21ST

PGDIS CONFERENCE

PREIMPLANTATION GENETIC DIAGNOSIS INTERNATIONAL SOCIETY

PGDIS

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PGT and BEYOND...

21ST PGDIS CONFERENCE

Clinician counseling of PGT- A for patients

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Introduction

- In the mid-1990s, the first version of PGT for aneuploidy
- Improve pregnancy rates for patients:

- advanced maternal age
- recurrent pregnancy loss
- implantation failure

- An overview of the process and components of counseling for PGT
- Evolving complexity of test platforms and applications
- Genetic counseling -more frequently incorporated in care of PGT patients.
- Highlights- practical and ethical challenges

Counseling

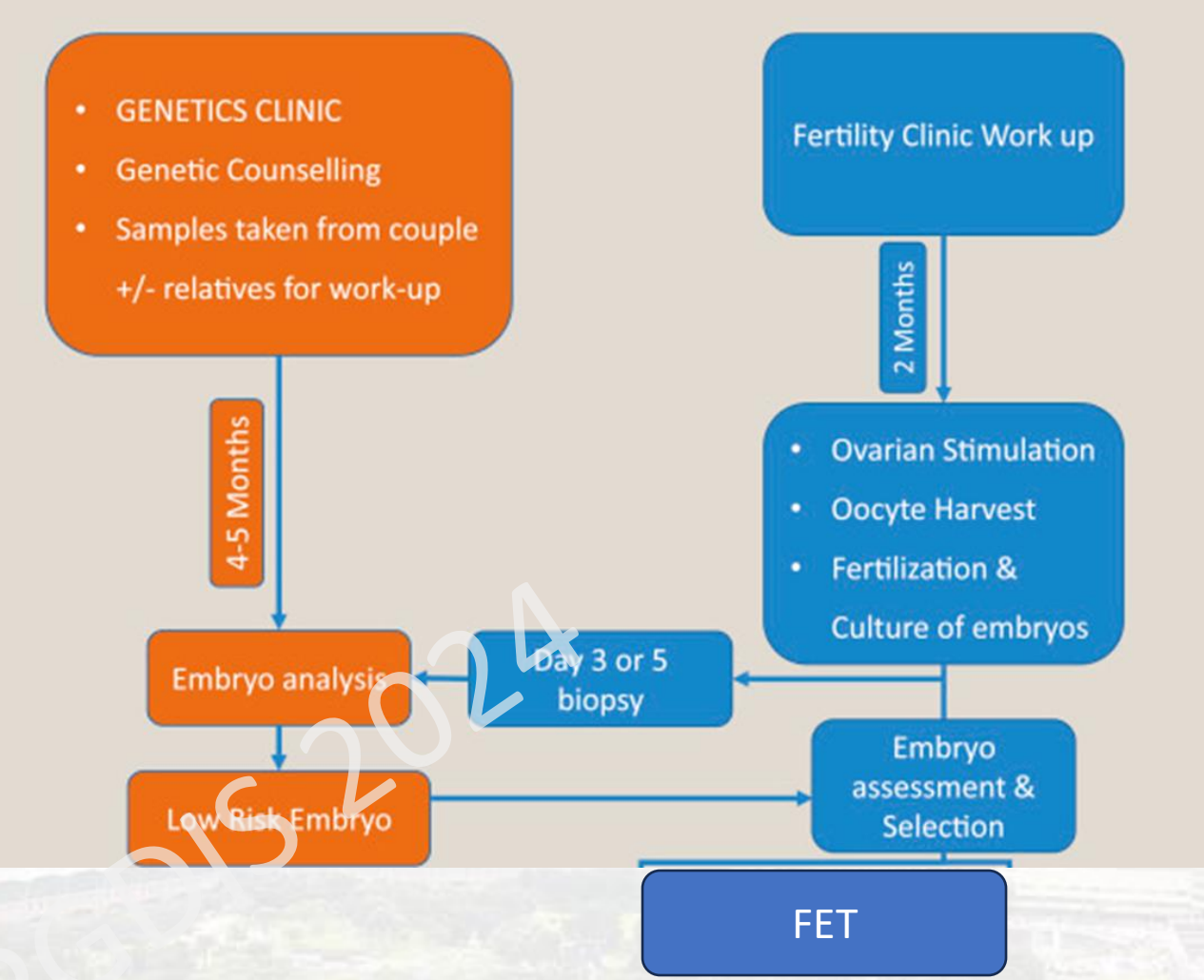
- The process of helping people
- Understand & adapt
- Medical, psychological & familial implications of genetic contributions to disease
- Informed choices

Counseling

Essential to communicate the:

- purpose of testing
- set appropriate expectations
- disclose relevant clinic policies – consent forms
- test benefits
- risk
- limitations.

PGT- work flow



- For PGT-A, counseling and genetic testing only involves the couple and usually requires about 1-2 months
- In centers using an out-sourced genetics lab it may take longer to obtain the PGT-A outcome.

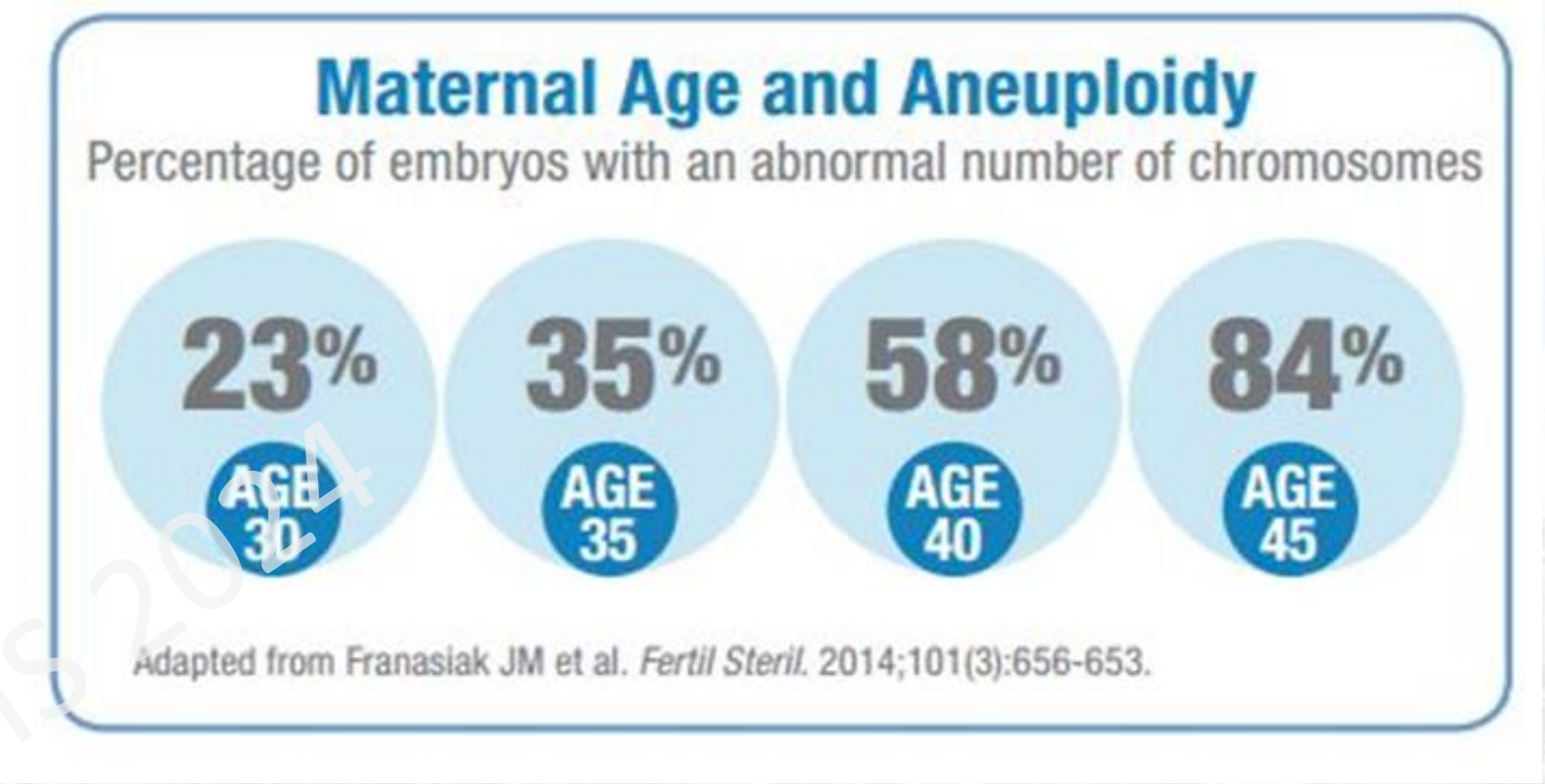
PGT-A requires a lot of resources

From stimulation to embryo transfer

To be effective, it must encompass:

- an excellent stimulation regime,
- ICSI for fertilization,
- long-term embryo culture,
- no-damage biopsy,
- good vitrification technique
- accurate analysis of PGT.

- Chromosomal aneuploidy occurs frequently in oocytes
- Main contributor to maternal age-related fertility decline
- Aneuploid embryos – no viable pregnancies
- Assists to select euploid embryos- maximize chances of a sustained pregnancy.
- General screening tool.


Maternal Age and Aneuploidy
Percentage of embryos with an abnormal number of chromosomes
23%
AGE 30
35%
AGE 35
58%
AGE 40
84%
AGE 45
Adapted from Franasiak JM et al. Fertil Steril. 2014;101(3):656-653.

PGT-A reporting outcome

There maybe up to 5 reported outcome depending on the genetic laboratory

- Normal/Euploid
- Abnormal/Aneuploid
- Mosaic (Low Risk)
- Mosaic (High Risk)
- Inconclusive Result /Amplification Failure

Setting patient expectation

- Euploid– no issues
- Aneuploid
- Trisomies 21, or those involving the sex chromosomes,
- Result in live births and with variable phenotypes.
- It is important for patients to be made aware of the variability that exists within the aneuploid category

Results with issues:

Lower degree of analytical certainty

Unknown clinical significance

- mosaicism
- segmental aneuploidy

No result

- Technical reasons
- Failed amplification
- Poor DNA quality

The expected rates of each PGT result type will vary depending:

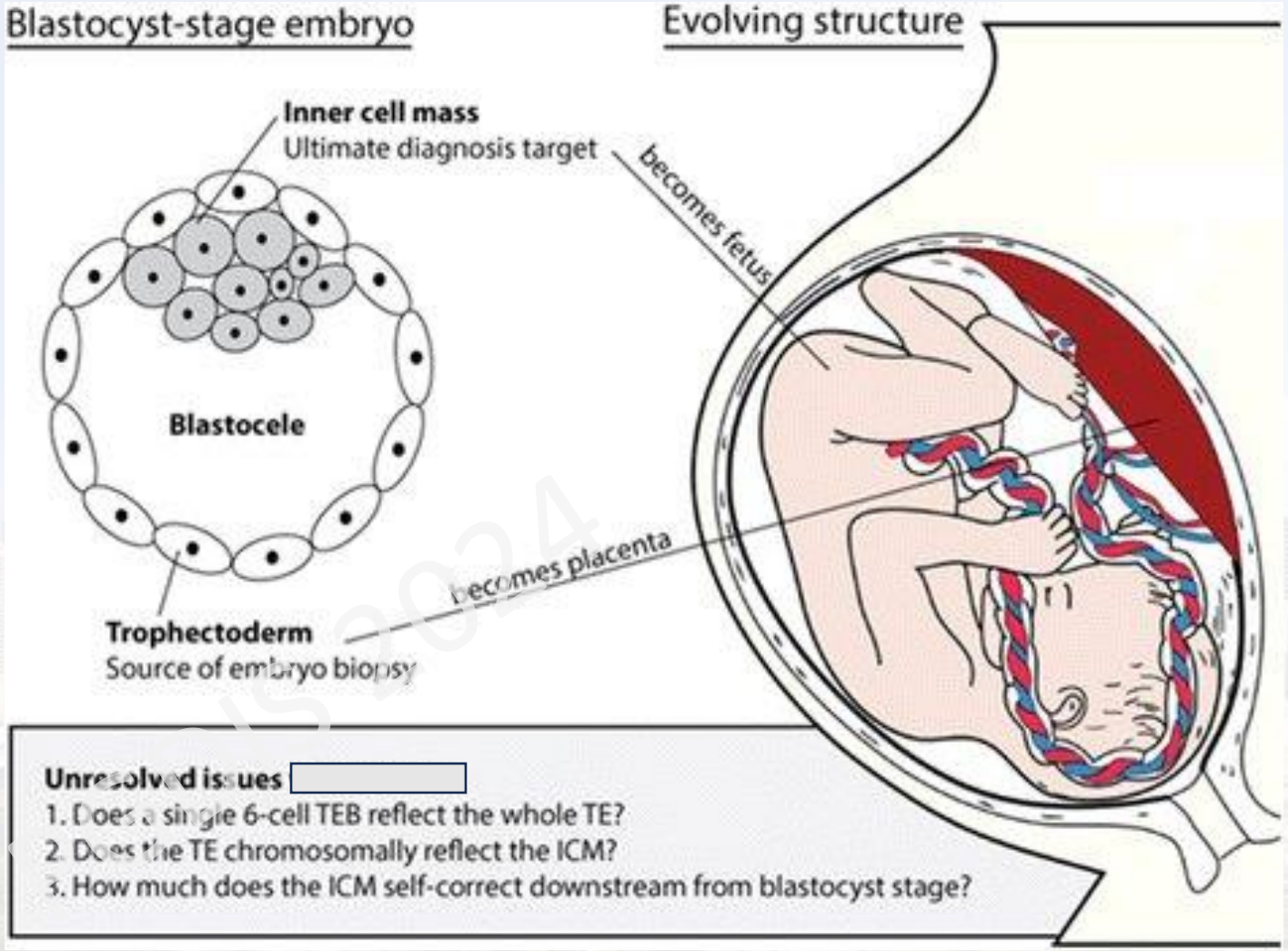
- test indication
- patient age
- laboratory used

? To do or not to do

- outweigh the risks? limitations? cost of testing ?
- widely debated.
- potential benefits frequently depend on a patient’s clinical indication.
- Without PGT-A:

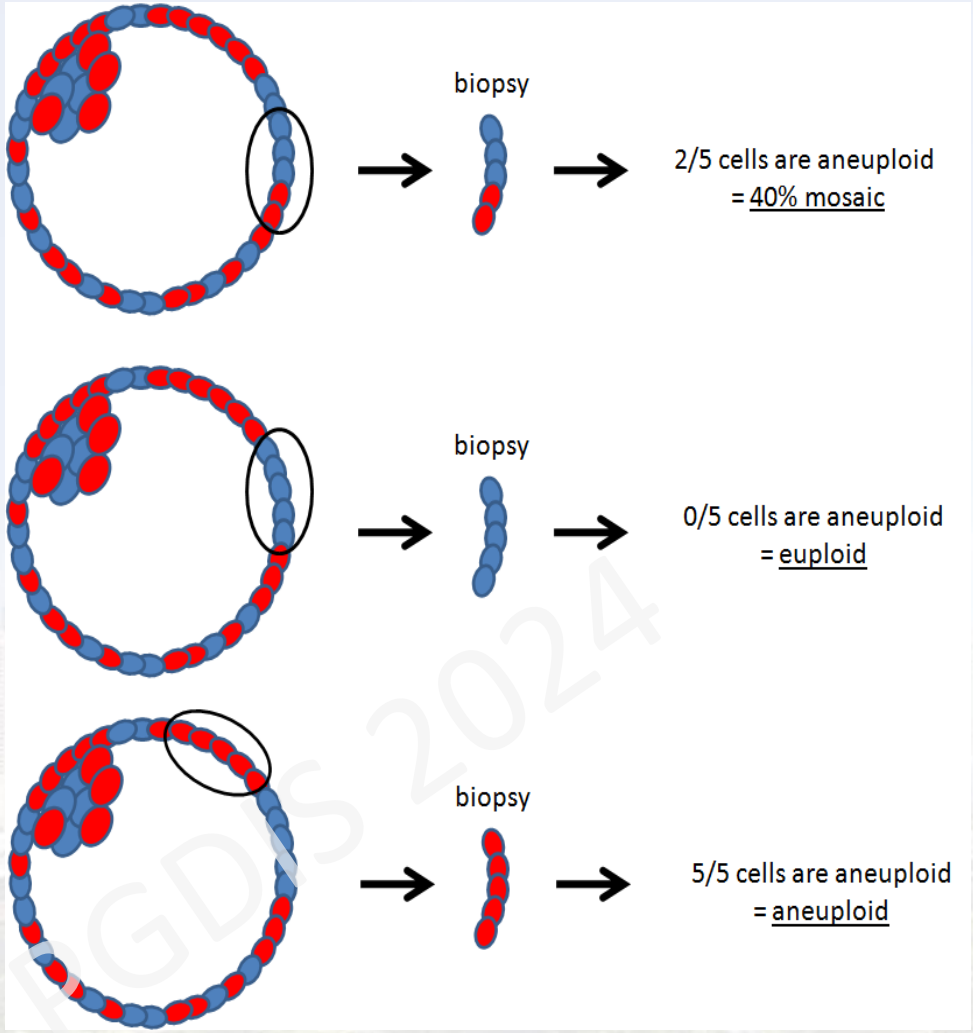
- based on morphology
- correlates poorly with implantation potential
- AI

Does the biopsy represent the WHOLE embryo?



The cells taken for testing are assumed to reflect the whole embryo, but this cannot be guaranteed.

Does the biopsy represent the WHOLE embryo?



Both normal and abnormal cells occurs in the embryo by chance during embryonic development

A biopsy of cells can cause PGT-A misdiagnosis if the biopsied cells do not reflect the rest of the embryo.

The PGT-A test will report the embryo as euploid if 75 or 80% of the cells are normal.

A biopsy should take preferably 5 cells to reduce chance of misdiagnosis and embryo wastage.

Accuracy of PGT-A testing

- Varies depending on quality of biopsied cells
- Quality of data from genetics lab
- There is also a small risk of misdiagnosis due to:
  1. embryo mosaicism
  2. parental cell contamination….mother's cumulus cells or father's sperms attached to the zona of the embryo.
  3. inherent weakness in the genetic test used –

current sequencing technology for PGT-A has a common resolution at 5 Mb to 10 Mb and a reproducible detection limit of the mosaic level at 20% or 30%.

Benefits

- Selection of euploid embryos, reduce fetal aneuploidy
- Increase implantation rates per embryo transferred
- Reduce rates of spontaneous miscarriages
- Single embryo transfer, reduce double embryo transfer
- Reducing the rate of multiple gestation and associated obstetrical complications

Benefits

- Reducing the time until a birth is achieved
- Maximize the per-transfer success rate
- Creating embryos for fertility preservation, avoid additional IVF cycles.

Pregnancy rate after PGT-A

Managing patient expectations……..
Overall pregnancy rate per transfer after PGT-A is around 50%, slightly higher than controls.
Women between the ages of 35 to 40 are most likely to benefit the most from PGT-A.

TABLE 3

Outcomes in patients undergoing an embryo transfer with embryo selection by means of preimplantation genetic testing for aneuploidy (PGT-A) versus morphology (Control), n (%).

	< 35 y		35–40 y		All patients		
Outcome	PGT-A (n = 152)	Control (n = 168)	PGT-A (n = 122)	Control (n = 145)	PGT-A (n = 274)	Control (n = 313)	*P* value[a]
Negative β-hCG	46 (30.3)	53 (31.5)	34 (27.9)	59 (40.7)	80 (29.2)	112 (35.8)	.0934
Positive β-hCG	106 (69.7)	115 (68.5)	88 (72.1)	86 (59.3)	194 (70.8)	201 (64.2)	ND
Biochemical pregnancy	14 (9.2)	10 (6.0)	15 (12.3)	16 (11.0)	29 (10.6)	26 (8.3)	.3315
Miscarriage	17 (11.2)	14 (8.3)	10 (8.2)	16 (11.0)	27 (9.9)	30 (9.6)	.8979
Elective termination	0	2 (1.2)	1 (0.8)	0	1 (0.4)	2 (0.6)	.6603
Ongoing pregnancy at 20 weeks' gestation	75 (49.3)	89 (53.0)	62 (50.8)	54 (37.2)	137 (50.0)	143 (45.7)	.3177
P value for age subgroups	*P*=.5757		*P*=.0349				

Note: ND = not determined.
[a] *P* value determined by means of Cochran-Mantel-Haenszel test.

Munné. RCT evaluating NGS-based PGT-A. Fertil Steril 2019.

Cumulative PR after 3 ET within 1 year with PGT-A embryos reaches 77% (Yan J et al, 2021).

TMCF Puchong PGTA outcome

TMC PUCHONG IVF LAB FET 2021-2023						
YEAR	NON PGTA(N)	PREG(N)	PREG%	PGTA(N)	PREG (N)	PREG%
2021	111	61	55	26	15	57.7
2022	139	72	51.8	70	47	67.1
2023	129	78	60.5	178	109	61.2

- The PGTA pregnancy outcome averages at 62.4% (from 2021 to 2023) as compared to non-PGTA outcome of 55.7%
- There is an increasing demand for PGTA reflecting the changing patient demography, of older women.

RISKS AND LIMITATIONS

- Common patient misconceptions regarding the accuracy
- the scope of information
- PGT does not detect :

- multifactorial conditions
- intellectual disability
- autism
- congenital anomalies

RISKS AND LIMITATIONS

- Difference between PGT
- other types of genetic testing PGT-M, PGT-SR
- carrier screening

Inaccurate results (false negatives and false positives)

- sample contamination,
- human or software error
- chromosomal mosaicism

- discuss the additional test
- prenatal diagnosis (chorionic villus sampling or amniocentesis):

- confirm PGT results with increased accuracy

RISKS AND LIMITATIONS

- Requires embryo biopsy
- Invasive nature of micromanipulation
- Trophectoderm biopsy is associated with reduced embryo damage compared with other biopsy techniques :

-polar body or cleavage-stage biopsy

- Lack of long-term safety outcome data

RISKS AND LIMITATIONS

- Requires embryo cryopreservation to accommodate the timeline associated with obtaining PGT results
- Patients should be counseled about clinic-specific risks associated with warming vitrified blastocysts

MOSAICISM

- Next-generation sequencing (NGS)
- Increased sensitivity of testing
- Unclear to what extent a mosaic biopsy represents the remainder (i.e. unsampled inner cell mass)
- Reduced implantation potential
- Increased risk for miscarriage

MOSAICISM

- Lack of phenotypic and long-term data
- No evidence-based guidelines are available to support
- Uncertainty associated with mosaic results may persist despite normal prenatal or postnatal testing
- Low risk mosaicism < 50%
- High risk mosaicism >50%

What if the patient plan for PGT-A but nothing can be done…..

Not all embryos are suitable for biopsy and PGT-A

- depends on the growth and quality of the embryos.
- none of the embryos will be suitable for PGT-A.
- performed on good quality embryos,

The advice is to transfer untested embryos based on the morphological quality

Priority for transfer

- Euploid
- low risk mosaic
- high risk mosaic or amplification failure/ no result
- aneuploid

Physicians

- Encounter a lack of data and consensus
- Struggle to stay abreast of new tests and technologies
- Burden of care and counseling
- Create clinic-specific written policies
- Sharing of such policies with patients before PGT
- Referral to a disease-specific specialist
- Ensure patient has complete understanding of natural history and management of the condition.

Counseling

- Discuss prenatal testing options
- Differences between prenatal screening and diagnosis
- Origin of the tissue type being analyzed

  (i.e. cells of placental origin in cell-free DNA and chorionic villi versus fetal ectodermal origin in amniotic fluid)
- In-house services or online/video educational modules

Ethical considerations

- There are ethical questions about
  - implications of selecting embryos based on genetic criteria
  - potential embryo discarding
  - gender selection / family balancing
  - embryo selection should aim for a healthy child not the selection of certain characteristics

Patient Support and Education

- Emotional support during the process
  – counsellors and geneticists

- Resources for additional information - websites

Ideally

- Non or minimally invasive
- Accurate
- Straightforward to interpret
- Low cost

Thank you for listening

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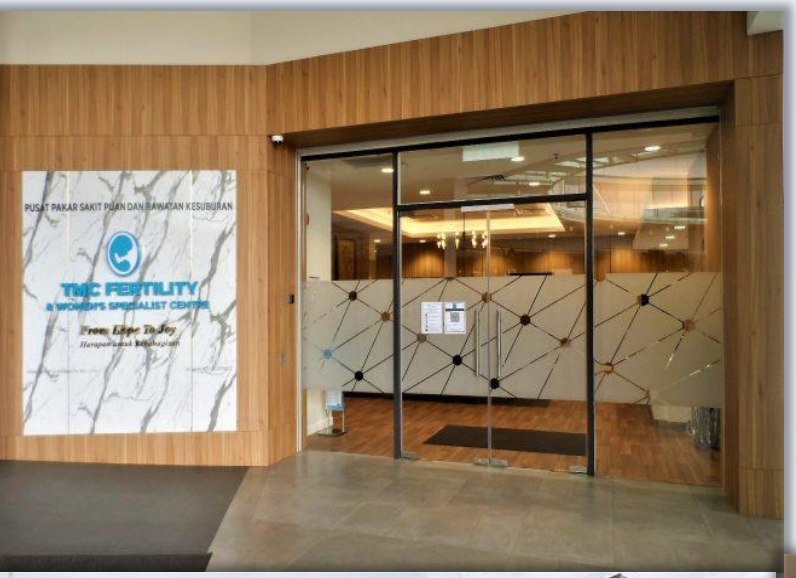

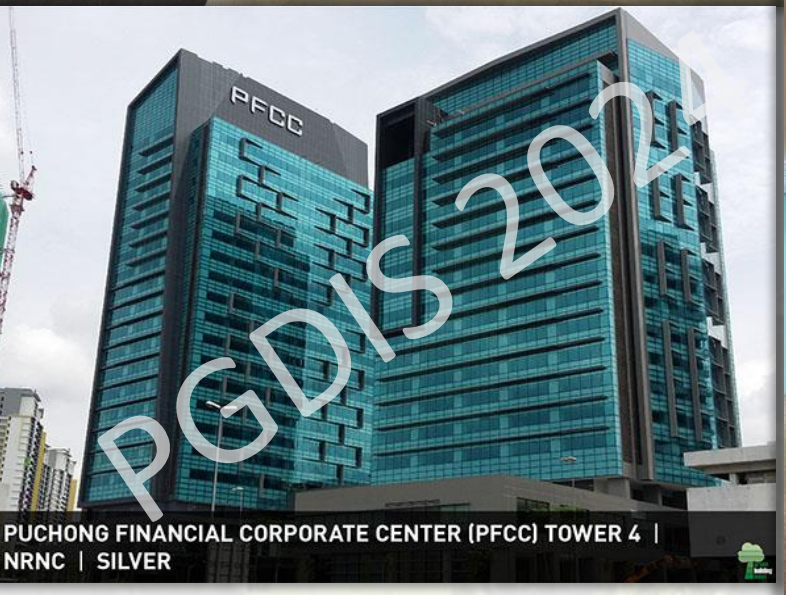

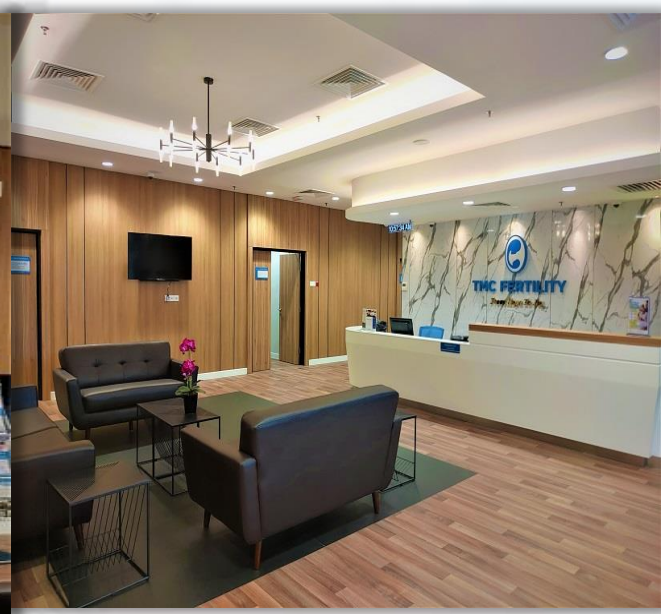

THANK YOU

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