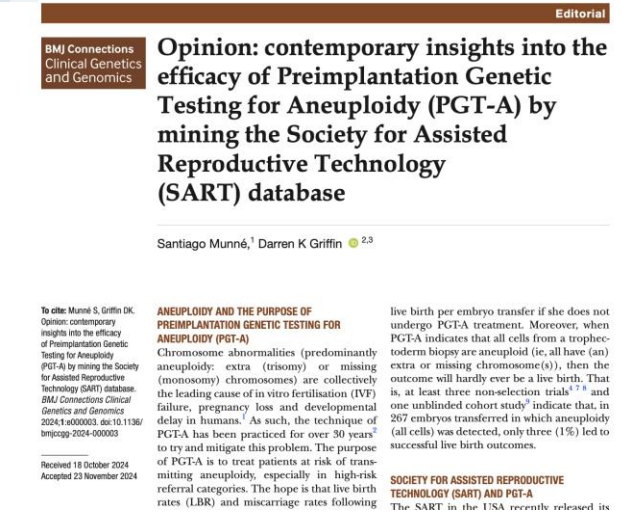
# What Does SART tell us about PGT-A?

# A Reanalysis of the Most Recent Dataset

Santiago Munné[1], Darren K Griffin[2,3]

1. Progenesis, 4150 Regents Park Row, Suite 245, La Jolla, CA 92037
2. School of Biosciences, University of Kent, Canterbury, Kent, CT2 7NZ, UK
3. Faculty of Science, Kasetsart University, Chatuchak, Bangkok 10900, Thailand



Editorial

BMJ Connections Clinical Genetics and Genomics

**Opinion: contemporary insights into the efficacy of Preimplantation Genetic Testing for Aneuploidy (PGT-A) by mining the Society for Assisted Reproductive Technology (SART) database**

Santiago Munné,[1] Darren K Griffin [2,3]

**To cite:** Munné S, Griffin DK. Opinion: contemporary insights into the efficacy of Preimplantation Genetic Testing for Aneuploidy (PGT-A) by mining the Society for Assisted Reproductive Technology (SART) database. *BMJ Connections Clinical Genetics and Genomics* 2024;1:e000003. doi:10.1136/bmjcgg-2024-000003

Received 18 October 2024
Accepted 23 November 2024

**ANEUPLOIDY AND THE PURPOSE OF PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A)**

Chromosome abnormalities (predominantly aneuploidy: extra (trisomy) or missing (monosomy) chromosomes) are collectively the leading cause of in vitro fertilisation (IVF) failure, pregnancy loss and developmental delay in humans.[1] As such, the technique of PGT-A has been practiced for over 30 years[2] to try and mitigate this problem. The purpose of PGT-A is to treat patients at risk of transmitting aneuploidy, especially in high-risk referral categories. The hope is that live birth rates (LBR) and miscarriage rates following live birth per embryo transfer if she does not undergo PGT-A treatment. Moreover, when PGT-A indicates that all cells from a trophectoderm biopsy are aneuploid (ie, all have (an) extra or missing chromosome(s)), then the outcome will hardly ever be a live birth. That is, at least three non-selection trials[3–5] and one unblinded cohort study[6] indicate that, in 267 embryos transferred in which aneuploidy (all cells) was detected, only three (1%) led to successful live birth outcomes.

**SOCIETY FOR ASSISTED REPRODUCTIVE TECHNOLOGY (SART) AND PGT-A**

The SART in the USA recently released its

- **Amritsar, India, 1993**

# Contemporary Insights into the Efficacy of PGT-A by Mining the SART Database

- Aneuploidy and the purpose of PGT-A
- SART and PGT-A
- Does PGT-A “work” and by what measure?
- Implantation rates and PGT-A
- PGT-A and pregnancy loss
- Miscellaneous points
- Conclusions

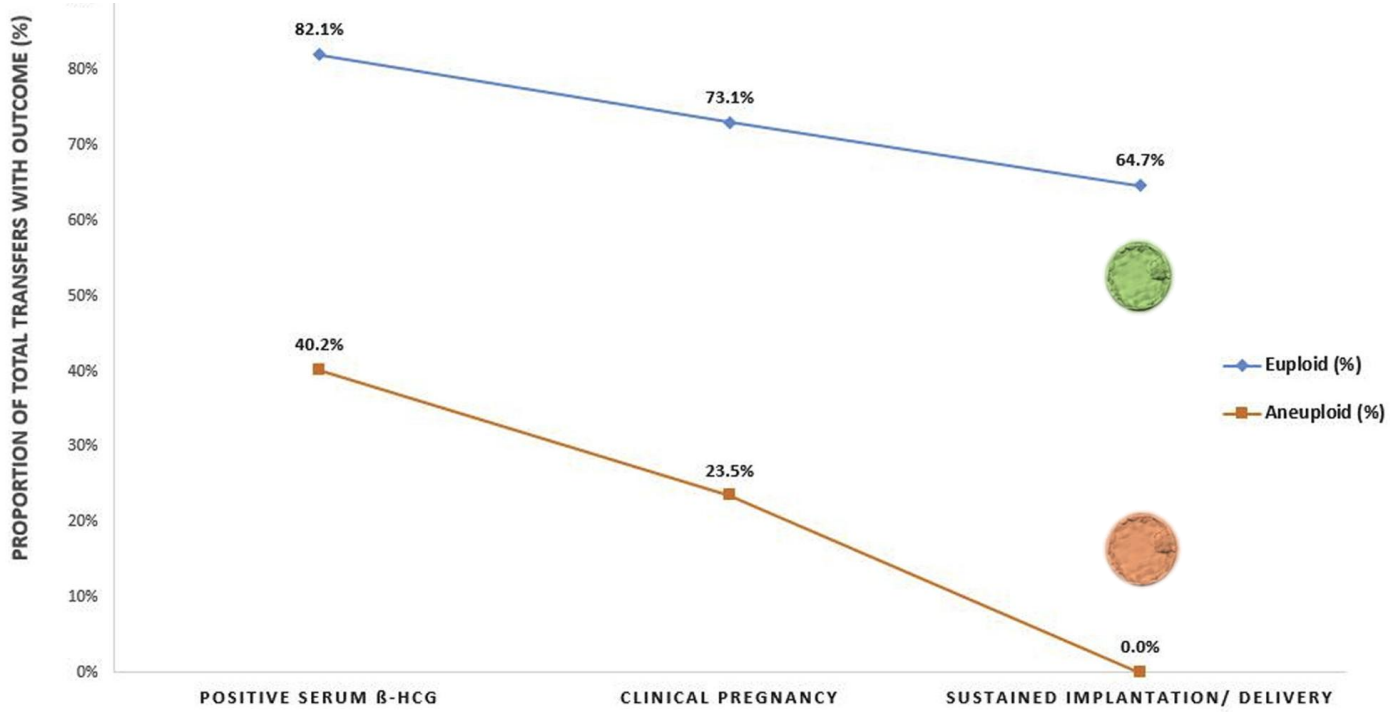
# Contemporary Insights into the Efficacy of PGT-A by Mining the SART Database

- Aneuploidy and the purpose of PGT-A
- SART and PGT-A
- Does PGT-A “work” and by what measure?
- Implantation rates and PGT-A
- PGT-A and pregnancy loss
- Miscellaneous points
- Conclusions

# Aneuploidy – Extra or Missing Chromosomes

| | |
|---|---|
| **The** leading cause of developmental delay in humans | • 1 in 700 children born with Down Syndrome |
| **The** leading cause of pregnancy loss | • ~80% of all first trimester losses are aneuploid<br>• Trisomy 16, 21, 22, monosomy X |
| **A** leading cause of obstetric complications | • 5% of stillbirths (trisomy 21, 18, 13, 22, 9)<br>• Intrauterine growth retardation/death (IUGR, IUD), high/low birth weight |
| Can lead to imprinting syndromes through uniparental disomy | • Prader Willi, Angelman |
| A/The leading cause of (repeated) IVF failure | |
| **The major reason for lack of implantation potential with age** | |

**Theoretically PGT-A should be a “no-brainer”**




Euploid diagnosis (5/5 cells normal)

- 64.7% chance of live birth
- 8% chance of miscarriage

Aneuploid Diagnosis (5/5 cells aneuploid)

- ZERO % chance of live birth (maybe 1%)
- 23.5% chance of miscarriage

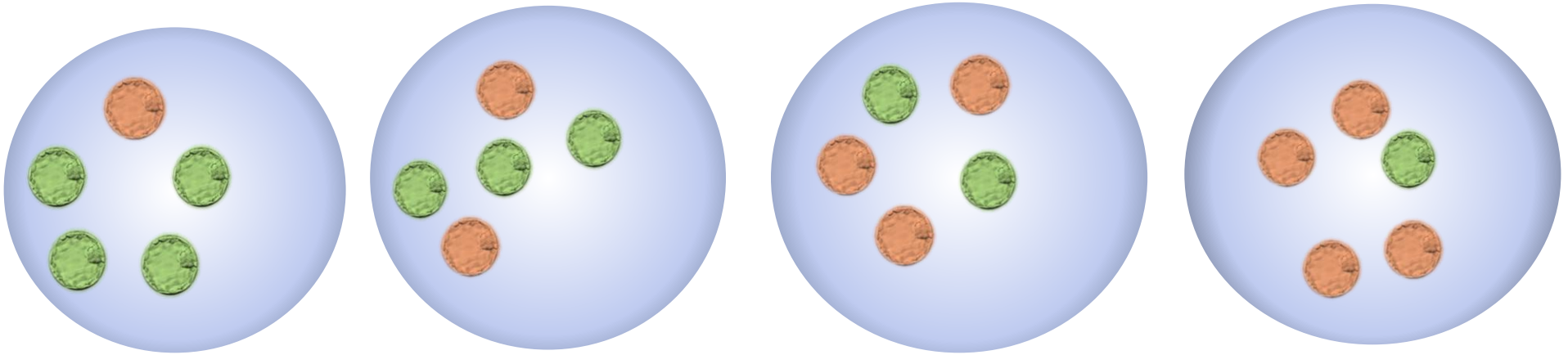
- The literature (post 2020) has 267 uniformly aneuploid diagnoses that were transferred
- **<u>THREE led to live birth (~1%)</u>**
- And they may be misdiagnoses

Tiegs et al Vol. 115, No. 3, March 2021,
Wang et al Prenatal Diagnosis. 2021;41:1709–1717.
Yang et al Nature cell Biology Vol 23 April 2021, 314-321
Barad et al Human Reproduction, Vol.37, No.6, pp. 1194–1206, 2022

# The Dilemma of a Prospective PGT-A Patient

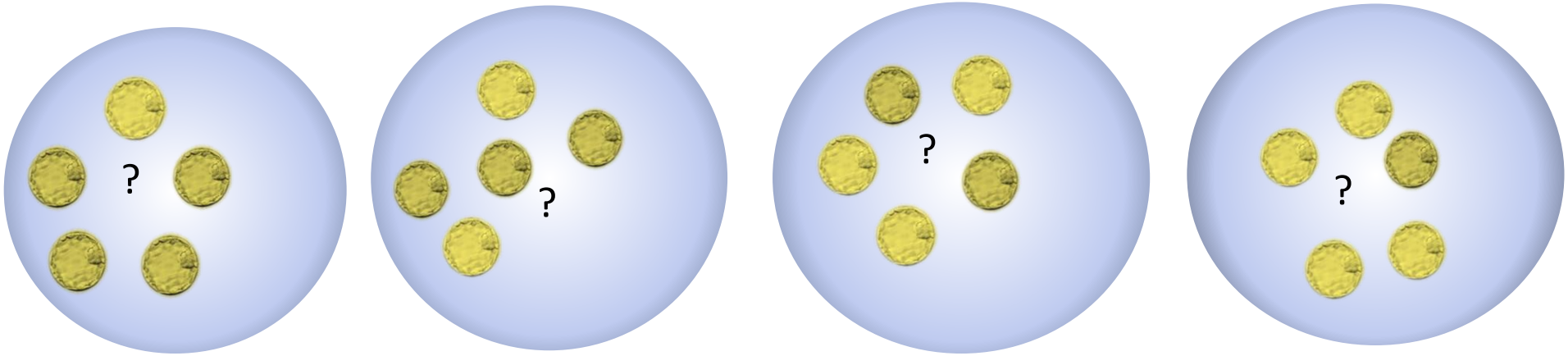
**With PGT-A**

25 year old | 30 year old | 35 year old | 40 year old



**Without PGT-A**

25 year old | 30 year old | 35 year old | 40 year old




# Method of Analysis

- The SART data for 2022 can be found online at https://sartcorsonline.com/Csr/Public?ClinicPKID=0&reportingYear=2021&newReport=True

# SART and PGT-A

- **Non-selection trials (NSTs) and Randomized clinical trials (RCTs)**
  - Outcome is blinded to both patient and practitioner at time of treatment
  - RCTs and NSTs are very expensive and difficult to reach large numbers needed to establish trend for younger patients
- **Society for Assisted Reproductive Technology (SART)**
  - SART database provides these large numbers
  - For 2022: there were 82,291 PGT-A retrievals (60% of the total) and 56,290 non-PGT (40%)
  - Extremely large numbers

# Contemporary Insights into the Efficacy of PGT-A by Mining the SART Database

Aneuploidy and the purpose of PGT-A

SART and PGT-A

**Does PGT-A “work” and by what measure?**

Implantation rates and PGT-A

PGT-A and pregnancy loss

Miscellaneous points

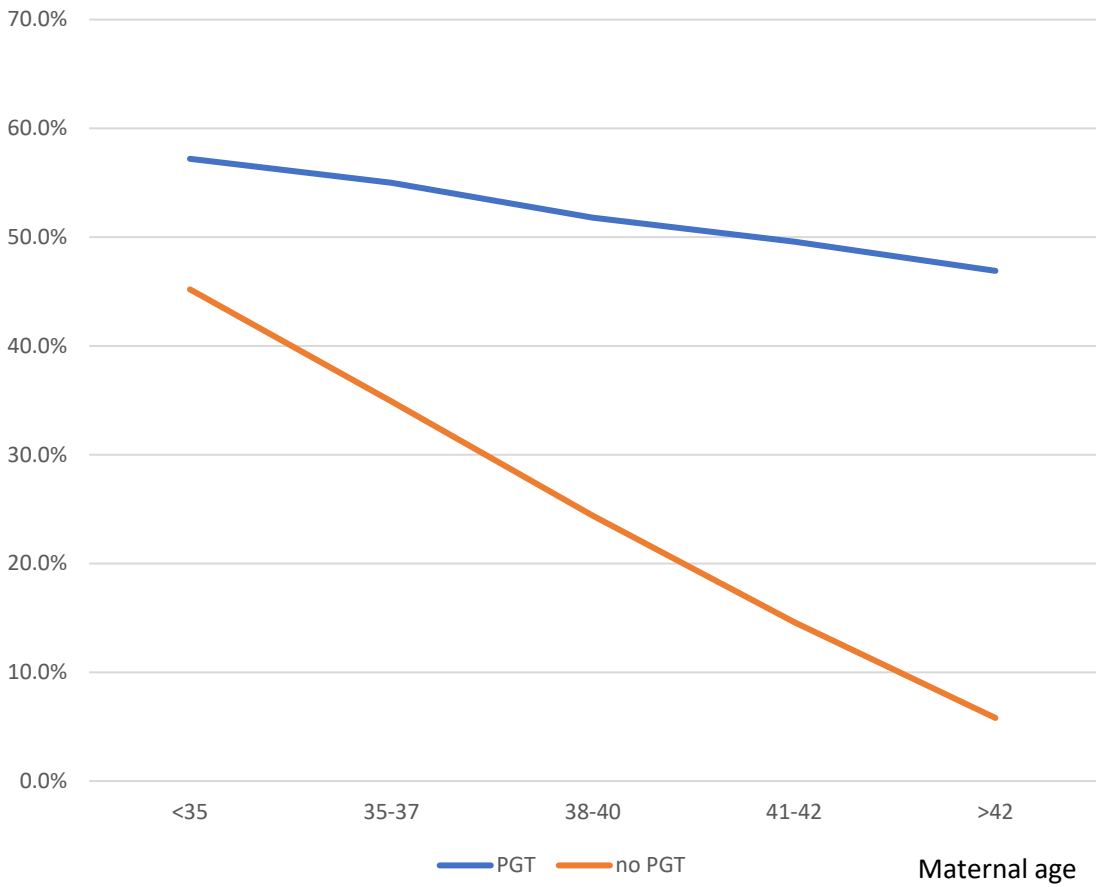
Conclusions

# Does PGT-A "Work" and by What Measure?

- Need to **consider carefully what we are measuring**
- Most RCTs focus attention on cumulative LBR
  - Not theoretically, anything that PGT-A can, nor was ever designed to, improve!
- LBR per treatment cycle
  - Theoretically similar to cumulative LBR
    - But all embryos in one cycle only
  - Possible improvement if time scale is put on counting (e.g. 6 months to pregnancy)
- **LBR per embryo transfer <u>much better</u> with PGT-A than without, even in younger patients**

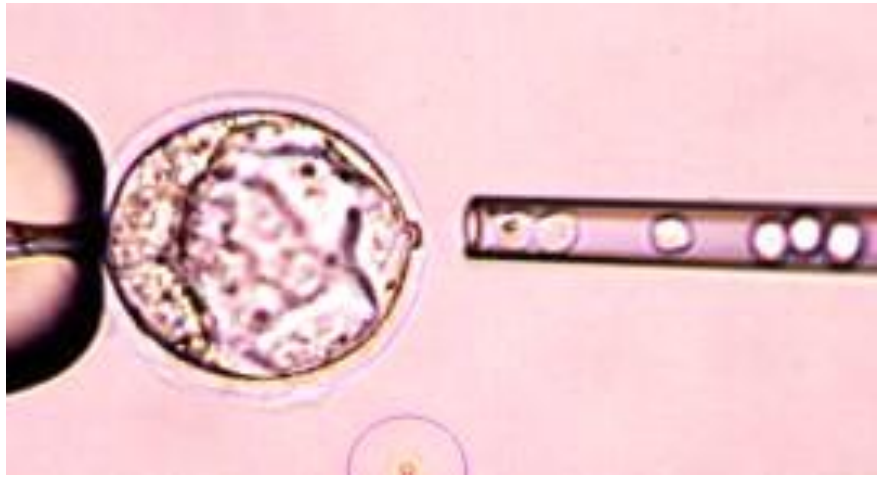
# Live Birth Rate Per Embryo Transfer

- With PGT-A - small decrease in LBR per embryo transfer associated with maternal age
  - 57.2% in <35 years - 49.6% at >42 years
- Without PGT-A – several-fold decline
  - 45.2% (<35) to 6.5% (>42)
- Even in younger patients (<35), LBR per embryo transfer
  - Significantly higher ($p<0.001$) when using PGT-A than when not
- PGT-A in >42 better than no PGT-A <35



# In a Nutshell

- Is PGT-A effective in improving LBR?
  - For cumulative LBR - no
  - For LBR per treatment cycle - maybe
  - For LBR per embryo transfer - yes



# Contemporary Insights into the Efficacy of PGT-A by Mining the SART Database

Aneuploidy and the purpose of PGT-A

SART and PGT-A

Does PGT-A “work” and by what measure?

**Implantation rates and PGT-A**

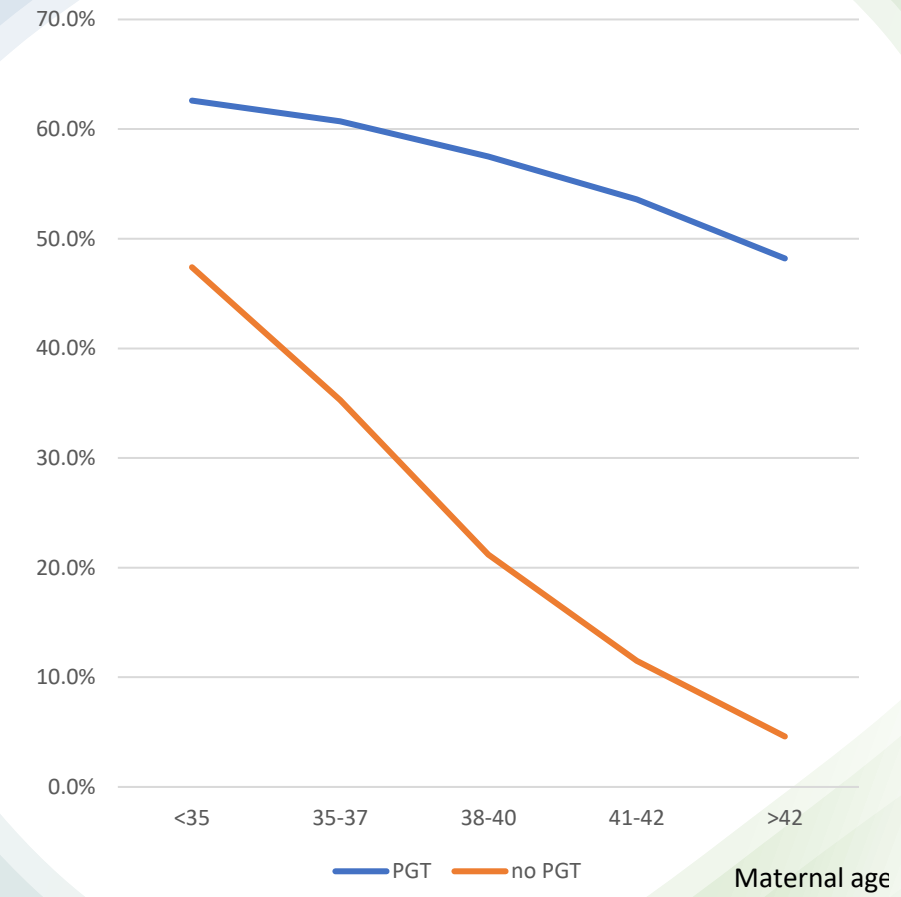
**PGT-A and pregnancy loss**

Miscellaneous points

Conclusions

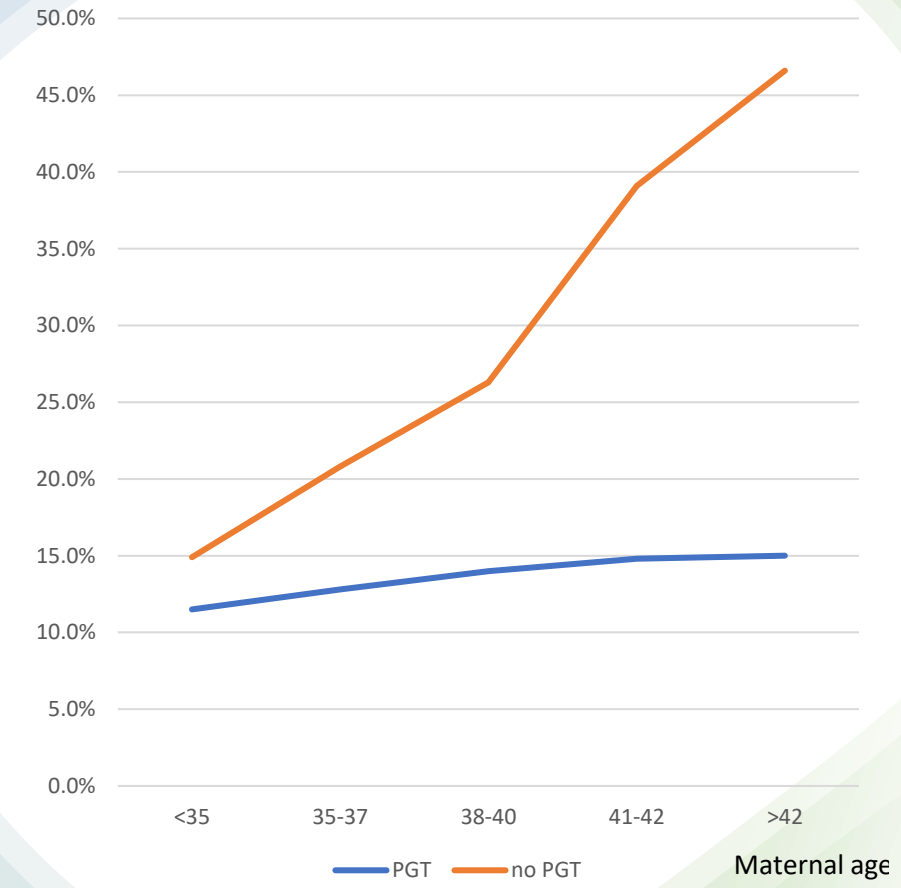
# Implantation Rates and PGT-A

- **Implantation rates only minimally decrease with advancing maternal age if PGT-A used**
- Implantation rates higher after PGT-A **even in young patients** <35
  - (62.6% vs 47.4%, p<0.001)
- >42 year-old
  - higher implantation rate with PGT-A (48.3%)
  - than a <35 year old without (47.4%)



# PGT-A and Pregnancy Loss

- **PGT-A reduces the chance of pregnancy loss**
  - With PGT-A - Miscarriage rate rises only marginally with age
    - 11.5% vs 14.8%
  - Without PGT-A - ***it more than trebles***
    - 14.9% - 46.1
- >42 with PGT-A (14.8%) nearly identical to <35 not (14.9%)
- Younger patients - significant benefit of PGT-A
  - Could only be observed with a large dataset like SART
  - 11.5% PGT-A vs. 14.9% not
  - Though small, is significant ($p<0.01$)
  - Similar in magnitude to combining all RCTs



**Tony Gordon** · 1st
Senior Director of Clinical Strategy and Market Devel...
2yr · Edited

Were 8500 miscarriages avoided with PGT-A?

It's great to see the first snapshot analysis of the 2022 SART preliminary data by **Santiago Munne** and **Darren Griffin**. It's free to access at **https://lnkd.in/gpis8zVm**. There will be more analysis of this dataset no doubt but it did get me thinking, especially Figure 3 (see below). So doing my "back of the envelop analysis" of miscarriage rates with PGT-A (82K cycles intended retrieval) and (56K) without PGT-A. What would have happed to those 82K cycles if they hadn't had PGT-A?

I haven't run the stats yet, but the numbers are huge for this dataset and the differences are clear.

The difference in miscarriage rates are stark for the all age groups over 35yrs

eg. 35-37yr - PGT-A 12.9 vs non-PGT-A 20.8
eg. 41-42yr - PGT-A 14.8 vs non-PGT-A 39.0

The 56K non-PGT-A cycles resulted in 17.6K miscarriage
The 82K PGT-A cycles resulted in 10.5K miscarriage.

So what if we hadn't performed PGT-A on those 82K cycles? Well we would have seen an additional 8.5K miscarriage (assuming the non-PGT-A miscarriage rate for each age group. The PGT-A group had a slightly lower proportion of patients over 38yrs than the non-PGT-A group hence why this isn't higher at the same overall % as the non-PGT-A group).

Sometimes we look at the numbers from papers without considering the individual impact. No doubt we will still argue about the usefulness of PGT-A (no it doesn't improve cumulative LBR if you transfer every embryo in a cycle) but the effectiveness on the reduction the number of miscarriages is clear. On a individual level the impact is huge.

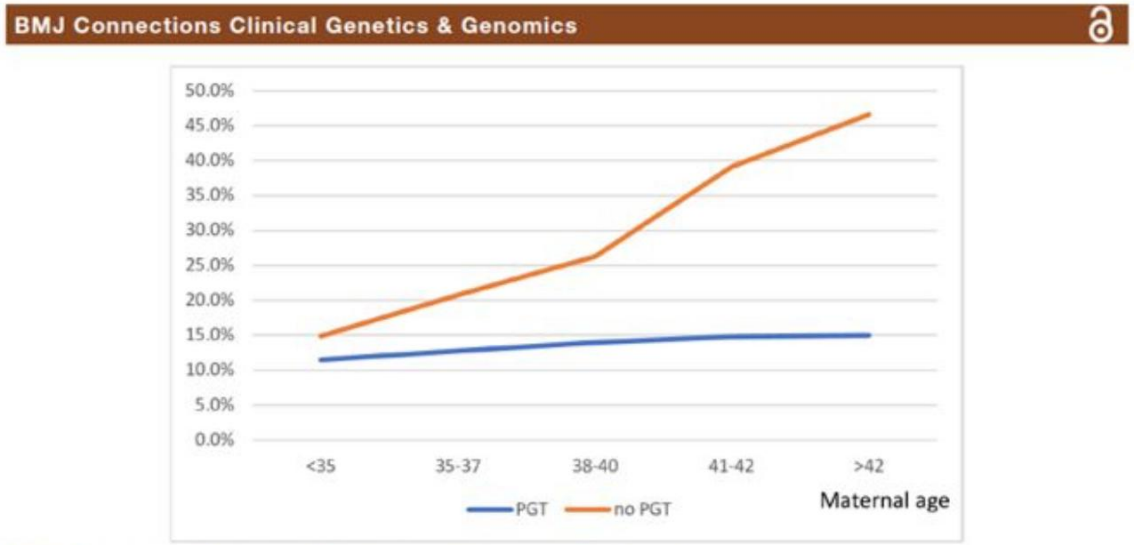



Figure 3 Miscarriage per maternal age. PGT, preimplantation genetic testing.

# Contemporary Insights into the Efficacy of PGT-A by Mining the SART Database

Aneuploidy and the purpose of PGT-A

SART and PGT-A

Does PGT-A “work” and by what measure?

Implantation rates and PGT-A

PGT-A and pregnancy loss

**Miscellaneous points**

**Conclusions**

# Miscellaneous Points

**PGT-A is not experimental**

**Standard of care** now in most (59.4%) IVF treatments in US

**Proportion varies from country to country**

Some clinics now use it routinely in all IVF cycles

**No room for complacency**

PGT-A is not 100% accurate and has 0-4% misdiagnosis rate

**Results could be improved further**

Suboptimal biopsy (which can lead to poor genetic results or embryonic arrest)

Maternal cell contamination

**Mosaicism**

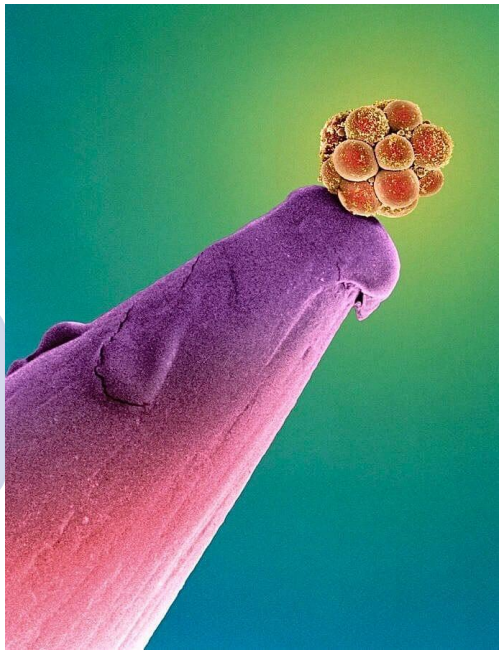
Where mosaicism appears in the biopsy, live birth can still ensue

> proportion of abnormal cells = less likely chances of live birth

**Biopsies harbouring mostly euploid cells**

Very little difference in LBR compared to biopsies where no aneuploidy found at all

# Conclusions



**PGT-A is a selection tool**

- Not designed to improve cumulative LBRs

**PGT-A prevented 8,500 miscarriages in one year**

**PGT-A works for all patients except those that do not produce enough blastocysts from which to select**

- Even with a single embryo it might be argued that knowing whether it has a 1% or a 65% chance of live birth is money well spent

**Cost-benefit**

- Average IVF cycle is $20,000 in the USA, average PGT-A is an additional $2,500
- More embryo transfers without PGT-A also lead to more cost
- Cost-benefit ratio needs to be considered

# What Does a Patient Want to Know?

## Question

- Will I get pregnant eventually?
- Will this transfer lead to live birth?
- Will I suffer pregnancy loss?
- How soon will I get pregnant?
- How much will it cost?
- How “satisfying was the experience?

## Outcome measure

- Cumulative LBR (LBR per cycle)
- LBR per embryo transfer
- Miscarriage rate
- Time to first pregnancy
- Varies per clinic and “package”
- Patient-dependent

# Does PGT-A Help?

| Outcome measure | Benefit of PGT-A? |
| --- | --- |
| • Cumulative LBR | • No |
| • LBR per cycle | • Subject of some debate |
| • LBR per embryo transfer | • Definitely |
| • Miscarriage rate | • Almost certainly |
| • Time to first pregnancy | • Yes |
| • Cost and satisfaction | • If cost of extra ET exceeds cost of PGT-A, and taking into account all the above |

# Some Feedback

**Lodovico Parmegiani** · 1st
Embryologist, Author, Founder, TEDx speaker. Head...
2w ·

"PGT-A should perhaps be recommended for all patients except those that do not produce enough blastocysts from which to select "
Thank you Santiago Munne and Darren Griffin this is the article we were waiting for. Wonderful!


**Kaj Rydman** · 2nd + Follow
A Finn, first and foremost. Helping ferti...
2w ·

An important contribution by Santiago Munne and Darren Griffin to what seems like an eternal discussion about PGT-A. As everyone knows, I can claim no scientific background, but I do have some experience about logical argument. I've noticed a familiar pattern in discussions about new reproductive technologies like PGT-A. Early on, there's a lot of excitement and big promises—sometimes overselling what the technology can really achieve. In response, some critics push back, and occasionally their counterarguments overshoot, taking down claims that were never actually made.