of clinical utility [60].

Although there is consensus that human embryos are deserving of special consideration in research [13], such ethical considerations are obviously absent when large numbers of human embryos with normal pregnancy and live birth potential are not used because of the diagnostic inadequacy of PGT-A.

However, assuming aneuploidy to be an adjuvant to implantation, the paradox of PGT-A comes into even better focus, as PGT-A and its forerunners were really conceived with the purpose of eliminating embryos with aneuploid cells. If aneuploidy can now be established as helping the implantation process, PGT-A may, finally, find a clinical purpose, although different from its original purpose (see Outstanding Questions). That purpose would, indeed, be exactly the opposite, to select out for transfer embryos with selected favorable aneuploidies for implantation.

Resources

http://pgdis.org/docs/newsletter_071816.html

1. www.ccrmivf.com/news-events/non-invasive-pgt/
2. www.newhopefertility.com/genetic-testing/non-invasive-chromosomal-screening-nics/

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