

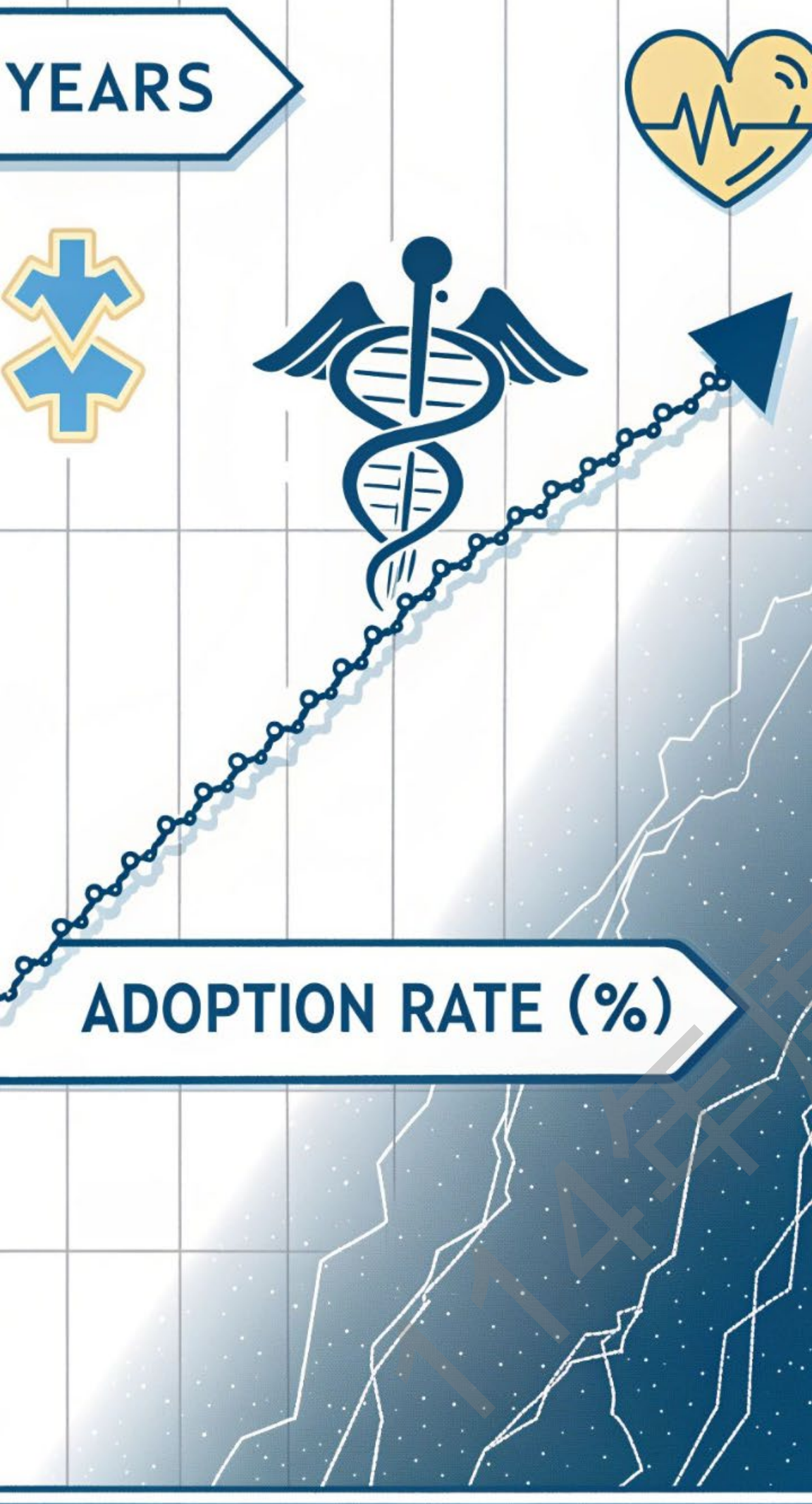
Do infertile couples or recurrent pregnancy loss would benefit from use of **PGT-A**



成大醫院 陳達生醫師

[LINK](#)





使用PGT-A比例越來越高

14%

2014 Usage

Percentage of IVF cycles using PGT in the United States

44%

2019 Usage

Dramatic increase in PGT utilization over five years

對懷孕真的有幫忙嗎?

The use of preimplantation genetic testing for aneuploidy: a committee opinion

Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

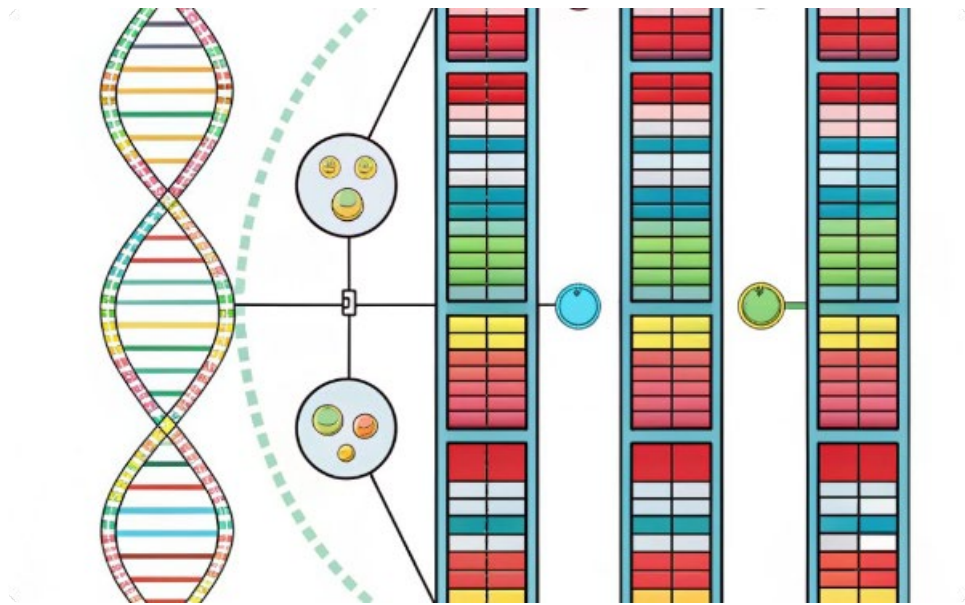
American Society for Reproductive Medicine, Washington, DC

The use of preimplantation genetic testing for aneuploidy (PGT-A) in the United States has been increasing steadily. Moreover, the underlying technology used for 24-chromosome analysis continues to evolve rapidly. The value of PGT-A as a routine screening test for all patients undergoing in vitro fertilization has not been demonstrated. Although some earlier single-center studies reported higher live-birth rates after PGT-A in favorable-prognosis patients, recent multicenter, randomized control trials in women with available blastocysts concluded that the overall pregnancy outcomes via frozen embryo transfer were similar between PGT-A and conventional in vitro fertilization. The value of PGT-A to lower the risk of clinical miscarriage is also unclear, although these studies have important limitations. This document replaces the document of the same name, last published in 2018. (*Fertil Steril*® 2024;122:421–34. ©2024 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

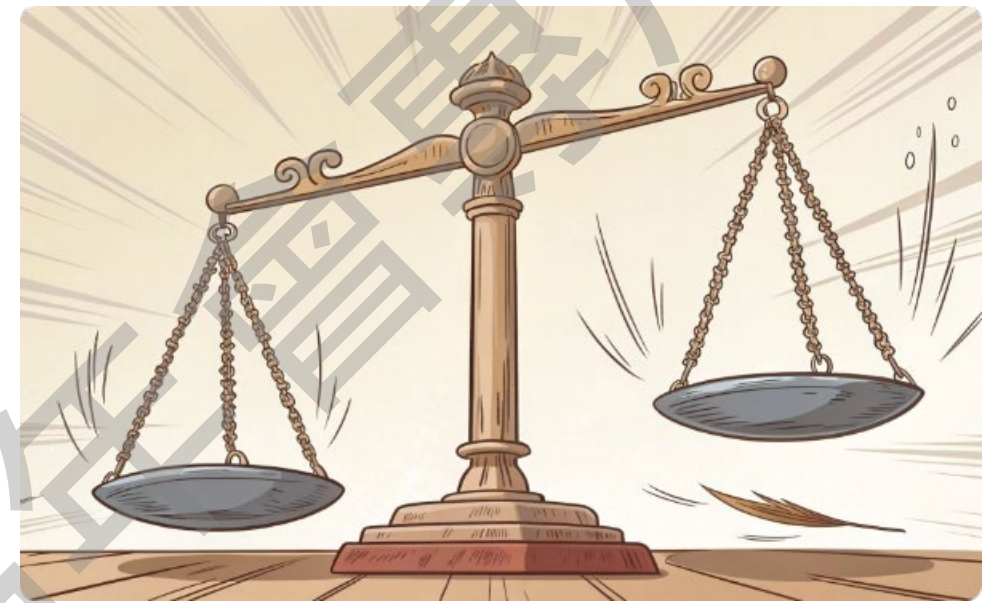
Key Words: Reproductive medicine, PGT, PGT-A, reproductive science, aneuploidy

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PGT-A原理

好處與壞處



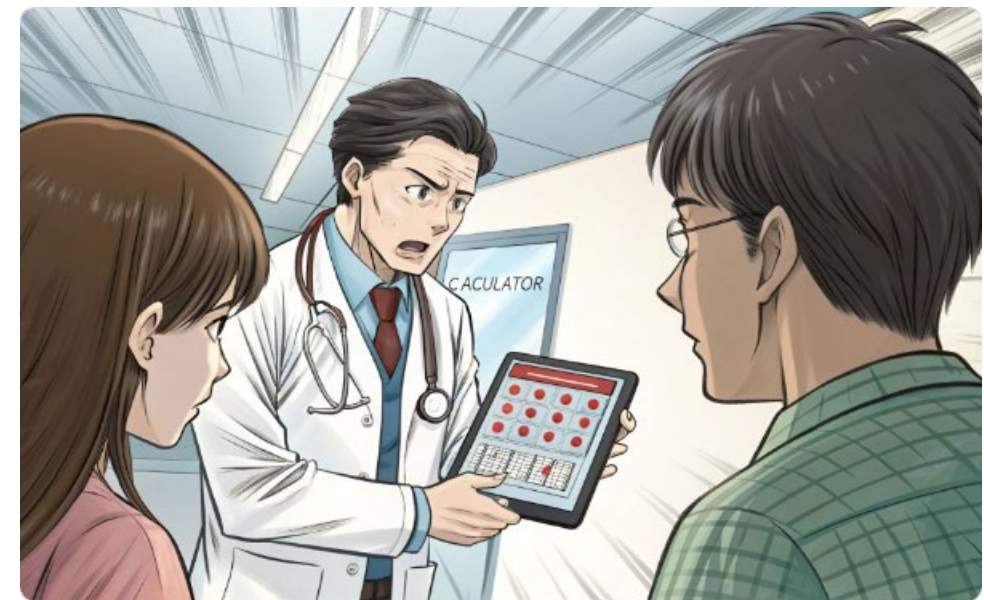
PGT-A對誰有幫助

EBM、效益面、心態面



PGT-A vs. RPL

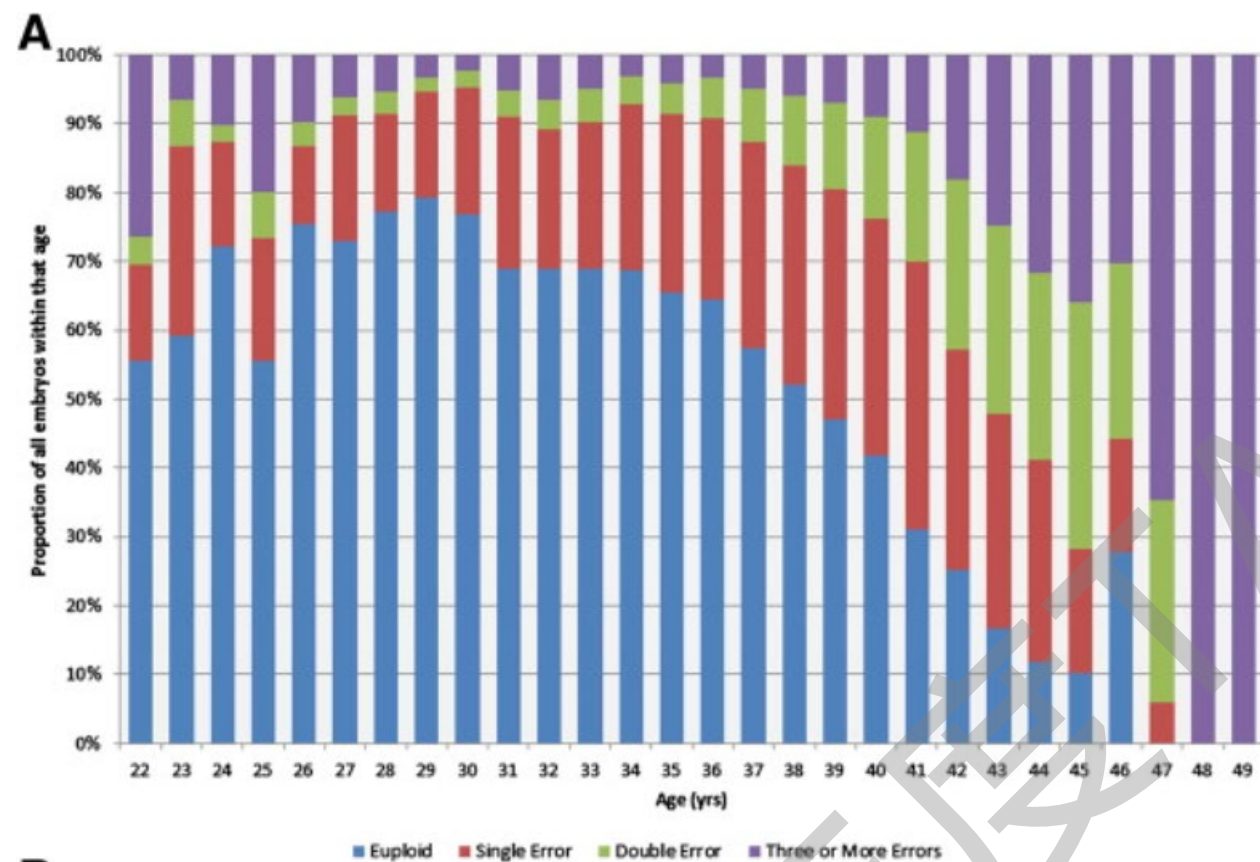
RPL原因的探究



Decision Calculator

個人化決策工具的應用

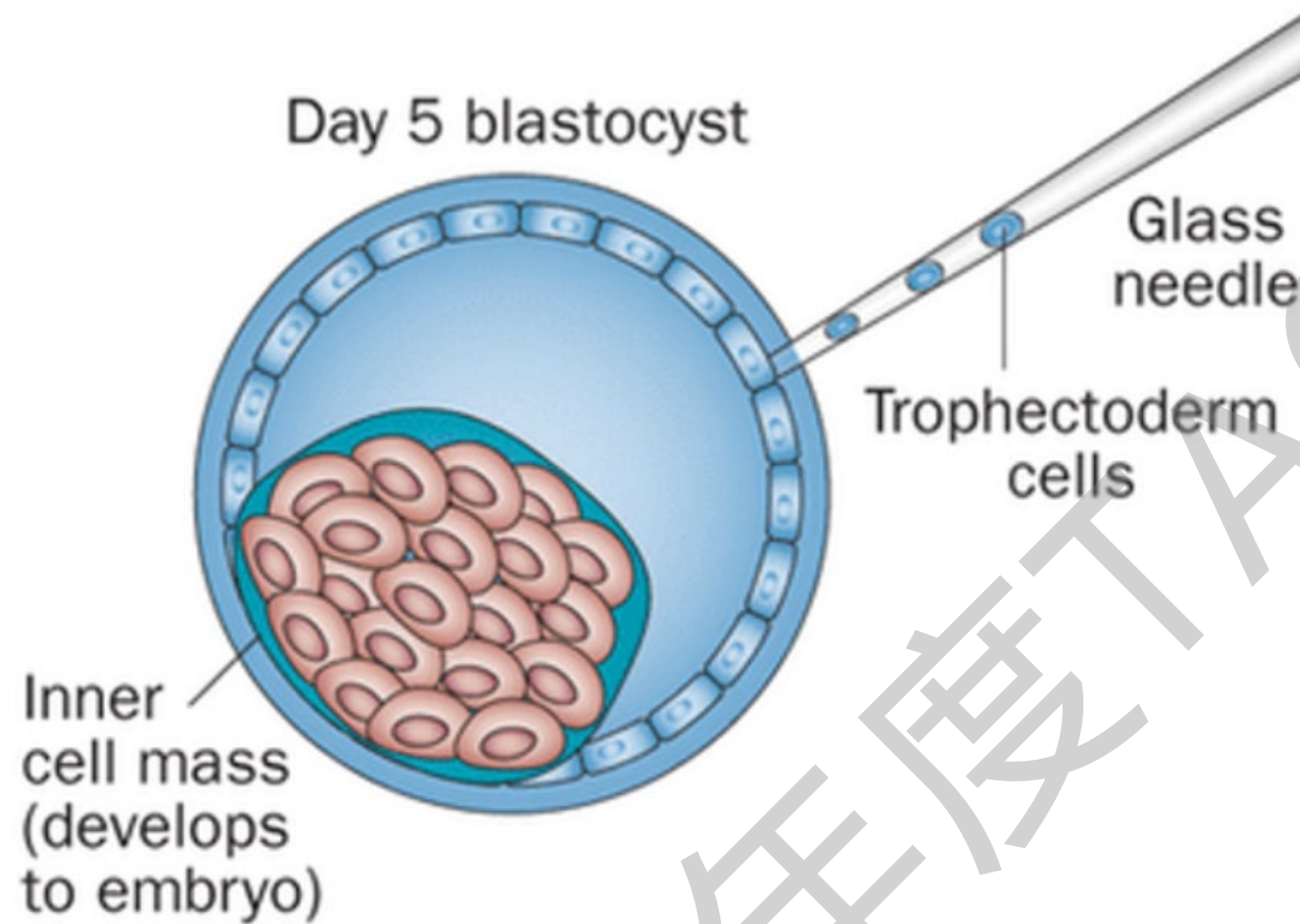
Why to Select Embryos



- Morphology-based grading
- Omics, time-lapse imaging also help
- **PGT-A**
 - 隨著年齡Euploidy Rate急劇下降
 - (40歲的Blastocyst僅有4成正常)
 - 外型與Euploid不一定相關
 - 使用PGT-A可有效挑出Euploid Embryo
 - 僅能在現有胚胎挑出高潛力懷孕者,
 - 而非能改善胚胎

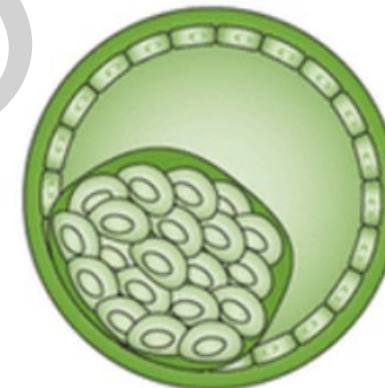
us Franasiak JM *et al. Fertil Steril* 2014;**101**:656-663.e1.

How Does PGT-A Work (Blastocyst TE biopsy as an Example) Example)



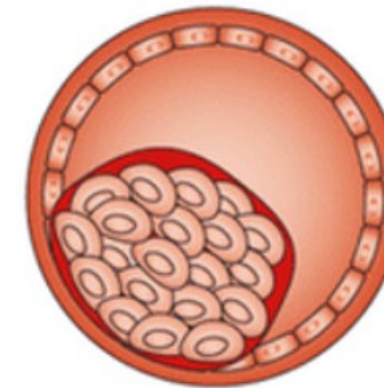
e Example PGD results

Embryo transfer
Unaffected/normal
chromosomes

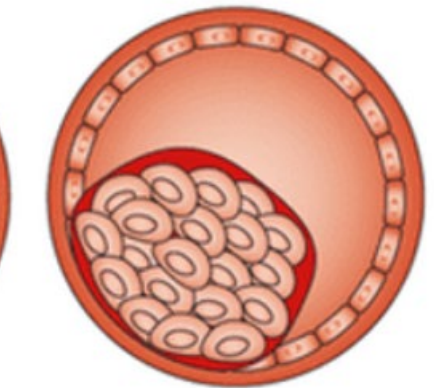


Unaffected for the
mutation and normal
for 24 chromosomes

Affected



Abnormal
chromosomes



Unaffected for the
mutation, but trisomy
chromosome 21
(Down syndrome)

PGT-A Biopsy Stages

Polar Body Biopsy

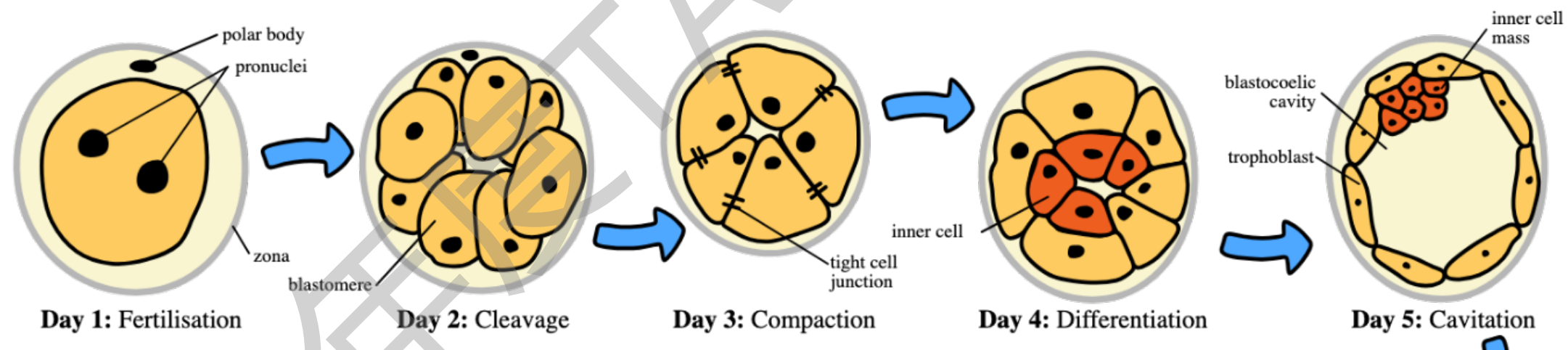
Day 0-1, less invasive
but provides limited genetic information.

Cleavage Stage

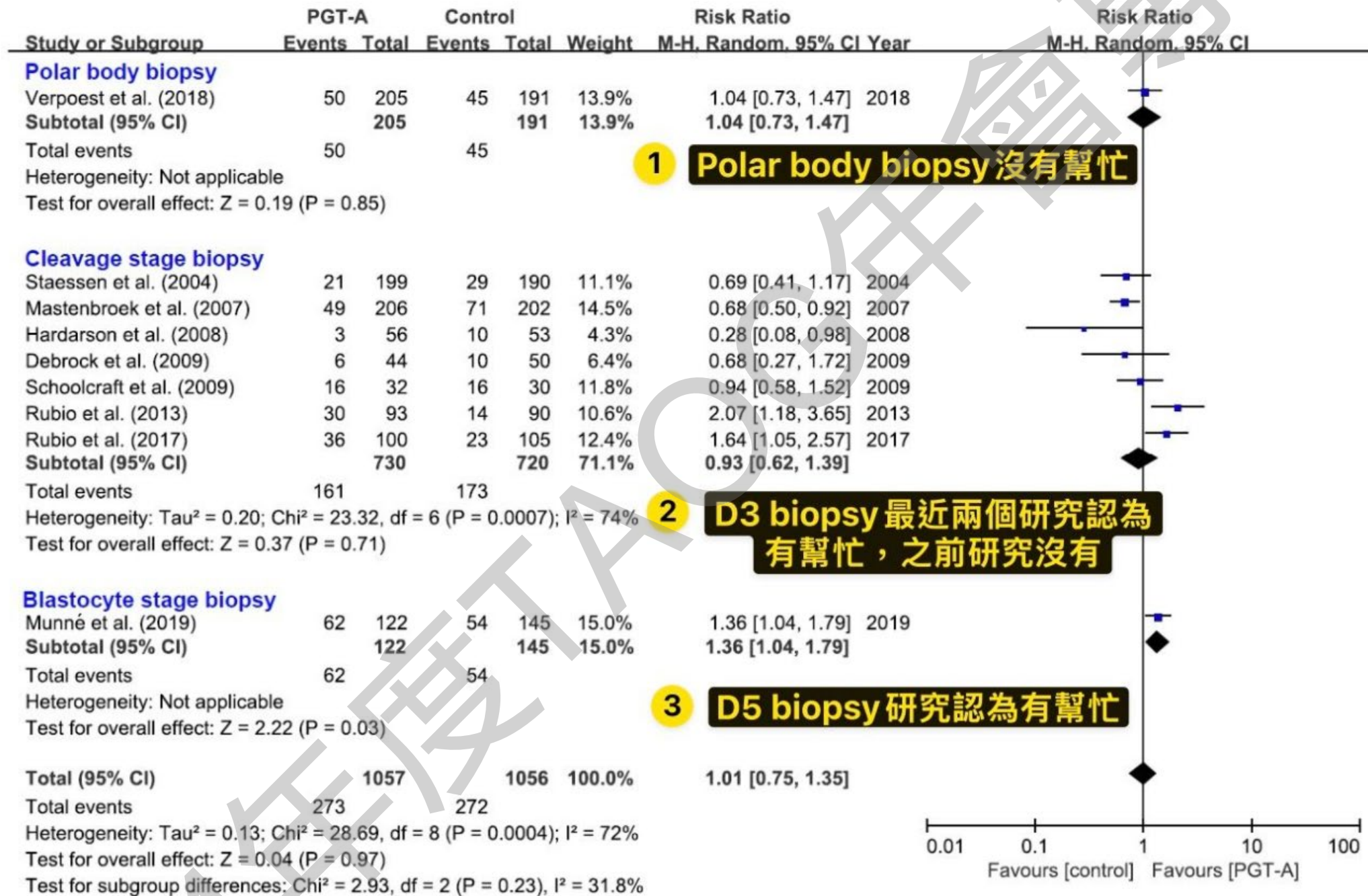
Day 3, 1-2 cells biopsied,
higher risk of embryo damage.

Blastocyst

Day 5, 5-10 cells from trophectoderm,
more accurate with less harm.



RCT 研究: PGT-A 對 LBR 有沒有幫助



Blastocyst Biopsy有實證支持, 因此我們主要討論D5-D7 Blastocyst Biopsy PGT-A cn Shi W-H et al. JCM 2021;10:3895.

Compare PGT-A Technology

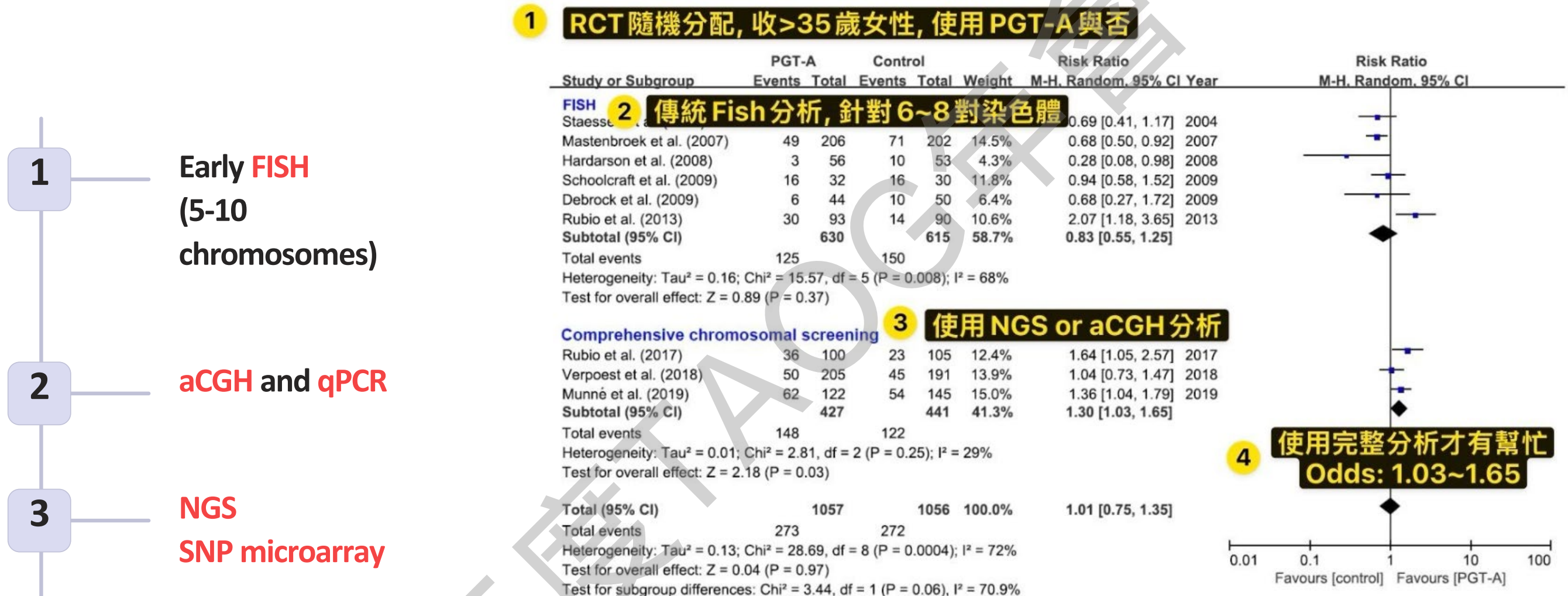


Figure 2. The effect of PGT-A with different techniques of genetic testing on live birth rate. Each study represented by a line. The square represents the point estimate of the effect for a single study, and its area is proportional to the weight of the study. The diamond represents the pooled effect estimate and the width of the diamond represents the 95% CI around this estimate.

Accuracy of PGT-A

Study	Technology	Focus	Key Findings
Fertil Steril 2012;97: 870–5	SNP-microarray PGT-A	Positive Predictive Value	96% positive predictive value
Fertil Steril 2021;115:627–37	NGS	Clinical Error Rate	No ongoing pregnancies after transferring 102 aneuploid embryos
Hum Reprod 2022;37:1194-206.	PGT-A (including mosaic)	Outcomes of abnormal embryo transfer	11 miscarriages and 8 live births from 141 abnormal embryos; poorer outcomes for complex aneuploidies

Specificity相當高

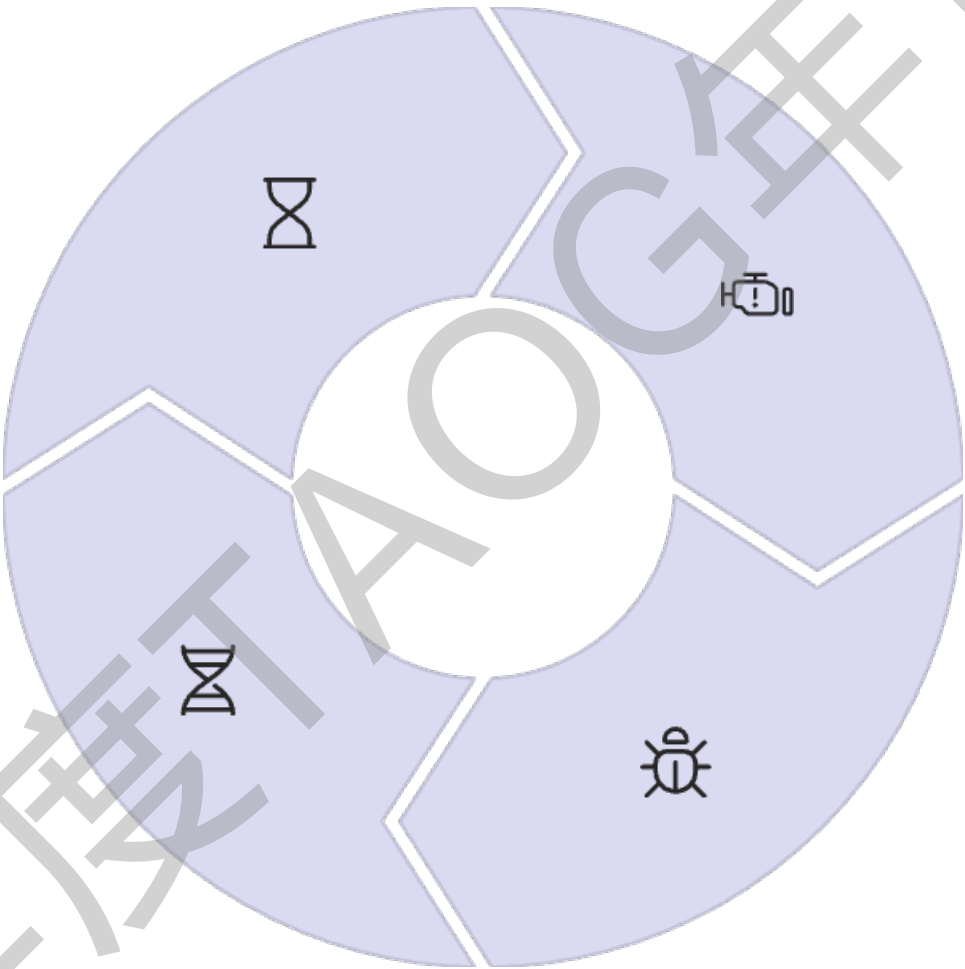
Potential Risks of PGT-A

D3 to D5 Attrition Rate
部分胚胎無法撐到D5切片
(甚至損失20% euploid embryos)

Mosaic Discard
鑲嵌型異常可能自我修正
仍可正常發育

Embryo Damage
切片造成胚胎傷害，尤其D3胚胎

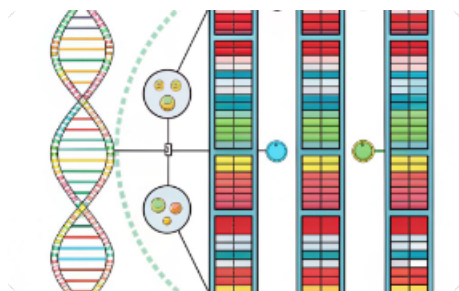
False Positives or No Signal
誤丟棄Euploid Embryo(TE與ICM差異)



us Franasia JM et al. Fertil Steril 2014;101:656-663.e1.



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Clinical Outcomes in Favorable-Prognosis Patients



Evidence Base

5 randomized controlled trials, several several retrospective cohort studies, studies, meta-analyses, and a systematic review



Pilot Study (2012)

Showed higher ongoing pregnancy pregnancy rates with aCGH (69.1% vs. vs. 41.7%) in favorable prognosis patients under 35

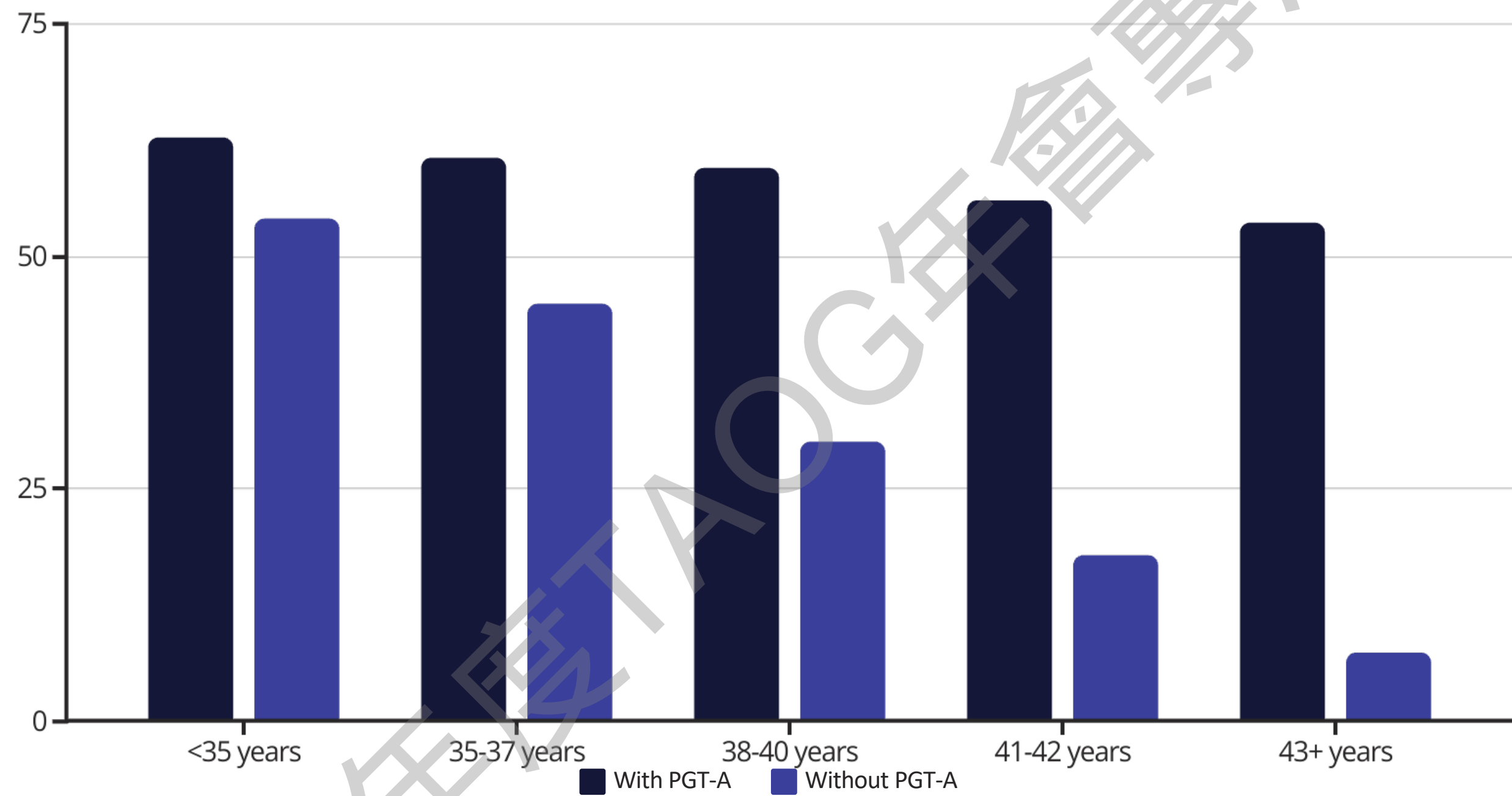


Recent Multicenter Trials

STAR trial and Chinese study **showed showed no improvement** in cumulative cumulative live birth rates with PGT-A PGT-A

us Practice Committees of the ASRM and the SART. *Fertil Steril* 2024;**122**:421–34.

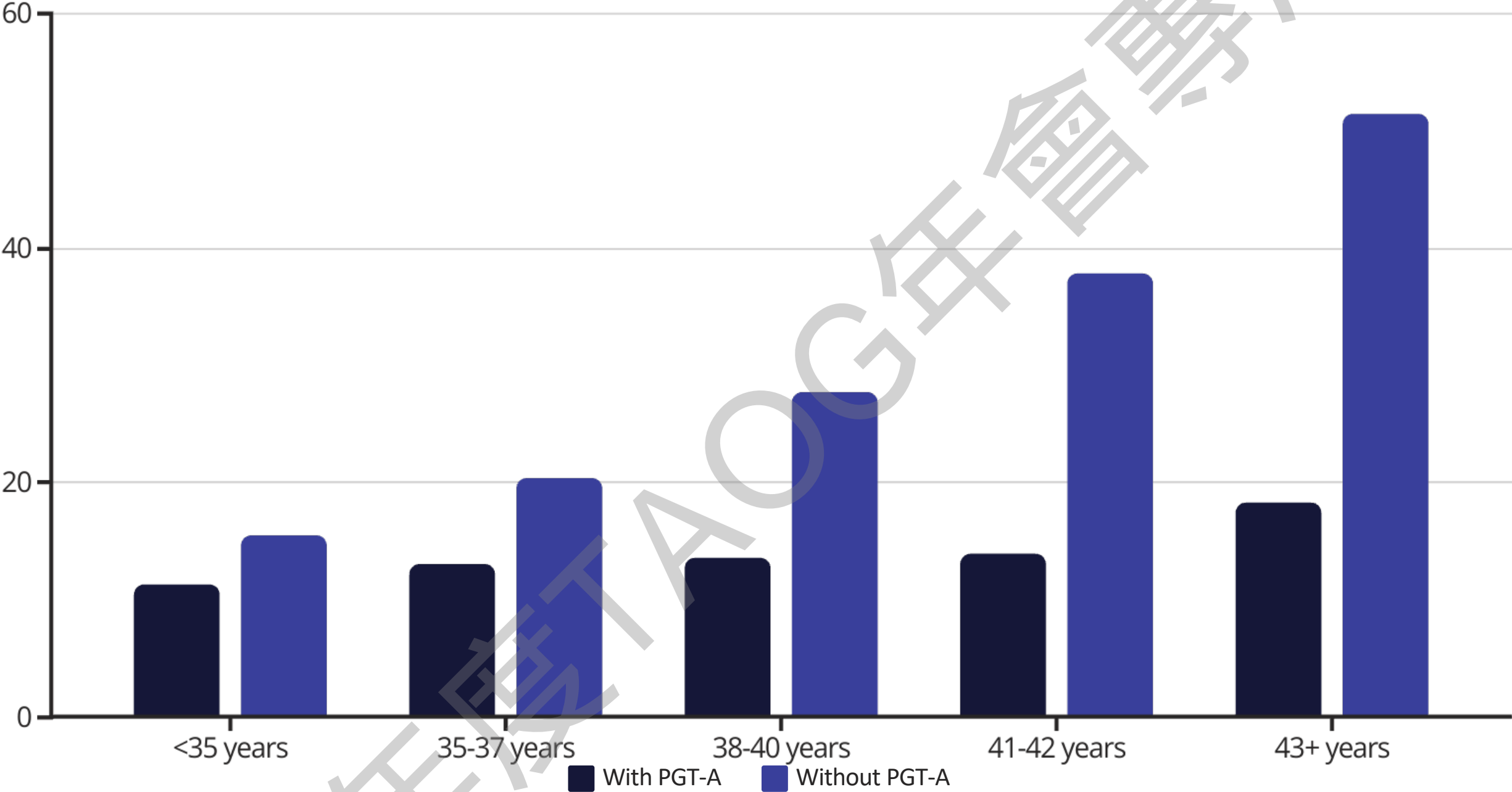
SART Data Analysis (2019)



Analysis of data from the Society for Assisted Reproductive Technology (SART) from 2019 found that the use of PGT-A is associated with higher implantation rates, implantation rates, particularly in older age groups. The difference becomes more pronounced with advancing maternal age.

PGT好棒棒！

Miscarriage Rates by Age Group (SART 2019)



SART data also shows that miscarriage rates are lower with PGT-A across all age groups, with the difference becoming more significant with advancing maternal age. advancing maternal age. The most dramatic difference is seen in women over 43 years, where the miscarriage rate is 18.3% with PGT-A versus 51.5% without. 51.5% without.

PGT好棒棒！

Key Randomized Controlled Trials

Study	Population	Primary Finding
Yang et al. (2012)	Favorable prognosis, <35 years	👍 Higher ongoing pregnancy rates with aCGH (69.1% vs. 41.7%)
Scott et al. (2013)	Age 21-42, N = 72 by qPCR qPCR	👍 improvement in implantation and LBR in AMA patients
Best Trial, Forman, 2013	Mean age ~35 years, ITT	LBR一樣，👍 但完全沒有多胞胎
STAR Trial (2019)	Ages 25-40, multicenter, ITT	No difference in ongoing pregnancy rates (50% vs. 46%)
Yan J. (2021)	No improvement in LBR for ages 20-37; more transfers needed, ITT	Conventional IVF non-inferior to PGT-A for cumulative live birth rate

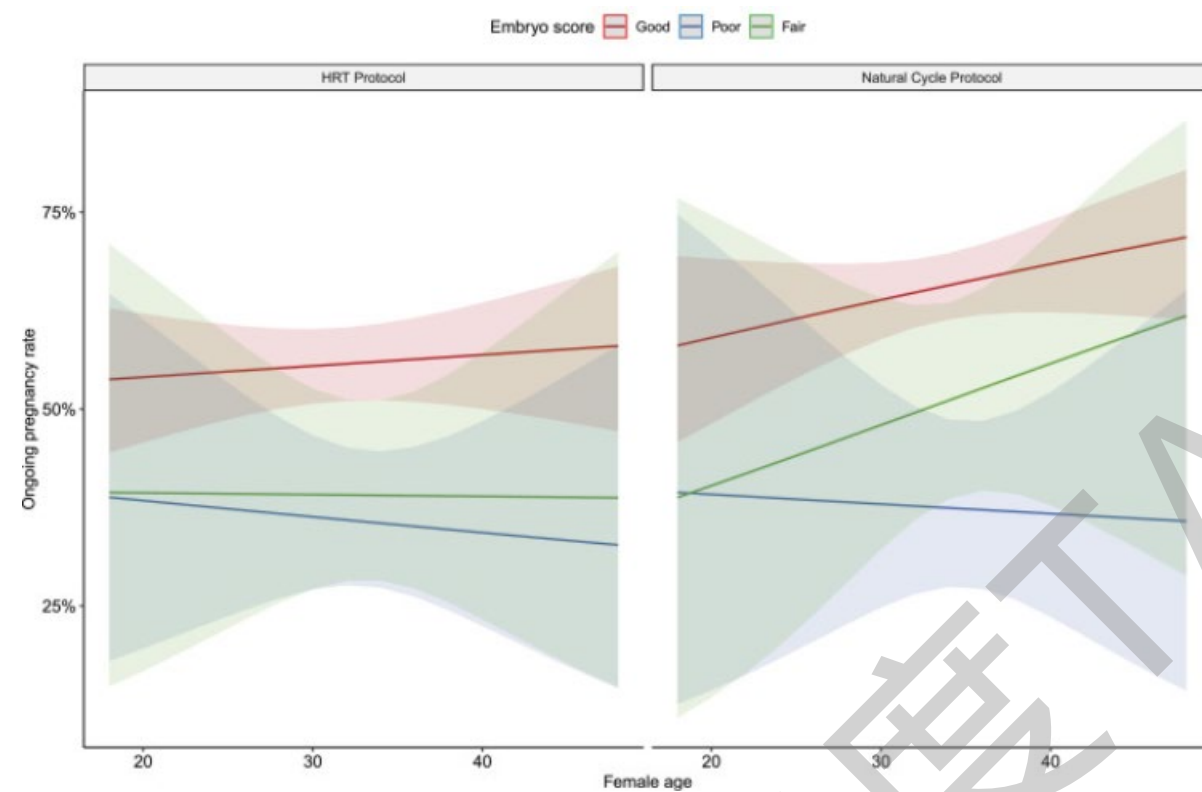
觀察此類研究：PGT-A的對手，是植入更多胚胎Transfer More(更多多胞胎、以及流產率)，或無法切的胚胎

RCT Evidence: PGT-A in Infertility

- 值得注意的是，這些 RCT 有明顯的限制。具體而言，隨機化僅針對擁有大量優質囊胚的患者，這可能意味著這些患者預後良好
- 如果在週期開始時進行隨機化，根據意向治療分析，PGT-A 組中一定比例的患者將沒有胚胎進行活檢或移植，因此可能會改變該組患者的成功率
- **STAR 試驗**的事後分析顯示，35-40 歲患者每次胚胎移植的 OPR 增加
- 回顧性研究表明，**PGT-A 檢測對高齡患者群體有益**，尤其是 43 歲以下的女性
- （接受 PGT-A 檢測的 38-40 歲女性每個週期的活產率提高），並且 40-43 歲女性的植入率提高(Lee, 2015)

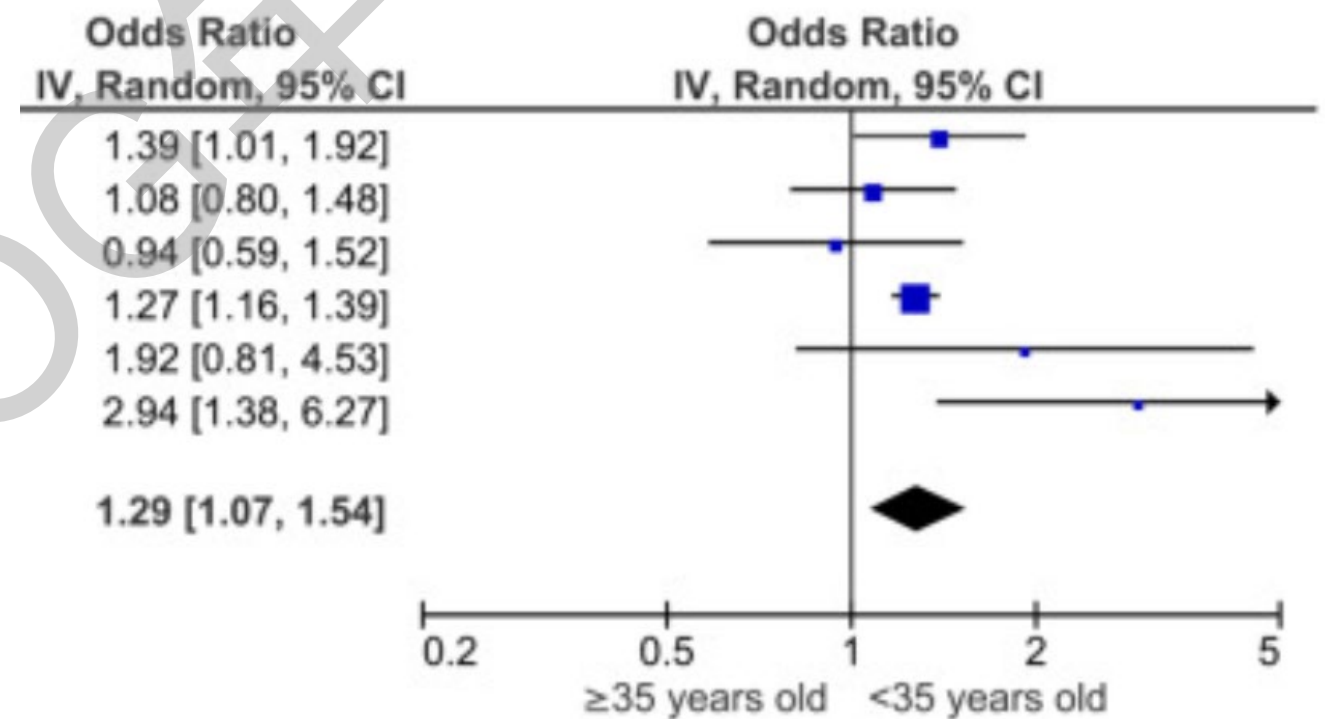
us Lee H-L et al. J Assist Reprod Genet 2015;32:435–44.

即使高齡, 若植入Euploid Embryo成功率相當高



年齡不影響Euploid Embryo成功率

BE Lawrenz B et al. Reprod Biomed Online 2024;49:104074.



年齡>35歲Euploid Embryo成功率下降

IT Vitagliano A et al. Fertil Steril 2023;120:251–65.

現實的落差



Specific Patient Scenarios: When PGT-A May Be Beneficial

Advanced Maternal Age

Women over 37 years with good ovarian reserve may benefit from PGT-A, as the difference in implantation and miscarriage rates becomes more pronounced with age

Recurrent Pregnancy Loss

Patients with history of recurrent miscarriages, especially if previous losses were due to chromosomal abnormalities

Previous Aneuploid Pregnancy

History of pregnancy with chromosomal abnormality may indicate increased risk for future aneuploidies

Single Embryo Transfer Goals

Patients strongly desiring single embryo transfer to avoid multiple pregnancy while maintaining good success rates

PGT-A的其他好處



心態面

減輕醫師與病人的壓力

若無Euploid Embryo, 再努力取卵就好,
但植入就是直球對決, 失敗彼此都會有挫敗感

減少植入多顆胚胎造成多胞胎的壓力



效益面

縮短Time to Pregnancy

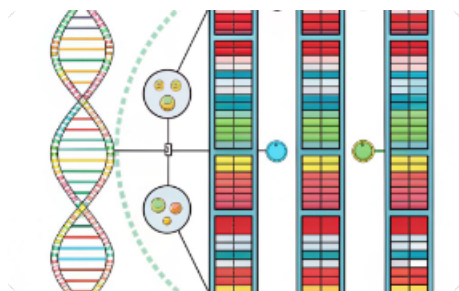
重複植入與流產相當耗費時間

減少流產的心理衝擊

減少多胞胎的機會



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RPL處置圖(Abortion ≥ 2 times)

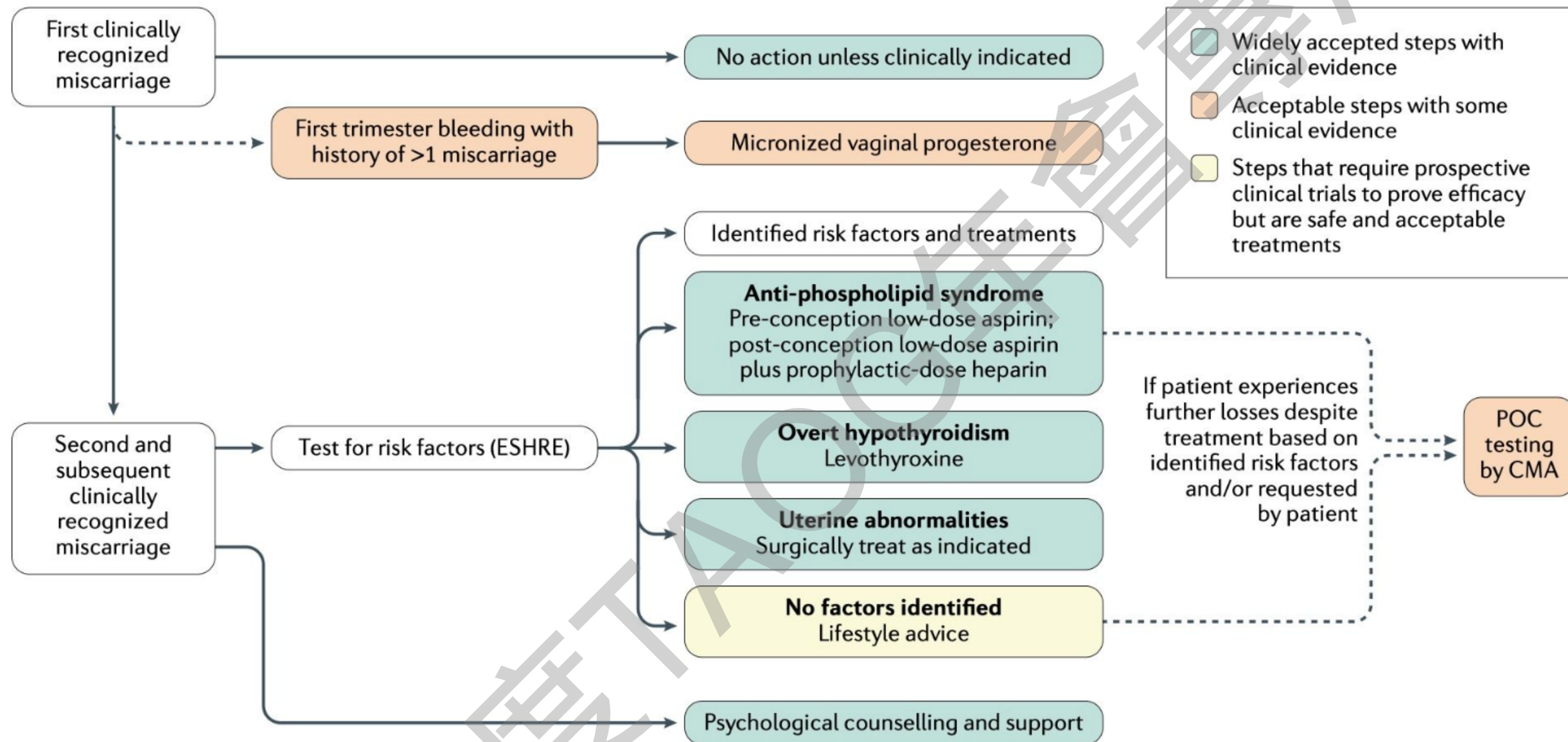
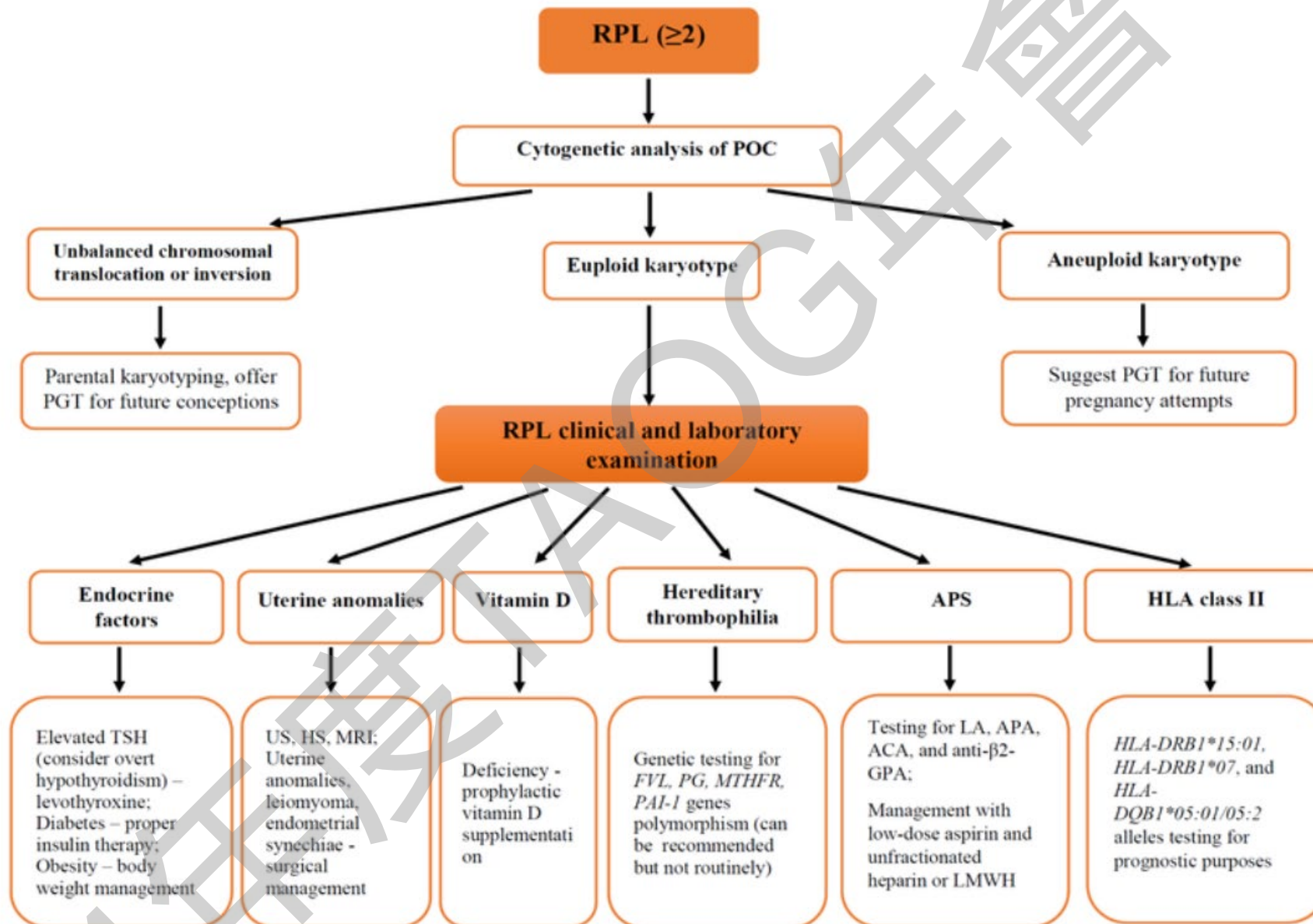


Fig. 5 | **An example of a clinical protocol for the management of recurrent pregnancy loss.** Treatment of recurrent pregnancy loss depends on the modifiable risk factors, which differ between patients. Importantly, the efficacy of different clinical protocols to improve the prognosis of affected couples has not been tested in well-designed prospective studies. CMA, chromosomal microarray; ESHRE, European Society of Human Reproduction and Embryology guidelines 2017; POC, products of conception. Data from REFS^{1,2,151}.

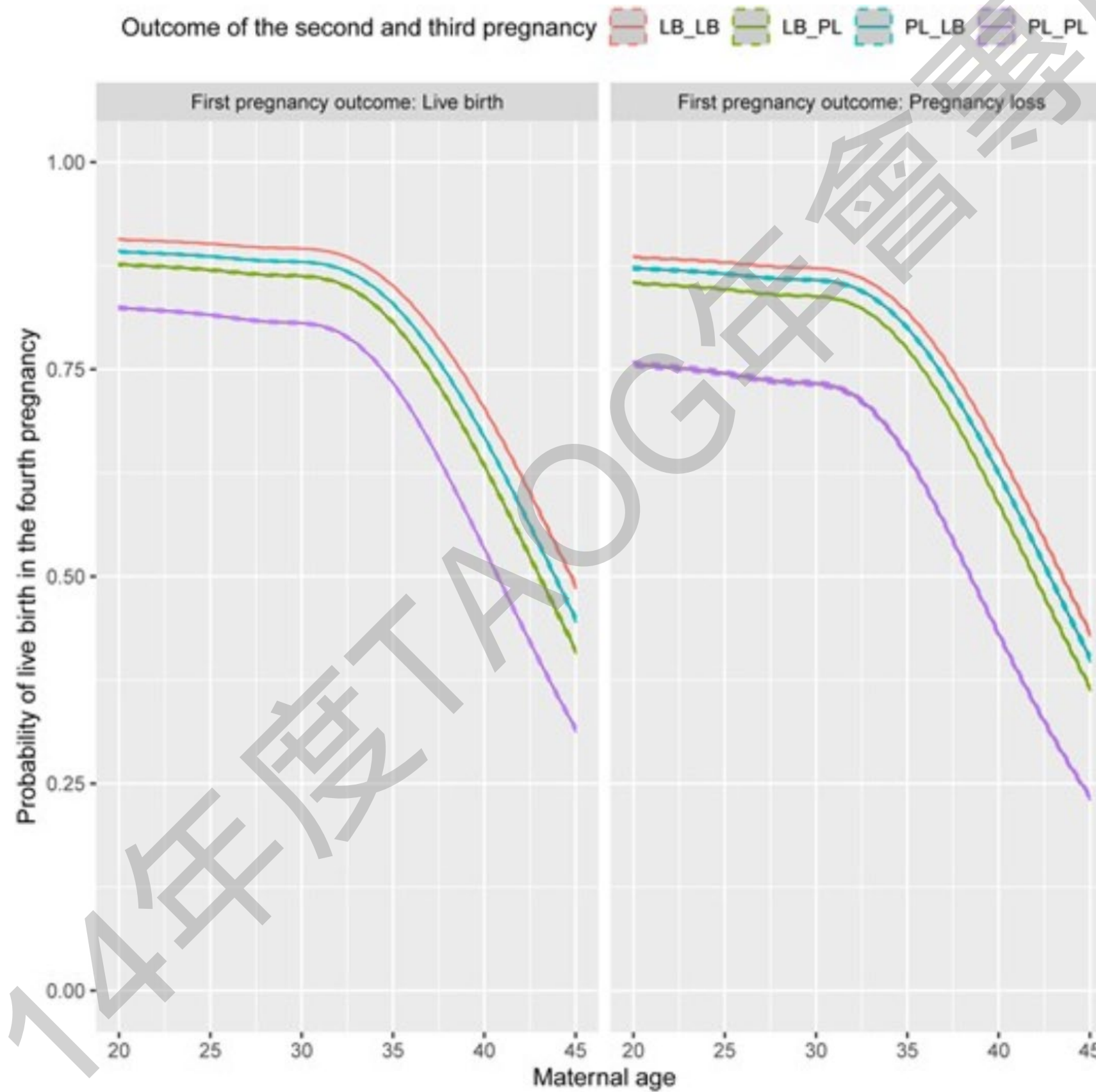
Other RPL...

10.3390/jcm12124074

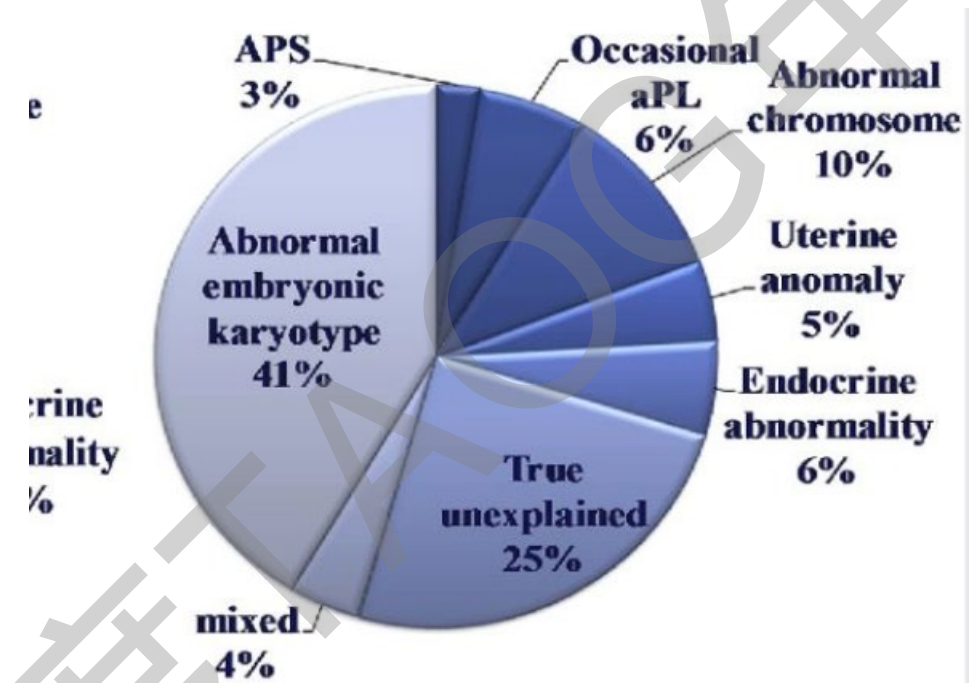
Other RPL exam



只要之前有活產, 即使兩次流產, 之後正常機會很高



RPL原因分析



b 482 patients with RPL, including those with an abnormal embryonic karyotype
Sugiura-Ogasawara et al., Hum Reprod 2012.

PGT-A似乎對一般RPL族群沒有幫忙

Parameter	Treatment (<i>n</i> = 198 attempts, 1)	Control (<i>n</i> = 202 attempts)	P-Value
Clinical pregnancy rate ^a	88 (44)	104 (51)	0.16
LB rate ^a	63 (32)	68 (34)	2 0.75
CM rate ^b	18 (20)	25 (24)	No Difference 0.61
Biochemical pregnancy rate ^b	5 (6)	6 (6)	1.00
Ectopic pregnancy rate ^b	2 (2)	1 (1)	0.59
Median time to pregnancy (months)	6.5	3.0	N/A

168 retrievals were performed and 38 cycles canceled their planned PGS

PGT-A似乎對RPL高齡組有幫忙

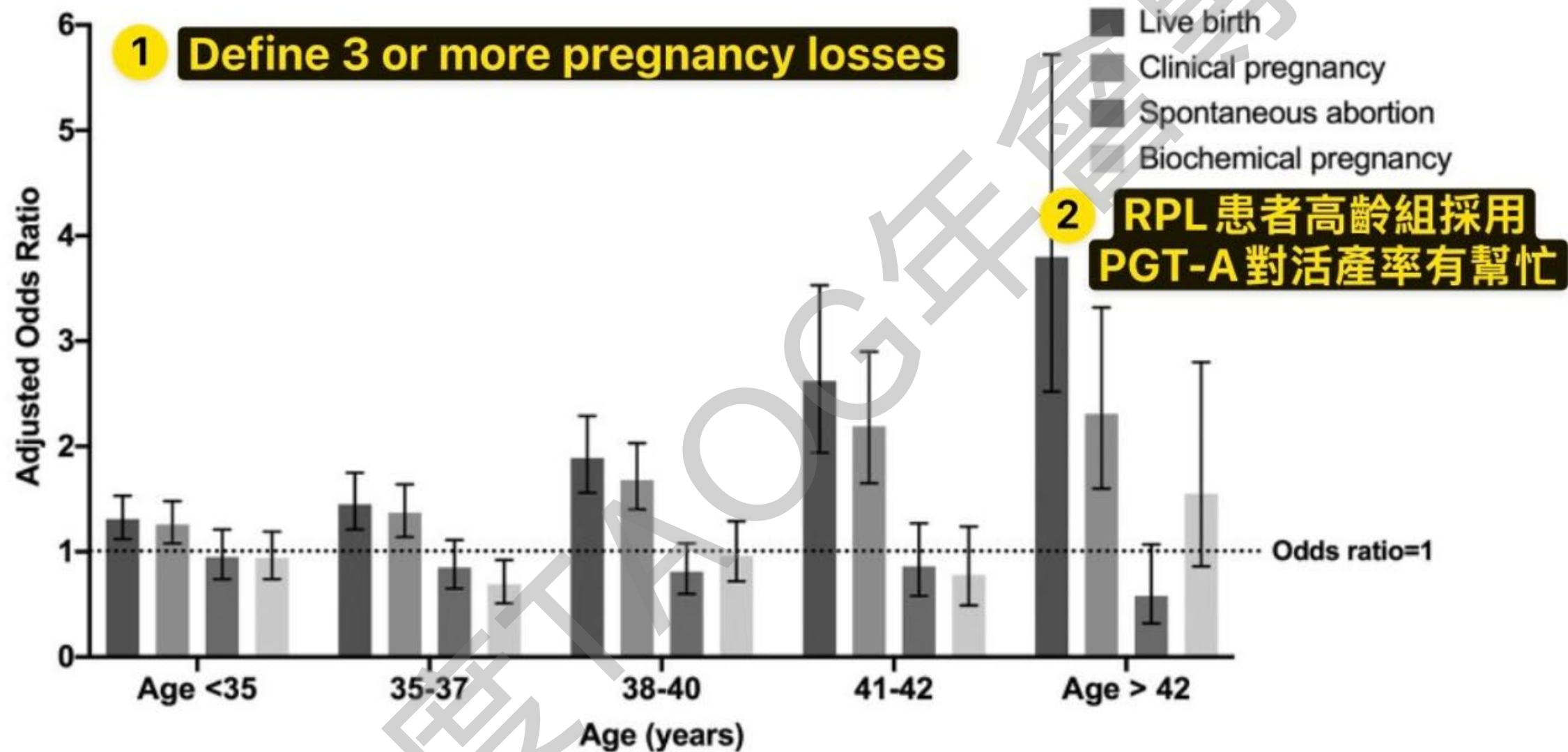


Figure 1. Adjusted odds ratio for pregnancy outcomes in women with recurrent pregnancy loss undergoing IVF-frozen embryo transfer (IVF-FET) with or without preimplantation genetic testing for aneuploidy (PGT-A) use. Women with recurrent pregnancy loss (RPL) who underwent PGT-A testing were compared with those who did not and were analyzed by stratified age groups. In women with RPL, the use of PGT-A with FET was associated with increased rates of clinical pregnancy and live birth. Data are presented as adjusted odds ratio. The dotted line represents an odds ratio of 1.

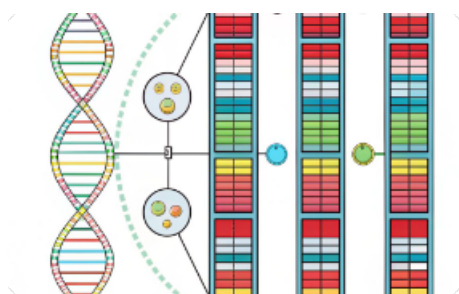
ESHRE 2022 RPL Guideline on PGT-A

- ESHRE Guideline on PGT-A in RPL: not recommended due to mixed evidence and limitations
- May be considered in specific cases, such as older women (>40) with RPL, where aneuploidy is more likely.
- Clinicians should discuss:
 - *Potential Benefit*: Possible reduction in miscarriage risk.
 - *Limitations*: Invasiveness, high cost, and lack of strong evidence.

GB Bender Atik R et al. Hum Reprod Open 2023

- 個人想法：病人高齡、有疑慮就考慮做PGT-A，避免植入失敗後做過多無實證的免疫療法，反而花費更多時間與金錢

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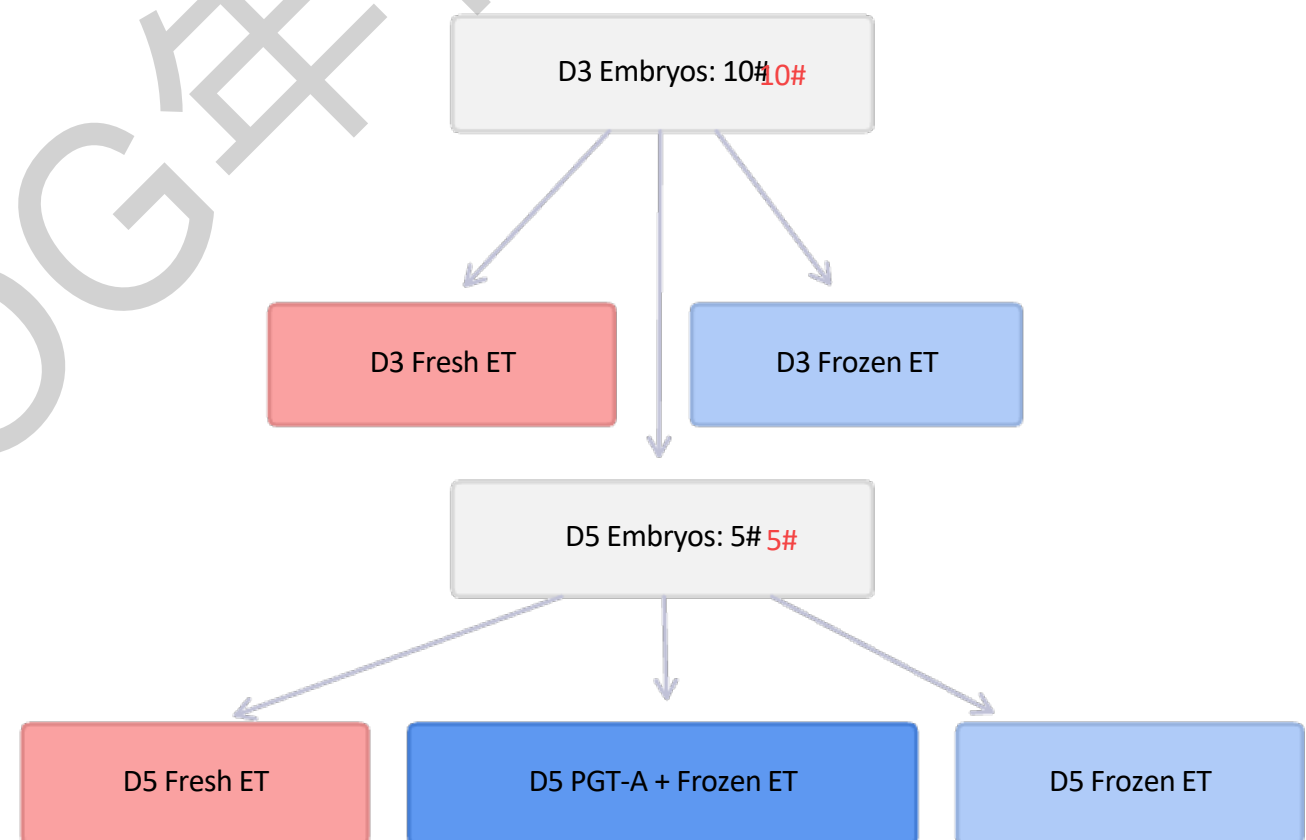


Decision Calculator

個人化決策工具的應用

Build Decision Calculator

- During the day 3 of embryo culture, doctor should consider the feasibility of applying PGT-A later or not
- At least 5 options available:
 - D3 Fresh ET
 - D3 Frozen-thawed ET
 - D5 Fresh ET
 - D5 Frozen-thawed ET
 - D5 PGT-A with Frozen-thawed ET



各種策略的成功機率計算



imgflip.com

JAKE-CLARK.TUMBLR



Interactive Tool

Guides PGT-A decisions based on patient age and number of Day 3 embryos.



Strategy Comparison

Compares D3 fresh ET, D3 biopsy, D5 fresh ET, D5 frozen ET, D5 PGT-A with frozen ET.



Shared Decision-Making

Facilitates informed discussions between patients and providers.

Input Parameters

Patient Age:

☐ 30

☐ 35

☒ 37

☐ 40

☐ 43

Number of Day 3 Embryos: 10 1 輸入年齡、與存活到 Day 3 的胚胎數

Strategy Comparison

Strategy ↓	CLBR (%) ↓	ExtraCost (\$) ↓
1. D3 Fresh ET	80.3%	\$0
2. D3 Frozen-thawed ET	54.6%	\$30,000
3. D5 Fresh ET	76.3%	\$0
4. D5 Frozen-thawed ET	79.0%	\$30,000
5. D5 PGT-A with Frozen ET	57.0%	\$118,000

Note: All strategies assume embryo transfer (ET) of all survived embryos at once.

Day3 Decision Tool

A tool to support clinicians in selecting embryo treatment strategies at day 3 of culture.

Input Parameters

Patient Age:

☐ 30

☐ 35

☒ 37

☐ 40

☐ 43

Number of Day 3 Embryos: 10



Strategy Comparison

Strategy ↓	CLBR (%) ↓	ExtraCost (\$) ↓
1. D3 Fresh ET	80.3%	\$0
2. D3 Frozen-thawed ET	54.6%	\$30,000
3. D5 Fresh ET	76.3%	\$0
4. D5 Frozen-thawed ET	79.0%	\$30,000
5. D5 PGT-A with Frozen ET	57.0%	\$118,000

4. D5 Frozen-thawed ET	79.0%	\$30,000
5. D5 PGT-A with Frozen ET 1 點選策略	57.0%	\$118,000

Note: All strategies assume embryo transfer (ET) of all survived embryos at once.

Calculation Details **2 顯示該策略懷孕率的計算公式，與假設參數**

Strategy 5: D5 PGT-A with Frozen ET (all euploid embryos)

Formula:

Sum of $[P(n) * (1 - (1 - p)^{n_{\text{thawed}}})]$ for $n = 0$ to 4 euploid embryos, where $n_{\text{thawed}} = n * \text{ThawSuccessRate}$

Variables:

$p = 70.0\%$ (D5 Euploid Frozen ET per embryo LBR)

$N = 10$ (Number of D3 embryos)

AttritionRate = 50.0%

BiopsyRate = 80.0%

EuploidRate = 30.0%

$D3ToEuploidProb = 12.0\%$ $((1 - \text{Attrition}) \times \text{Biopsy} \times \text{Euploid})$

ThawSuccessRate = 95.0%

$N_{d5} = 10 * (1 - 0.500) = 5.0$

$N_{pgta} = 5.0 * 0.800 = 4.0$

P_{euploid} = Dynamically calculated probabilities of 0-4 euploid embryos: [0.279, 0.380, 0.233, 0.085, 0.020]

Advanced Settings 1 點選進階設定，可以自行調整參數

Fixed Parameters

D3 Thaw Rate:

0.750

D5 Thaw Rate:

0.950

PGT-A Cost (\$):

22000.000

Freeze-Thaw Cost (\$):

30000.000

Age-Specific Parameters

Parameter	Age 30	Age 35	Age 37	Age 40	Age 43
Attrition Rate	0.300	0.350	0.500	0.600	0.700
Biopsy Rate	0.800	0.800	0.800	0.800	0.800
Euploid Rate	0.500	0.400	0.300	0.200	0.100
D3 Fresh LBR	0.400	0.200	0.150	0.100	0.050
D3 Frozen LBR	0.350	0.150	0.100	0.100	0.050

Decision Calculator



Day3 Decision Tool

A tool to support clinicians in selecting embryo treatment strategies at day 3 of culture.

Input Parameters

Patient Age:

☐ 30 ☒ 35 ☐ 37 ☐ 40 ☐ 43

Number of Day 3 Embryos: 10

Strategy Comparison

Strategy †	CLBR (%) ‡	ExtraCost (\$) ‡
1. D3 Fresh ET	89.3%	\$0
2. D3 Frozen-thawed ET	70.4%	\$30,000
3. D5 Fresh ET	90.2%	\$0
4. D5 Frozen-thawed ET	90.8%	\$30,000
5. D5 PGT-A with Frozen ET	74.5%	\$144,400

Note: All strategies assume embryo transfer (ET) of all survived embryos at once.

ivfd3.vercel.app

歡迎提供改進意見 cedricchen@gmail.com

凍卵估計數量APP



統整比較



簡報連結

ivfd3.vercel.app 療程計算機連結

	PGT-A	Transfer More(No PGT-A)
\$\$\$	切片、冷凍解凍(通常較高)	👍 植入藥費(多次)
Time	👍 比FreshET慢, 但比多次植入快	FreshET可能較快, 一般來說較慢
Multiple Pregnancy	👍 低風險	高風險
單次植入活產率	👍 高	視植入胚胎數而定
累積活產率	一樣	一樣
醫師與病患壓力	👍 低	高(植入失敗、多胞胎風險)
適用族群	高齡、打算eSET、RPL	Attrition Rate高者



Questions and Discussion

Day of Embryo Biopsy

Day 5 vs. Day 6 Blastocysts

When comparing outcomes for blastocysts biopsied on day 5 versus day 6, studies show the aneuploidy rate is not significantly different.

Implantation rates, clinical pregnancy rates, and live-birth rates were also comparable between day 5 and day 6 euploid embryos.

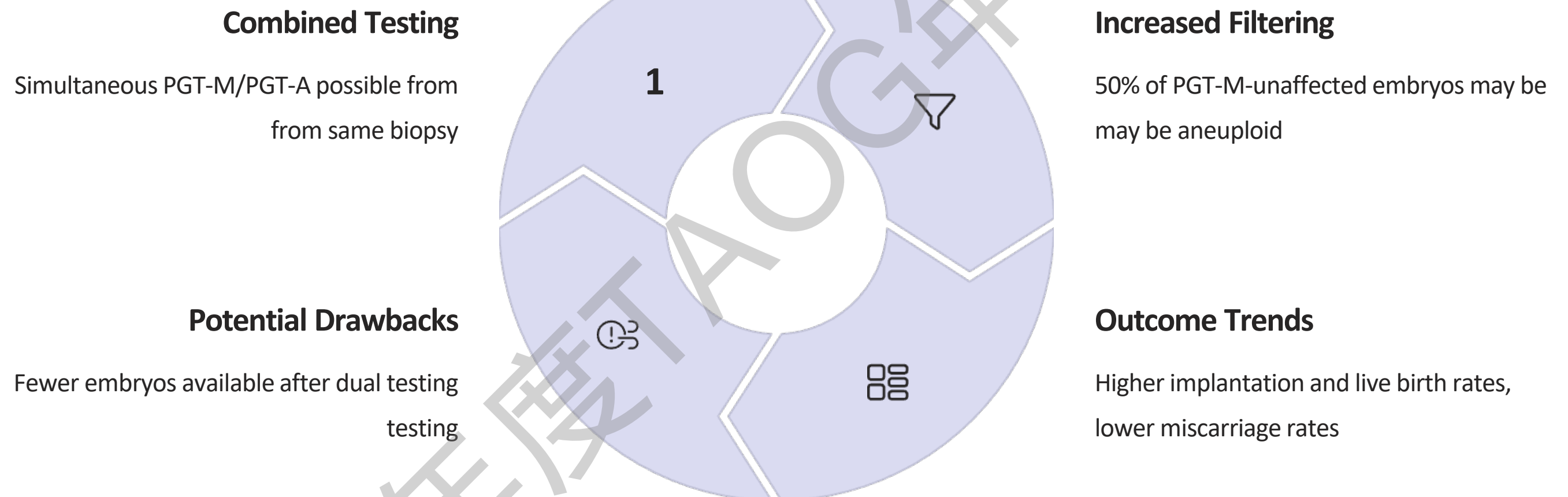
This suggests that the developmental rate of euploid blastocysts that form on day 6 may be approximately as likely to result in live birth as those that form on day 5, although day 6 blastocysts typically require cryopreservation for future transfer.

Day 7 Blastocysts

Embryos that reach blastocyst stage on day 7 may have a higher risk of aneuploidy and lower implantation potential if euploid. Studies show mixed results, with some finding slightly reduced but not significantly different pregnancy rates, while others report significantly lower euploidy and implantation rates.

These data generally support the selection of day 5 and day 6 blastocysts over day 7 blastocysts when available.

PGT-A with Preimplantation Genetic Testing for Monogenic Disorders (PGT-M)



With improvements in embryo biopsy and DNA amplification techniques, it became possible to perform simultaneous PGT-M/PGT-A in the same biopsy sample. One study found that 50% of PGT-M-unaffected embryos were aneuploid, suggesting potential benefit to combined testing, though further studies are needed.

Thawing, Biopsy, and Re-Cryopreservation



Initial Cryopreservation

Embryos previously frozen without biopsy



Thawing Process

Careful warming of embryos

3

Biopsy Procedure

Trophectoderm cells removed for testing



Re-Cryopreservation

Embryos refrozen while awaiting results

Patients with previously cryopreserved unbiopsied embryos may wish to thaw their embryos their embryos for biopsy and testing followed by repeat cryopreservation. Although fresh Although fresh biopsy is preferable, reproductive outcomes did not seem significantly significantly compromised for surviving euploid embryos after this process, though survival though survival rates may be lower for the second warming.

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Neonatal and Childhood Outcomes



Generally Reassuring

Most studies do not show a negative impact of PGT on obstetric, neonatal, and childhood outcomes



Cognitive Development

Kindergarten-aged PGT offspring perform as well as IVF, ICSI, and naturally conceived peers on measures of cognition



Physical Health

No differences in body composition and blood pressure measurements between PGT and non-PGT children



Preeclampsia Risk

One study found threefold higher odds of preeclampsia with trophectoderm biopsy

