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A Preliminary Economic Evaluation of PGT-A in a Danish Clinical Setting

Master Thesis Project

10th semester

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May 28, 2025

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Title:

A Preliminary Economic Evaluation of PGT-A in a Danish Clinical Setting

Project:

A preliminary economic evaluation with a hospital perspective comparing PGT-A freeze-all to non-PGT-A (IVF/ICSI) with fresh embryo transfer, through a cost-utility analysis and a cost-consequence analysis in a Danish clinical setting. The study population consist of women of advanced maternal age (37-41) in fertility treatment either single or with a partner.

Project Period:

February 3th 2025 - May 28th 2025

Project Group:

1006

Student:

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Semester:

10th Semester, Medicine with Industrial Specialization: Medical Market Access (MMA)

Supervisor & Co-supervisor:

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Total Number of Words and Pages:

This study contains 13,846 words on 28 pages.

Appendix: In Appendix there is a total of 23 pages.

Abstract

Introduction

A plummeting decline in fertility is currently observed with a Total Fertility Rate (TFR) of 1.5 across European countries. According to The World Health Organization (WHO) infertility is the inability to get pregnant after one year of trying to conceive. Fertility treatments are reproductive technologies to help individuals and couples to conceive. Assisted Reproduction Technology (ART) are fertility procedures outside of the uterus, known as in vitro. Preimplantation genetic testing - for aneuploidy (PGT-A) is a technique to predict aneuploid embryos, which are established to be more frequent in women of advanced maternal age and a majority of spontaneous miscarriage are linked to the presence of chromosomal abnormalities. PGT-A has the potential to improve fertility outcomes by only transferring euploid embryos. PGT-A has been formerly economically assessed through cost-effectiveness studies. Thus, such studies fail to include beyond-health outcomes, and do not capture the true value of PGT-A.

Methods

A preliminary economic evaluation of PGT-A with a hospital perspective was conducted through a cost-utility analysis (CUA) and a cost-consequence analysis (CCA). The PGT-A RCT protocol 7.3 was utilized as the premise of this study. A systematic literature search was conducted to obtain relevant input parameters for both analyses. A hybrid decision analytic model incorporating both a Markov model and a decision tree was generated in Tree Age to carry the CUA, and to support the results of the Incremental Cost-Effectiveness ratio (ICER) a deterministic and probabilistic sensitivity analyses was performed. The decision analytic model was developed with a parental perspective including Quality-adjusted life-year (QALY)s of both prospective parents. A time horizon of 24 months, divided in four Markov cycles of six months each, was applied. The CCA was carried out in addition to the CUA, and presented beyond-health outcomes to adequately assess the cost-effectiveness of PGT-A.

Results

PGT-A was more effective, however more costly compared to non-PGT-A. The ICER was 62,262.26 DKK/QALY, and PGT-A is cost-effective with the chosen WTP threshold 180,000 (£20,000) DKK/QALY. The CCA comprehended relevant clinical outcomes with PGT-A improve Live birth rate (LBR), ongoing pregnancy rate, and reducing the risk of miscarriage. Patient centred outcomes encapsulated preferences and motivations towards PGT-A, where the increased probability of a healthy child were reported as the primary motivator.

Conclusion

The CUA showed PGT-A to be cost-effective compared to non-PGT-A with the employed WTP threshold. Supplementary, the CCA indicated that PGT-A improved several clinical outcomes, having the potential to reduce time-to-pregnancy. Reducing the time spent in fertility treatment is advantageous for patients and couples due to the toll fertility treatment has on individuals well-being. This preliminary economic evaluation provides a foundation for future researchers and decision-makers, and a framework for the definitive economic evaluation.

Acronyms

ART Assisted Reproduction Technology. ii, 3, 5, 7, 8, 15, 27, 30–32

CASP Critical Appraisal Skills Programme. 14

Cost-Effectiveness Acceptability Curve Cost-Effectiveness Acceptability Curve. 21, 22

EQ-5D EuroQol- 5 dimensions. 14, 29, 32

FET Frozen Embryo Transfer. 8

HRQoL Health related quality of life. 14

ICER Incremental Cost-Effectiveness ratio. ii, 15, 17, 19–21, 26, 34

ICSI Intracytoplasmic Sperm Injection. 3–5, 7–9, 11, 13–15, 17–19, 22, 23, 26

IUI Intrauterine insemination. 3

IVF In vitro fertilization. 3–5, 7–9, 11, 13–15, 17–19, 22, 23, 26, 34

LBR Live birth rate. ii, 4, 5, 16, 17, 23, 24, 27, 28, 34

NGS Next Generation Sequencing. 8, 12, 18, 22, 24, 29

NICE Natioanl Institute for Health and Care Exellence. 15, 30

PGT-A Preimplantation genetic testing - for aneuploidy. ii, 3–32, 34

PGT-M Preimplantation genetic testing - for monogenic. 7

PGT-SR Preimplantation genetic testing - for structural rearrangements. 7

QALY Quality-adjusted life-year. ii, 14, 15, 19–22, 26, 28–30, 34

QoL Quality of life. 7, 9, 25, 27

RCT Randomised Control trial. ii, 4–7, 9, 11, 12, 14–16, 18, 22–30, 32, 34

TFR Total Fertility Rate. ii, 1, 31

WGA Whole Genome Amplification. 8

WTP Willingness to Pay. ii, 15, 17, 19–22, 26, 30, 34

Contents

1 Introduction

1.1 Declining Fertility

Fertility and especially infertility have received increased attention internationally. The Total Fertility Rate (TFR) across European countries is currently 1.5 births per woman [1]. This fertility rate is below the replacement level of 2.1 births per woman, which is a minimum set rate needed to sufficiently maintain generational replacement and population size over time [1]. In Denmark 1,446 children were live-born per 1,000 women in 2024, which translates to a TFR of approximately 1.5 births per woman [2].

The plummeting decline in total fertility is not a tendency observed only in Europe, it has become a worldwide issue with a global TFR of 4.8 births per woman in the 1950 to a TFR of only 2.2 births per woman in 2021 [3]. The change in fertility have and will continue to have a profound effect on economics, geopolitics, health, and the environment. A demographic shift with an ageing population and a shrinking labour force has already inaugurated, and will further contribute to economic challenges, and an increased pressure on healthcare systems and social security systems [3]. The demographic transition has altered the mortality and fertility rates going from high to low, which have also had a negative impact on the population momentum. The population momentum is the effect of the age structure in the current population on the population size of the future, and a negative population momentum means that the population is pre-set to decline due to the ageing structure of the current population [1]. A negative population momentum and continuously smaller cohorts of women in their reproductive age signify that not only will children be missing in the future, but there will also be a shortage of parents [1].

1.2 Drivers of Low Fertility

One of the key drivers to explain the historically low fertility rate is postponement of childbearing, and that individuals are of older age before they choose to have their first child, which further can be explained by factors such as longer education and increased level of complexity in modern career paths [1]. Moreover, other factors such as cohabitation and partnering have changed over time and a delay in partnering in combination with an increase in solo living, is observed. In addition, there has been an alternation in the norms of how a family can be constructed. These drivers together with general world uncertainties, inadequate or missing support from family, economic constraints e.g. the costs of housing and living are cultural, structural and societal changes in the postmodern society contributing to low fertility [1].

Moreover, even though the TFR is presently 1.5 i Europe the ideal number of children, from the perspective of European individuals and couples, have notably not changed. The fertility intentions of European couples or individuals have remained a two-child family, which underlines a "fertility gap" between intentions and enabled fertility [1]. Pro natal policies or family friendly policies are policies developed with the purpose of increasing fer-

tility rates, and could potentially narrow the gap between intentions and realized fertility, by addressing fertility barriers such as a manageable work-life balances, access to quality child care, improved sex education, addressing the aggravating economic position of young people, and inequality in access to assisted reproductive treatment etc. [1].

1.3 Consequences of Infertility

Infertility is described by the The World Health Organization (WHO) as the inability to get pregnant after one year or more of trying to conceive [4]. Approximately, one in six people in the reproductive age will experience infertility at some point throughout their lifetime [4]. Infertility can further be categorized as primary infertility which is when an individual never have achieved a pregnancy, and secondary infertility which is infertility after at least one achieved pregnancy [4]. A successful conception and further clinical pregnancy is dependent on a series of physiological mechanisms, and a problem in the reproductive organs or the gametes of both men and women can cause infertility [5]. Risk factors for infertility in both women and men are genetic conditions which can be either single gene disorders or chromosomal abnormalities, medical- or health conditions, ageing, environmental, occupational health issues, and infections. These risk factors along with overall lifestyle factors such as alcohol and obesity are all conditions, which can potentially contribute to failure of embryo implantation [5]. The gender based causes of infertility are distributed broadly as 20-40% being only female factor causes, 20-30% being only male factor causes, and 20-40% being a mutual cause [5].

Infertility can result in a number of consequences for both the individual and couples including both physical and psychological consequences. Failure to fulfil personal- or societal expectations for a child and a family can lead to stigma, ultimately in the form of self-stigma [5]. Even though evidence underlines that women and men equally contribute to infertility, women especially experience stigma and blame for infertility, which can provoke worse mental health. Especially as it is primarily the women who must take on the burden of fertility and subject their body to a variety of tests and treatment procedures [5]. A gender asymmetry is seen in fertility treatment with mens' role often reduced to delivering semen samples. However, a Danish study by Selvest et al. 2018 interviewing participants with severe male factor infertility identified that the men experienced a threatening of their masculinity, since they could not live up to the expectations to conceive naturally with their partner and become a father [6].Both infertile men and women show higher levels of stress, depression, anxiety, lower self-esteem, and general lower satisfaction of life compared to couples not going through fertility treatment [5].

In a qualitative meta-synthesis by Assaysh-Öberg et al. 2023 investigating women's experiences in fertility treatment, infertility was described as an invisible condition with an invisible loss being the loss of a possible future [7]. The meta-synthesis found several factors which had a significant impact on the women, e.g. psychosomatic pain from the treatment procedures and medication, grief over childlessness, grief of a miscarriage, distress in relationships, and an overall lack of support from society and the health care system [7].

1.4 Fertility Treatment in Denmark

In Denmark publicly funded fertility treatment is confined to single women with no more than one child and couples who does not have more than one joint child [8]. In Denmark fertility treatment is offered to women until the age of 45, however in the public sector it is only offered to women until the age of 40 [8]. In 2024 fertility treatment was in the centre of the public eye in Denmark, and the Danish government appointed a multi-million sum towards an expansion of treatment capacity in extension of the new right to receive publicly funded help to get a second child, and the right to get a total of six In vitro fertilization (IVF) cycles [9]. The decision to expand capacity was carried through due to, since the right to a second child became effective in December 2024, and the allocation of money will go towards new equipment and personnel [9]. In addition, more and more individuals and couples require assistance to bring children into the world and in 2024 every ninth child in Denmark was born through fertility treatment, and a total of approximately 38,000 fertility treatments were carried out. [10].

Fertility treatments are reproductive technologies designed to help individuals or couples to conceive. Fertility treatment to battle childlessness can be differentiated into Intrauterine insemination (IUI) and Assisted Reproduction Technology (ART). In IUI procedures only the sperm is manipulated, whereas in Assisted Reproduction Technology (ART) treatments both sperm and oocytes are manipulated [11]. Most often IUI is the first initiated treatment offered to individuals or couples. IUI fertilization takes place within the uterus, also referred to as in vivo [11]. On the other hand, ART fertilization takes place outside of the uterus, in vitro [11]. ART refers to fertility treatment in which oocytes or embryos are handled outside of the patient´s body with the purpose of enhancing implantation and the probability of a successful pregnancy. IVF is the most common ART treatment, and fertilization is achieved by adding a semen sample to the oocyte in vitro, allowing natural sperm penetration of the oocyte. IVF can also be carried out with Intracytoplasmic Sperm Injection (ICSI), in which a single spermatozoon is manually selected and injected into the oocyte to achieve fertilization [11]. In 2024 the percentage of clinical pregnancies following IVF/ICSI, was only 14.95% out of all IVF/ICSI treatments started [12]. The success rate declines with increased reproductive age and for patients above the age of 40 only 1.7% acquired a clinical pregnancy in 2024 out of all initiated IVF/ICSI treatments [12].

1.5 Preimplantation Genetic Testing - Aneuploidy

It has been established that the frequency of aneuploidy known as chromosomal abnormalities in human preimplantation embryos increase with advanced maternal age, and that the majority of spontaneous miscarriage are linked to the presence of aneuploidy. Hence, in theory utilization of Preimplantation genetic testing - for aneuploidy (PGT-A) to select and only transfer euploid embryos with a normal chromosomal concentration could potentially improve fertility outcomes [13]. In Denmark PGT-A is only legal within a research protocol, which have been approved by the Medical Research Ethics Committees [14] [8], [15]. Similarly, other European countries like Germany, France, Sweden, Norway, Hungary, Lithuania, and the Netherlands have not legalized utilization of PGT-A in a clinical setting [16]. However, other countries have adopted the procedure broadly as within the

United states where PGT-A was performed in 44% of all IVF cycles in 2019 [17].

PGT-A involve performing a trophectoderm biopsy of all eligible embryos. The biopsy will be performed on embryos in a blastocyst stage, which are on day five to six after oocyte pick up and fertilization. Subsequently, a genetic analysis is performed to evaluate the ploidy status of the extracted biopsies. The biopsy is essential in identifying the euploid status of embryos, and discarding aneuploid embryos. Potentially, PGT-A could improve implantation rates by only transferring euploid embryos, reduce time-to-pregnancy, reduce the rate of miscarriage, improve LBR, and improve other fertility outcomes especially in women of advanced maternal age 7.3.

1.5.1 PGT-A RCT study

A PGT-A multinational multicentre Randomised Control trial (RCT) study of women aged 37-41 years undergoing fertility treatment has been initiated in three fertility clinics in Denmark (Herlev Hospital, Aalborg University Hospital and Rigshospitalet), and a clinic in Spain (Dexus Major, Barcelona). The protocol of the PGT-A RCT study is available in Appendix 7.3, and will function as the premise of this study. The study population will be randomized 1:1 into either of the two study arms: PGT-A freeze all and non-PGT-A (IVF/ICSI) with fresh embryo transfer. The objective of the ongoing Danish PGT-A RCT study is to investigate whether PGT-A can improve Live birth rate (LBR) meaning prove superiority of PGT-A, and simultaneously prove non-inferiority of PGT-A in comparison to non-PGT-A in regard to cumulative LBR 7.3.

1.5.2 The Effect of PGT-A

Even though the PGT-A procedures was developed almost 30 years ago, the effect of PGT-A is still highly disputed. PGT-A has a factual complexity, and there is significant heterogeneity in the execution of the procedures within studies [13]. In assessment of the effect PGT-A is dependent of the age of the study population due to a certain aneuploidy percentage needed, the number of eligible blastocysts, efficiency of the PGT-A as a selection-tool to avoid misdiagnosis, and lastly the selection success criteria reported within the study [18]. For this reason, a non-selections study assessing the predictive values of PGT-A is carried out simultaneously with the PGT-A RCT study. It is important to establish the predictive values of PGT-A under the most optimal clinical conditions, especially due to the challenging aspect of mosaicism. Mosaicism refers to when the cell linage of the embryo consist of a mix of both euploid and aneuploid cells. Mosaicism complicates PGT-A, since a trophectoderm biopsy can not feasibly capture the degree of mosaicism of the whole embryo including inner cell mass [13]. Mosaic embryos has a 38% chance of turning into a clinical pregnancy, which are embryos that would otherwise have been discarded [19]. Moreover, it is important to be attentive to the clinical practice used in determination of the degree of mosaicism since each laboratory often has subjective cut-offs, which may be one explanation to the variation observed between studies [19]. The clinical significance of mosaicism in embryos are still being studied, but can lead to misdiagnosis following trophectoderm biopsy as a false negative or false positive result, where false positive results are when viable embryos are discarded [20]. The effect of PGT-A is therefore also highly dependent on the clinical procedures performed such as fresh versus frozen em-

bryo transfer, biopsy at the blastocyst stage, single embryo transfer, and the techniques applied for genetic testing.

The true clinical effect of PGT-A still remains undisclosed indifferently from which criterion have been investigated: LBR, cumulative LBR, pregnancy rate, miscarriage rate, time-to pregnancy etc.[18]. A review by Viville et al. 2025 have assessed the controversy of PGT-A and found that several randomized studies and meta-analyses have showed an improved ongoing pregnancy rate and LBR in comparison to conventional IVF/ICSI [13]. However, one major point of criticism of the studies reporting beneficial results is that outcomes were investigated per embryo transfer, which may have excluded several attempts of failed fertilization and embryo development errors [13]. Other studies have presented results per ART cycle posing similar results in regard to overall pregnancy outcomes between PGT-A and conventional IVF/ICSI [13]. However, according to a review by Seckin and Forman 2023, RCT studies observing an increase in LBR and cumulative LBR in women of advanced reproductive age also observe a decrease in cumulative live birth in younger study population [19]. Thereby, no change in cumulative live birth is observed when all age groups are taken into account, emphasizing why the cumulative LBR should not be a succescriterion of PGT-A [19].

In addition, to the efficiency dispute, PGT-A as an add-on to conventional fertility treatment also incur large additional costs [13]. Thus, costs of genetic testing are decreasing, the costs of fertility treatment is evidently rising with the increase of add-ons to IVF procedures [21]. Implementation of PGT-A adds an increased complexity level and additional unavoidable costs [21]. In a retrospective review by Davis et. al 2024 the population with the most economic benefits of PGT-A would be women of advanced maternal age [22]. Furthermore, the study reported that women under the age of 35 may not benefit economically from PGT-A, since top ranked embryos chosen for transfer in this age group had a higher probability of being euploid based on only morphological assessment compared to women of advanced reproductive age [22]. PGT-A becomes unnecessary, and even provide more detrimental effects to women of younger age.

Only a limited number of cost-effectiveness studies have been generated comparing PGT-A to non-PGT-A. In a systematic review by Olive et al. 2014 only seven cost-effectiveness studies were identified [23]. However, the identified cost-effectiveness studies presented heterogeneity in conformity of the executed procedures with missing evidence of the effect of PGT-A [23]. One of the cost-effectiveness studies was by Somigliana et al. 2019, and results implied that implementation of PGT-A could have potential of being cost-effective, however a successful implementation would be dependent on the local clinical setting and the age of the population group [21]. Furthermore, increased reproductive age and the number of blastocysts available enhanced the cost-effectiveness of the strategy [21]. Scarcity of resources is a crucial challenge within healthcare settings underscoring the importance of conducting a solid economic assessment prior to a potential implementation of fertility technologies as PGT-A.

1.6 Project Aim

The true clinical effect of PGT-A is still highly disputed and the procedure comes with large additional costs. The efficiency of PGT-A is highly contextualized underscoring the value of the initiated PGT-A non-selection and RCT study, which are carried out in a Danish clinical setting. However, since the RCT study have just initiated no real world data is available for application in this study. To the knowledge of this study a economic evaluation incorporating both a cost-utility analysis and a cost-consequence analysis comparing PGT-A to non-PGT-A have not yet been carried out. Thus, it is of importance to assess the cost-effectiveness of new technologies to support decision-makers in selecting the most optimal strategy. A preliminary economic evaluation will contribute to a improved understanding of the value of PGT-A beyond health-effects.

Therefore, the aim of this project is:

"To investigate costs and consequences of PGT-A in comparison to non-PGT-A through an economic evaluation from hospital perspective of patients and their partners in fertility treatment in a Danish clinical setting, through a cost-utility analysis and a cost-consequence analysis"

2 Method

The method will consist of two sections, where the first section 2.1 will comprehend a comprehensive description of the two strategies: PGT-A compared to non-PGT-A (IVF/ICSI). The second section 2.2 will present the methodological considerations of the economic evaluation incorporating both a cost-utility analysis generated through a decision analytic model and verified with sensitivity analyses, and a cost-consequence analysis.

2.1 Comprehensive description of PGT-A vs. non-PGT-A

To generate the economic evaluation a comprehensive description of the two strategies: PGT-A compared to non-PGT-A (IVF/ICSI) was developed to emphasize the difference of the two strategies, and identify all relevant costs and consequences of each strategy for inclusion in the economic assessment. The description was be applied in the development of this preliminary economic evaluation, and the PGT-A RCT protocol served as the foundation for the description. The protocol can be accessed in Appendix 7.3. The PGT-A RCT study is a multinational multi-centre, randomized controlled non-blinded trial. The study population will be recruited from three Danish fertility clinics (Rigshospitalet, Aalborg University Hospital and Herlev Hospital), and a fertility clinic in Spain (Dexeus Majour, Barcelona). PGT-A is an specialized and complex intervention, which requires personnel executing the procedures to be highly skilled, as any other in vitro technique [13]. Rigshospitalet and Aalborg fertility clinic already perform PGT-M and PGT-SR, and Herlev Hospital already perform PGT-A, qualifying them to undertake the execution of an advanced technology as PGT-A.

Patient enrolment was initiated in 2024 and will continue until 2028, which was why no real world data were applicable for utilization of this study. The study population eligible for randomization are women aged 37-41 years of age in fertility treatment either solo or with a partner. Patients are eligible if they are in their 1-5 round of IVF/ICSI and previous cycles will not be counted if the patient are recruited after a live birth. Moreover, a validated questionnaire concerning Quality of life (QoL) will be handed out three times during the study to the patient, and their partner, to monitor the patients or couples quality of life throughout the study. Study inclusion will take place around menstrual cycle day two to five at the initiation of the ovarian stimulation induced with gonadotrophins and ovarian triggers. At ovulation oocytes are retrieved from the ovaries, and the fertilization will be performed in vitro with ICSI. Patients with at least one good quality blastocyst is eligible and will be randomized on day five, six or seven after oocyte pick up. Reasons for exclusion are utilization of PGT-M or PGT-SR, male partners with severely compromised semen quality (<1 million), if the patient has stage 3-4 endometriosis, patients with severe thyroid disease, patients anti- Müllerin hormone level must be $\geq$ 6.28 pmol/L, if patients have had $\leq$ 2 prior ART treatments which resulted in no blastocysts formation, and if patients have severe comorbidities as diabetes mellitus 1, Morbus Chron and Colitis ulcerosa, systemic lupus erythematosus, HIV, Hepatitis B/C or a disregulated thyroid disease.

If a minimum of one blastocyst is applicable after fertilization, patients will be randomized 1:1 in two groups PGT-A or non-PGT-A. The first group will receive PGT-A with freeze all trough vitrification of embryos fol-

lowing trophectoderm biopsy, and subsequent transfer of suitable embryos. Embryos are suitable for transfer if they are euploid and has a mosaicism percentage $\geq 80\%$. Embryos are ranked according to their euploidy status so embryos with the highest implantation potential are transferred first. The highest rank are embryos with euploidy defined as $\geq 50\%$ mosaic results identified in the biopsy. Secondly, blastocysts with a mosaic results $>$ 50-80% in the biopsy, and the lowest rank are blastocysts with a mosaic result above 80%. A (Whole Genome Amplification (WGA))-Next Generation Sequencing (NGS) setup with a sequencing depth of 0.01x will be used to perform whole genome sequencing and allow chromosome enumeration (ploidy status). The second group will receive standard of care treatment, non-PGT-A with fresh embryo transfer, where eligible blastocysts will be evaluated with morphokinetic assessment to rank implantation potential. The first embryo will be transferred fresh as a day five blastocysts, while the following embryos will be transferred with FET as day 6-7 blastocysts. For both strategies only one embryo is transferred at a time. Patients and couples are recruited and randomized for one ART treatment only. One full ART treatment is defined as utilization of all viable blastocysts both frozen and fresh until live birth or 18 months after study randomization. The patient pathway of the two alternatives are visualized in figure 2.1.

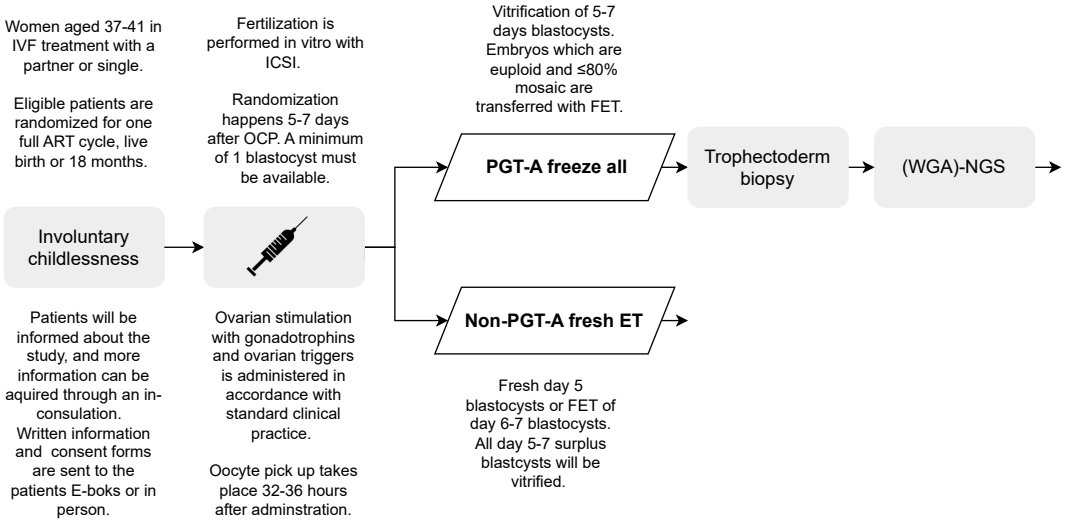

Figure 2.1: *Visualization of the patient pathway from cohort randomization if indication of IVF/ICSI to embryo transfer. Patients are randomized equally 1:1 into the two alternatives PGT-A and Non-PGT-A. The final arrows of each strategy indicate transfer of an embryo. OPU = Oocyte pick up, WGA = Whole Genome Amplification, NGS = New Generation Sequencing, FET = Frozen embryo transfer, ET = Embryo transfer, and ART = Assisted reproductive treatment. Moreover, vitrification is a technique to cryopreserve embryos.*

PGT-A predicts euploidy status of embryos before transfer with the purpose of improving implantation potential of the embryo compared to non-PGT-A (IVF/IVF). In a study by Davis et al. 2024 it was reported that by the age $\leq$38 only 32% of the embryos with the highest implantation potential were predicted correctly by

the morphological test only, underscoring the significant potential of a more effective selection tool as PGT-A [22]. As a part of the PGT-A RCT study, patients and their partners in both treatment arms will be asked to answer a QoL questionnaire to asses satisfaction and QoL for a total of three times during the study period. As mentioned, going through fertility treatment can have a crucial impact on individuals and couples overall well-being. Moreover, fertility treatment and infertility are about more than just health outcomes, it is about a dream and unfulfilled intentions. Former cost-effectiveness studies have assessed PGT-A economically based on clinical success criteria, with a majority of the studies focusing on the value of a live birth [23]. However, to properly capture the complexity of PGT-A and elaborate on beyond-health effects a different approach is needed.

2.2 Economic Evaluation

A full economic evaluation was chosen as the preferred method to assess the cost-effectiveness of PGT-A compared to non-PGT-A (IVF/ICSI). A full health economic evaluation compares all relevant costs and consequences of at least two alternatives; the health intervention and the comparator, which are the current standard of care [24]. An economic evaluation with a hospital perspective, incorporating both a cost-utility analysis (CUA) and a cost-consequence analysis (CCA) were carried out.

2.3 Systematic Literature Search

Input parameters for the economic evaluation were found through a systematic literature search. Prior to the systematic literature search an unsystematic search was conducted in gray literature with reference- and chain search to identify relevant search terms and synonymous. The PICO model was utilized to establish a framework to generate the block search evolving around the four facets; Population, Intervention, Comparison, and Outcome. The PICO framework are presented in table 2.1. The desired population were female patients aged 37-41 in fertility treatment either solo or with a partner. The intervention of interest was PGT-A, conventional IVF or ICSI. The comparison facet was omitted in the search, since the comparator non-PGT-A was included in the intervention facet. Outcomes of relevance were utilities/disutilities, transitions probabilities, and overall outcomes including beyond health outcomes such as quality of life.

Population	Infertile women (37-41) and their partners in fertility treatment
Intervention	PGT-A, IVF or ICSI
Comparison	Omitted*
Outcomes	Utilities/disutilities, probabilities, and overall non-health outcomes

Table 2.1: PICO framework for the systematic literature search. The table outlines the targeted search of the four facets; Population, Intervention, Comparison, and Outcome. The comparison facet was omitted indicated with a *.

The systematic literature search was conducted as a broad search to ensure identification of all relevant outcomes. The systematic literature search was carried out on the 30th of April 2025 as a block search in the databases PubMed and Embase. The search strategy included both free text words, searched in title or abstract (ti/ab) and thesaurus terms, MeSH terms in PubMed and Emtree terms in Embase, which were all searched unexploded (exp). All words in each facet were linked with "OR" and the facets were connected with "AND". Moreover, truncation of specific words allowed for capturing all versions of a word. Search strategies and the search strings from both databases are presented in Appendix 7.1.

2.3.1 Study selection

Studies found through the systematic literature search were screened with the software Rayyan [25]. Duplicates were sorted out by including the study with the most detailed and newest information. The included studies were screened based on title, abstract, and full text in accordance with the eligibility criteria. The screening process was carried out entirely by the author (EME). The systematic literature search resulted initially in identification of 1,085 studies found through Embase and 449 studies found through PubMed, with a total of 1,368 studies eligible for screening. 166 studies were removed as duplicates. After title screening 195 studies were left, and after abstract screening 53 studies were left for full-text screening. 2 studies were applicable for study inclusion. Despite the fact that a large number of studies were identified a supplementary unsystematic search was conducted to guarantee inclusion of all relevant studies within the research scope. Completing literature were primarily found to systematic reviews and meta-analysis of PGT-A [23], [18]. The PRISMA flowchart in figure 2.2 visualizes the selection process of the systematic literature search and the inclusion of supplementary literature.

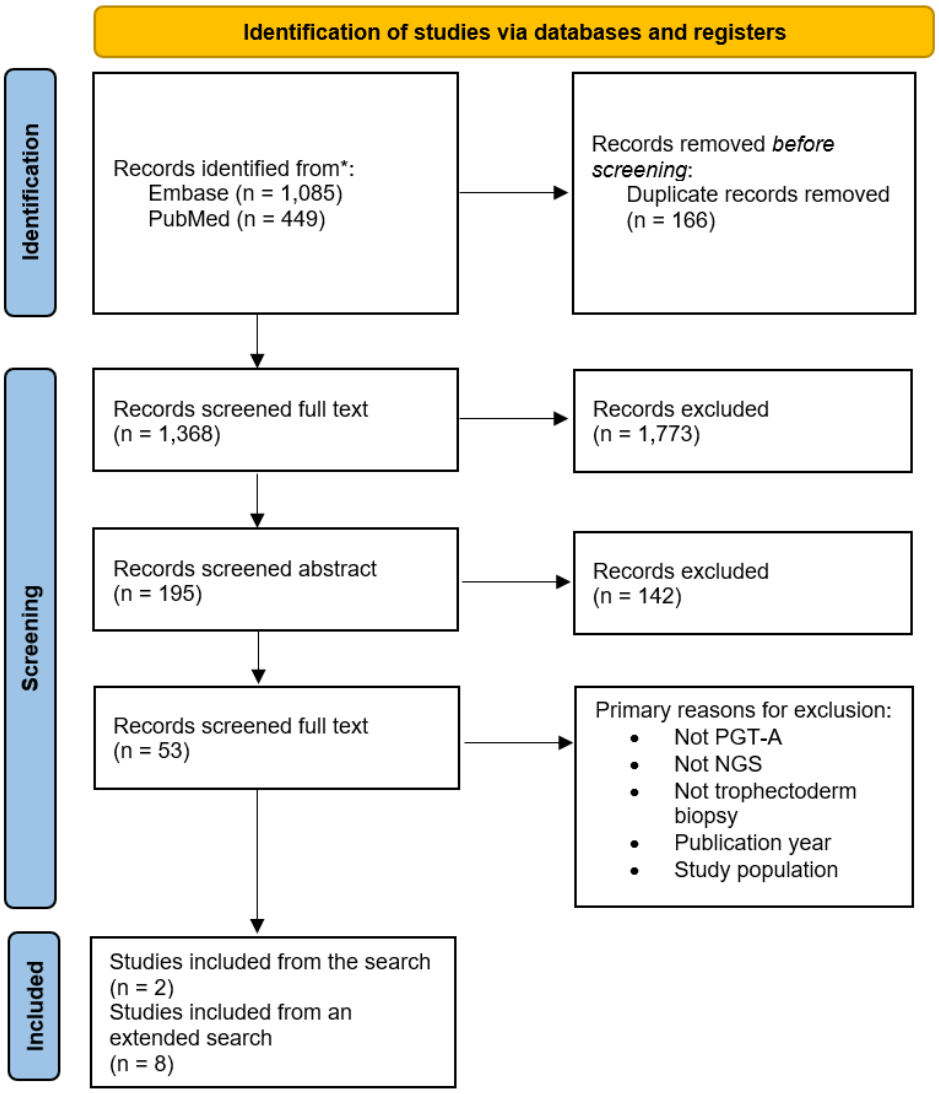

Figure 2.2: *PRISMA flowchart visualizing the study selection process.*

2.3.2 Eligibility Criteria

Eligibility criteria employed to the systematic literature search and supplementary search. Inclusion- and exclusion criteria applied are presented in table 2.2. Studies for inclusion should investigate the desired study population, which was women, preferably aged 37-41, in fertility treatment either single or with a partner, in alignment with the PGT-A RCT study. Specifically, the fertility treatment had to be either PGT-A or conventional IVF and ICSI. However for outcomes of the cost-consequence analysis generalized outcomes of fertility treatment were of interest. Additionally, since very few cost-utility studies of fertility treatments have been developed and none have been published specifically for PGT-A utilities and disutilities were sought for in a more generalized manner

to be applied to specific infertility health states e.g. miscarriage.
Studies were excluded if they had no title, no abstract or were not available in full text or in English. Furthermore, studies with potential input parameters in relation to PGT-A´s effects were excluded if the concept of PGT-A did not align with the PGT-A RCT protocol [Appendix 7.3]. The concept of PGT-A is by this study understood as essential methodological procedures including a trophectoderm biopsy, the utilization of NGS, and single embryo transfer. Lastly, the study population within the studies had to come from a country with a similar health care system to a Danish setting, preferably a high income country for transferability of the results.

Inclusion criteria	Exclusion criteria
• Infertile woman (preferably aged 37-41) and couples	• Studies without a title or an abstract
• Patients/couples going through or have gone through fertility treatment (IVF/ICSI/PGT-A)	• Not available in full text
• Studies investigating both benefits, harms and overall outcomes of PGT-A and non-PGT-A (fertility treatment)	• Not available in English
• Studies presenting utilities/disutilities of health states within fertility treatment	• Studies not investigating a concept of PGT-A in alignment with the PGT- RCT protocol (trophectoderm biopsy, single embryo transfer, NGS)
	• Study population preferably from a country with a comparable health care system to a Danish setting

Table 2.2: *Eligibility criteria applied to the systematic literature search and the supplementary literature in the search of the outcomes utilities/disutilities, probabilities, and overall outcomes for the economic evaluation*

2.3.3 Included Studies

Included studies were used for extraction of input parameter for utilization in the cost-utility analysis and the cost-consequence analysis. In addition, title, publication year, study design, interventions investigated, characteristics of the study population including nationality, cohort size, and age were extracted from the studies. Studies for inclusion in the economic evaluation with directly outcomes can be seen in table 2.3. Studies utilized for the patient-centred outcomes in the cost-consequence analysis are not presented.

Of the studies used for extraction of clinical outcomes three were RCT studies, two were cost-effectiveness studies, and one systematic review and network meta-analysis. Population size varied within the studies with the smallest population size being 220 in Ozgur et al. 2019 [26]. The nationality of the cohorts of the studies assessing PGT-A were the United states, Canada, UK, Australia, Turkey, and China. All three RCT studies had reported the utilization of NGS for genetic testing of the biopsy. Thus, only Ozgur et al. 2019 and Yan et al.

reported that ICSI was used for fertilzation within the study [26], [27]. Age of the study population varies greatly, however both Munné et al. 2019 and Somigliana et al. 2019 performed subgroup analysis [28], [21]. Mennini et al. 2018 was the only study that did not investigate PGT-A compared to non-PGT-A, butcompared different strategies in the treatment of controlled ovarian stimulation (COS). However, input parameters extracted from the study were utilities, which applied to general events of IVF [29].

Author (s) / Publication year:	Study design:	Intervention:	Population:	Input parameter(s):
Munné et al. 2019	RCT multicentre multinational study	PGT-A vs IVF +NGS	661 women aged 25-40 (38-40) of US, Canada, UK or Australia	Probabilities/ Clinical outcomes
Mennini et al. 2018	Cost-effectiveness study	rFSH + rLH vs hMG in treatment of COS	848 Italian women with a mean age of 36.7 years	Utilities/disutilities
Ozgur et al. 2019	RCT single centre study	PGT-A vs. IVF (ICSI) + WGA-NGS	220 Turkish women ≥35 years	Clinical outcomes
Yan et al. 2021	RCT Multicentre study	PGT-A vs. IVF (ICSI) + NGS	1212 subfertile Chinese women aged 20-37 years	Clinical outcomes
Simopoulou et al. 2020	Systematic Review & Network Metanalysis of RCTs	Efficiency of PGT-A and day 5 vs. day 3 biopsy	11 RCT studies age of the study populations 21-42 years	Clinical outcomes
Somigliana et al. 2019	Cost-effectiveness study	PGT-A vs. IVF	Based on a theoretical model, women aged <35 to 44.	Costs

Table 2.3: *A table of included studies from which input parameters where extracted are presented. Studies utilized for patient-centred outcomes are not included in this table. Author(s), publication year, study design, intervention, population characteristics, time horizon, perspective, and which input parameter(s) were extracted from each study are presented. RCT = randomized control trial. NGS = next-generation sequencing. WGA = whole genome amplification. rFSH = recombinant follicle stimulating hormone. rLH = recombinant luteinizing hormone. hMG = human menopausal gonadothropin. COS = controlled ovarian stimulation. aCGH = micro-array based comparative genomic hybridization * indicates information not applicable, since the studies were not cost-effectiveness studies.*

2.3.4 Quality Assessment

All studies were assessed with Critical Appraisal Skills Programme (CASP) for the risk of bias and quality assessment. The CASP checklist ensures a structured and more accurate critical assessment [30]. CASP checklist are made for specific study designs and consists almost always of 12 questions covering validity, results, and clinical relevance of the study assessed [30]. None of the included studies had major evidence concerns with a fraction of questions marked with ´Can´t tell´. A filled out CASP checklist of Munné et al. 2019 is available in Appendix 7.4 for reference.

2.4 Cost-Utility Analysis

A cost-utility analysis is a variant of a cost-effectiveness analysis where the generic effect measure for health benefit Quality-adjusted life-year (QALY) is utilized. In contrast to a disease specific effect measure QALY allows for comparison across different disease areas [24]. Thereby, QALY permit decision-makers to assess the opportunity cost of adopting and implementing a new intervention. QALY combines Health related quality of life (HRQoL) scores with life years lived in a given health state. Utility values represent Health related quality of life (HRQoL) scores of given health states and range from 1 (perfect health) to 0 (death= on a vertical scale [31]. Utility values can be elicited with both direct methods e.g. time trade-off (TTO) or indirect methods e.g. EuroQol-5 dimensions (EQ-5D) [31]. As the economic evaluation was carried out from a hospital perspective, only costs related to hospital procedures were included. A time horizon of 24 months was adapted to imitate the setting of the PGT-A RCT protocol, where effects were no longer recorded 18 months after randomization [Appendix 7.3].

2.4.1 Decision Analytic Model

In order to develop the cost-utility analysis a decision analytic model (DAM) was generated. The decision analytic model was generated in TreeAge Pro 2024 R2.1 Healthcare, as a hybrid model incorporating both a Markov model and a decision tree to simulate the two strategies; PGT-A and non-PGT-A (IVF/ICSI) [32]. A decision tree is adequate when the course of treatment includes distinct events, which depends on probabilities and a limited time frame. On the contrary, a Markov model is memoryless, which means that the probability of transitioning to a given health state is not dependent on earlier health states [31]. A combination of the two allowed for properly imitating the course of fertility treatment through through cycles imitating a new embryo transfer.

Moreover, defined Markov health states made it possible to simulate transition probabilities between health states. A total of five health states for either of the two alternative strategies PGT-A and non-PGT-A (IVF/ICSI) were developed; 'Involuntary childlessness´, ´New embryo transfer 1´, ´New embryo transfer 2´, ´Given birth´, and ´No embryo transfer´. The entire cohort of both strategies starts in the health state ´Involuntary childlessness´. This health state represents the first embryo transfer and patients will experience either a live birth, a miscarriage, or a failed implantation. If a miscarriage or a failed implantation is incurred patients will at the end transition to the health state ´New embryo transfer 1´, where the decision are entirely the same. Patients who experience a miscarriage or a failed implantation in this health state patients will transfer to the health state ´New

embryo transfer 2´, where the decision probabilities are the same as the two others, thus if patients experience a miscarriage or a failed implantation they will transfer to the health state ´No embryo transfer´, which is an absorbent health state. Patients who give birth at any cycle will transfer to the health state ´Given birth´, which is also an absorbing health state. Moreover, miscarriages are subdivided into spontaneous miscarriage happening before 13 week, and miscarriages happening after 13 weeks. A model visualizing the five Markov health states are presented below in figure 2.3, capturing how the decision tree is repeated three times to simulate a total of three embryo transfers.

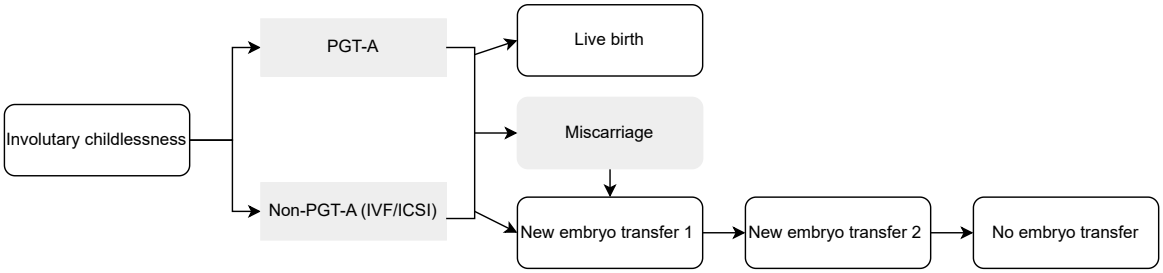

Figure 2.3: *The model visualizes the decision analytic model with the five Markov health states, and a linear display of the patient pathway for the two strategies PGT-A and Non-PGT-A. The decision is repeated for a total of three embryo transfers, and the health states ´Live birth´ and ´No embryo transfer´ are absorbing health states.*

The decision analysis model corresponds to one complete ART cycle, which is defined as the use of all eligible blastocysts both fresh and frozen, a live birth or 18 months after randomization by the PGT-A RCT protocol [Appendix 7.3]. One complete ART cycle were chosen to be a total of three embryo transfers based on data from the PGT-A RCT study which showed that patients had an average of 1.9 eligible embryos, thus recognizing variation since some patients will experience a miscarriage or failed implantation, while others will go through a full-term pregnancy and reach live birth. Each Markov cycle translates to an embryo transfer in the first three cycles. The time horizon was set to 24 months or four cycles of a six month period each. The last cycle was included to capture all costs of effects. Half cycles correction were applied to the model account transitions more accurately and not improperly estimate input parameters. Moreover, utilities within the model were applied from a parental perspective, implicating benefits and decrements in relation to fertility treatment for both prospective parents. A list of all assumptions applied in the model is accessible in Appendix 7.2. The outcome of the model were the accumulated costs and QALY for both PGT-A and non-PGT-A (IVF/ICSI, and an Incremental Cost-Effectiveness ratio (ICER). Since no fixed Willingness to Pay (WTP) threshold is set in Denmark, the adopted threshold of this study were the one currently applied by Natioanl Institute for Health and Care Exellence (NICE) in the UK of £20,000-30,000, which corresponds to approximately 180,000-267,000 DKK, as of may 2025 [33].

2.4.2 Data Collection Cost-Utility Analysis

Anchored in the PGT-A multicentre multinational RCT study this project will describe the method utilized in the generation of the present results, thus also impute recommendations for which data to utilize as input parameters

when real world data from the RCT study is available in the future. In the future, when data have been assimilated, probability data on the specific study cohort should be utilized along with elicited utilities. However, to develop and generate results through a preliminary economic evaluation, probability data were primarily sought from included studies. The expected LBR of the two strategies were extracted from the PGT-A RCT protocol, expected to be 30% for PGT-A and 20% for non-PGT-A [Appendix 7.3]. The probability of a miscarriage was extracted from a study by Munné et al. 2019, due to the risk being aggregated by age subgroups in the RCT study and the risk was extracted for the age group 38-40 [28]. Furthermore, the probability of a late miscarriage was extracted from a study by Wyatt et al. 2005 [34]. An average probability of a late spontaneous miscarriage was calculated for the age group 37-41 to be 1.82%.

Input parameter:	**Variable:**	**Source:**
Probabilities:		
Miscarriage rate PGT-A	8.2%	Munné et al. 2019
Miscarriage rate Non-PGT-A	11%	Munné et al. 2019
Live birth rate PGT-A (expected)	30%	PGT-A RCT protocol (Appendix)
Live birth rate Non-PGT-A	20%	PGT-A RCT protocol (Appendix)
Costs (DKK):		
PGT-A	45,065	13PR01 DRG tariffs (2024)
IVF/ICSI	10,066	13PR03 DRG tariffs (2024)
Miscarriage (after 13 weeks)	11,618	13MP01 DRG tariffs (2024)
Miscarriage (medical)	2,286^	Somigliana et al. 2019
Utilities/disutilities:		
Baseline parental utility	1.815	Jensen et al. 2021
Clinical pregnancy	0.0495* (2 months)	Mennini et al. 2018
Miscarriage	-0.6225* (2 months)	Mennini et al. 2018
Negative hCG test	-0.3735* (5 months)	Mennini et al. 2018
Positive hCG test	-0.075* (3 months)	Mennini et al. 2018
Freeze embryo transfer	-0.0249* (1 month)	Mennini et al. 2018
Fresh embryo transfer	-0.0498* (1 month)	Mennini et al. 2018

Table 2.4: A presentation of probability, cost, and utility input parameters for the decision analytic model. The hat-sign indicates the costs have been discounted from 2018 costs. The $*$ indicate that parental utilities have been calculated with a 1:0.5 ratio (woman/partner).

Data on costs were primarily obtained through the DRG tariffs. However, for the cost of a miscarriage only a DRG tariff in relation to late abortions were applicable, translating to a spontaneous abortion after week 13. For all other miscarriage a costs of a medical miscarriage was applied obtained from Somigliana et al. 2019. The cost was originally obtained from the Italian DRG tariffs from 2018 and were therefore discounted to the present with a discount rate of 3.5% per year [35]. In addition, the same discount rate was applied to all costs within the decision analytic model to account for future decrements, thus altered to fit to the cycle length of six months.

Age and gender-specific baseline utilities were extracted from the normative utility values of the Danish population elicited by Jensen et al. 2021 [36]. An average of the age groups 30-39 and 40-49 was extracted for both women and men, and multiplied together to generate parental baseline utilities. Utilities and disutilities for given health states within fertility treatment were extracted from a study by Mennini et al. 2018 [29]. The Health state utilities were generated from IVF expert opinions a state of perfect health of one [29]. In order to generate input parameters the decrement from one was equal to the applied disutility. It was assumed that the magnitude of the partners´ utility were 1:0.5 ratio (woman/partner) of the maternal utility, since fertility treatment has been reported to be more burdensome to women. Input parameters for probabilities, costs, and utilities are all presented in table 2.4

2.4.3 Sensitivity Analyses

To test the robustness of the decision analytic model, and uncertainties of both input parameters and the model, sensitivity analyses were performed. A one-way deterministic sensitivity analysis (DSA) was generated in the form of a Tornado diagram of the ICER. Higher and lower values were created for input parameters except LBRs, parental baseline utility, and the probability of a late miscarriage, since these input parameters were constants. High and low values for the probability of miscarriage for each strategy were chosen to vary with 5% in accordance with literature, while utilities and costs varied with 10% [28], [26]. Thus, the costs of miscarriage were chosen to vary to 20% due to large disparities in literature [21], [37]. A Tornado diagram visualizes the impact each parameter have on the decision.

Additionally, to test for model uncertainty a probabilistic sensitivity analysis (PSA) was developed. In a probabilistic sensitivity analysis distributions are assigned to each input parameter, which are then sampled at random. However, since no distributions were available in the literature, distributions were generated with the same percentage variation from the mean as applied in the deterministic sensitivity analyses. All input parameters were sampled except LBRs, parental baseline utility and the probability of a late miscarriage. Beta distributions were utilized for all probabilities, while gamma distributions were utilized for utilities and cost parameters. Moreover, a second order Monte-Carlo simulation with 10,000 iterations was used to generate incremental cost-effectiveness scatter plot (ICE-scatter plot. The ICE-scatter plot shows the number of iterations which are cost-effective at the applied WTP and in which quadrant of the ICE-plane the strategi is placed. Lastly, a cost-effectiveness acceptability curce (CEAC) was developed for the two alternatives PGT-A and non-PGT-A to visualize the probability of PGT-A being cost-effective at different WTP thresholds.

2.5 Cost-Consequence Analysis

The cost-consequence analysis (CCA) will be performed as an elongations of the cost-utility analysis to provide a comprehensive analyses of consequences in regard to the two alternative strategies PGT-A and Non-PGT-A (IVF/ICSI), and to inform decision-makers about the best course of action. The cost-consequence analysis will contribute with a comparative and aggregated analysis presenting all relevant clinical and pregnancy outcomes

from the included studies, and an analysis of patient centred outcomes incorporating non-health outcomes which have an impact on the patient and the partner [24]. The advantage of a cost-consequence analysis is that results are not reported in a single metric, and all consequences of interest including qualitative outcomes can be reported [24]. The const-consequence analysis will contribute with a broader perspective beyond clinical outcomes on the different impact of both strategies.

2.5.1 Data collection and data analysis

In the comparative analysis of clinical and pregnancy outcomes, outcomes often reported in other studies in relation to the efficiency of PGT-A was compared. Input parameters were only extracted from RCT studies which were in alignment with the described concept of PGT-A. The utilization of NGS for gene amplification, trophectoderm biopsy, and single embryo transfer were of importance for comparison. Outcomes were extracted per embryo transfer if applicable. Moreover, relative risk ratios (RR) were extracted from a systematic review and meta-analysis by Simopoulou et al. 2020 to underline the validity of the extracted outcomes, since most of the outcomes only were investigated by one study. If studies had performed an age subgroup aggregation outcomes were extracted with the goal of imitating the desired study population of women aged 37-41 in alignment with the PGT-A RCT study [Appendix 7.3].

For the patient centred outcomes studies directly comparing PGT-A to non-PGT-A (IVF/ICSI) were of interest, however a limited number of studies were applicable in the literature. Thus studies investigating conventional fertility treatment were employed to capture the impact of fertility treatment on individuals and couples. However, seen in the light of the potential of PGT-A in regards to improving clinical outcomes. Studies reporting patients´ preferences, motivations, concerns and regrets in regard to PGT-A were included, and all relevant data was synthesized in the analysis.

3 Results

In the following section the results of the preliminary economic evaluation are presented. In section 3.1 the results of the cost-utility analysis generated from the decision analytic model are established. The results of the cost-utility analysis are supported by a presentation of the performed deterministic and probabilistic sensitivity analyses. Secondly, the results of the cost-consequence analysis are presented in section showing disparities in clinical and pregnancy outcomes, and present patients motivations and preferences in regard to PGT-A 3.3.

3.1 Cost-Utility Analysis

The decision analytic model generated accumulated costs and accumulated effects, where the latter translates to the accumulated QALYs over the 24 months time horizon. The accumulated costs and effects of the two interventions, as well as the calculated ICER are presented below in table 3.1. The costs of PGT-A is higher compared to the cost of non-PGT-A (34,952.06 vs. 20,187.19), but the effect of PGT-A is slightly higher (4.83 vs. 4.60). The ICER comparing the cost and effects of PGT-A compared in comparison to non-PGT-A (IVF/ICSI) was 62,262.34 DKK/QALY. This means that for every additional QALY PGT-A provides the cost incurred is 62,262.34 DKK/QALY. Since, neither of the strategies were dominated the decision is dependent on the WTP threshold. The threshold applied was 180,000 DKK/QALY based on the lower bound of the threshold £20,000-£30,000 deployed by NICE (The National Institute for Clinical Exellence) [33].

Strategy:	Costs (DKK):	QALYs:	ICER:
PGT-A	34,952.06	4.83	62,262.34
Non-PGT-A (IVF/ICSI)	20,187.19	4.60	

Table 3.1: *Presentation of accumulated costs and accumulated QALYs of the two strategies PGT-A and non-PGT-A (IVF/ICSI). Calculated ICER showing both strategies are undominated indicated by the yellow dot.*

3.2 Sensitivity Analyses

3.2.1 Tornado diagram

To investigate parameter uncertainty of the model a deterministic sensitivity analysis was performed in the form of a Tornado diagram. Only the input parameters with the highest impact on the model is presented in figure 3.1. The higher a bar within the Tornado diagram is the more impact did the input parameter have on the ICER and the model. The length of the bars indicates the magnitude of the impact. The input parameters with the highest impact were the costs of either of the two strategies, c_PGTAwgenetictesting and c_IVF. Followed by the disutility values applied to the events of having a negative hCG test, a miscarriage or a fresh embryo transfer, u_negativehCGtest, u_miscarraige, and u_freshembryotransfer. However, none of the bars cross the reference line (0,0), which means they do not alter the optimal strategy.

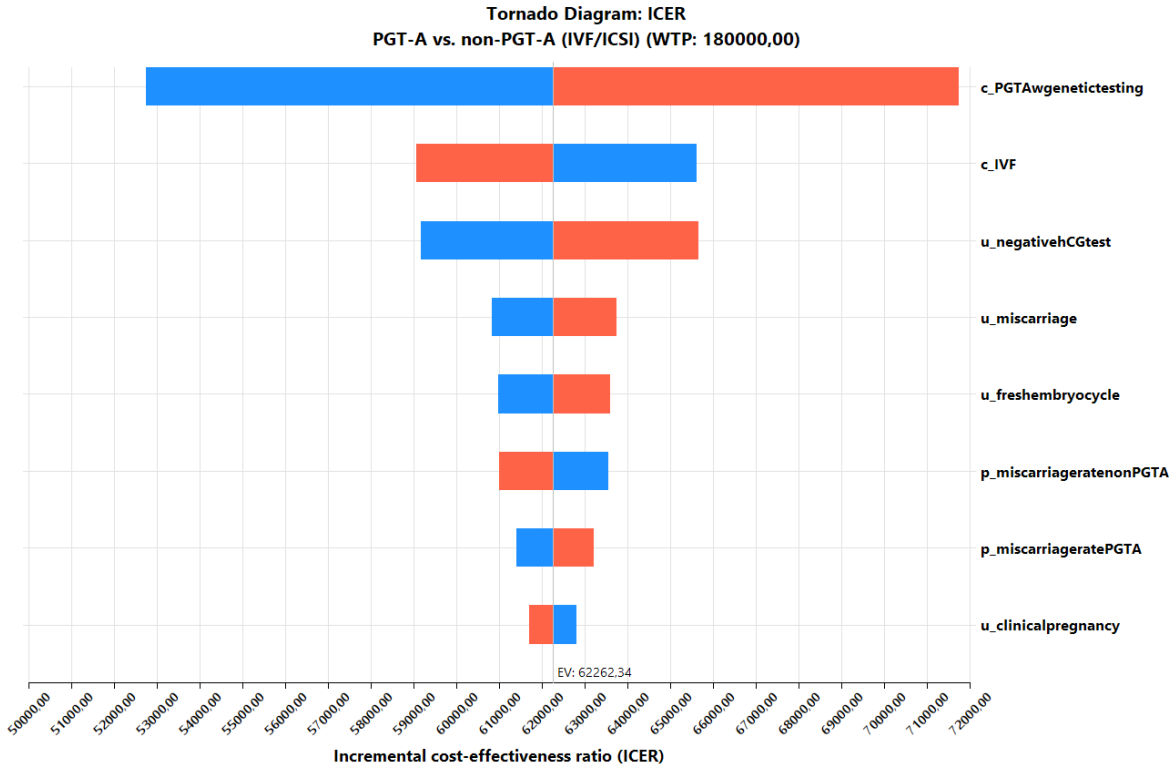

Figure 3.1: *An illustration of the Tornado diagram with all input parameters. p_ indicating a probability, u_ indicating a utility or disutility value, and c_ indicating a costs deployed within the decision analytic model. EV: Expected Value, which is equal to the ICER. WTP: Willingness-to-pay, set to 180,000 DKK/QALY.*

3.2.2 Incremental Cost-Effectiveness Plane

A probabilistic sensitivity analysis was performed to assess model uncertainty. A second-order Monte Carlo sensitivity analysis with 10,000 iterations was performed and the incremental costs-effectiveness plane is presented in figure 3.2. The green ellipse shows the 95% confidence interval of the iterations. All iterations are placed in the north-east quadrant of the ICE-plane (undominated), which is where the new strategy is more effective although more costly, and the strategy is dependent on the WTP threshold. With the adopted WTP threshold of 180,000 DKK (£20,000)/QALY PGT-A is cost-effective.

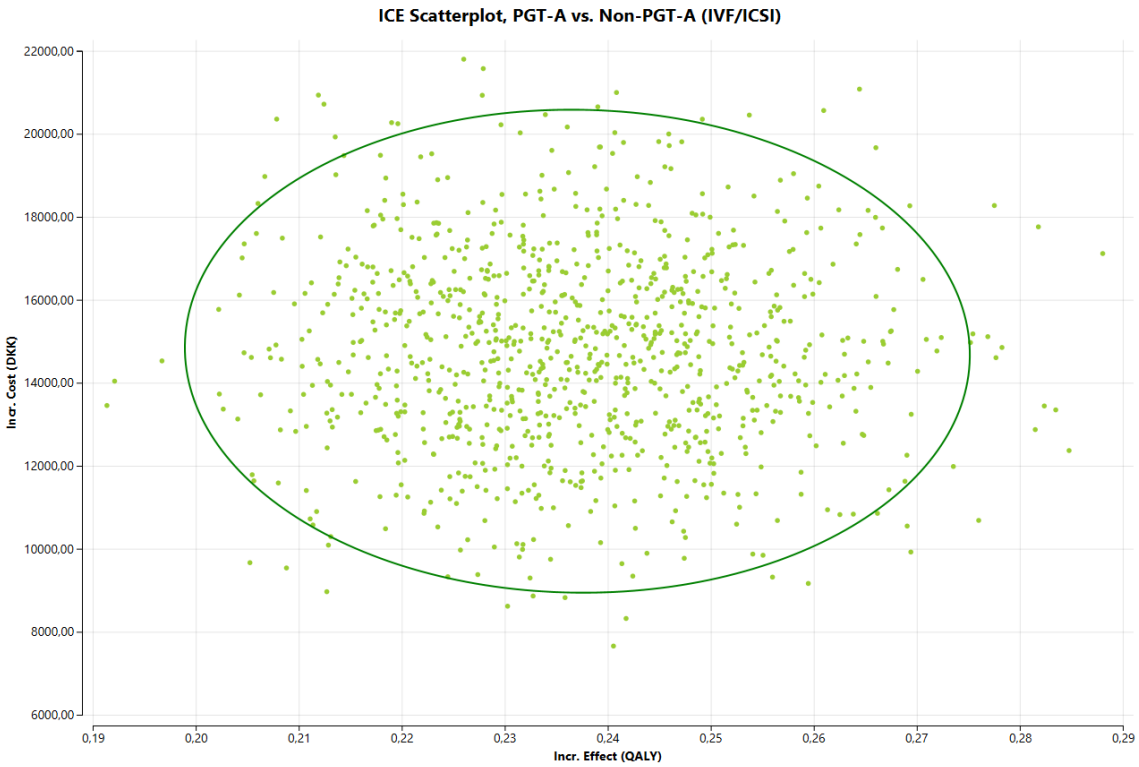

Figure 3.2: *Visualization of the ICE scatter-plot of the ICER developed. The green ellipse circles the area where 95% of the iterations are located. WTP: Willingness-to-pay, set to 180,000 DKK/QALY.*

3.2.3 Cost-effectiveness Acceptability Curve

As a part of the probabilistic sensitivity analysis a Cost-Effectiveness Acceptability Curve (Cost-Effectiveness Acceptability Curve) was generated to assess how variation in the WTP threshold would impact the optimal strategy. The Cost-Effectiveness Acceptability Curve visualizes the probability of cost-effectiveness at a given WTP threshold presented in figure 3.3 below. At the chosen WTP threshold of 180,000 DKK (£30,000)/QALY, there is a 100% probability of PGT-A being cost-effective. The Cost-Effectiveness Acceptability Curve shows that the optimal strategy changes from non-PGT-A to PGT-A at approximately 60,000 DKK, and a 100% probability of PGT-A being cost-effective is already achieved at a WTP of approximately 110,000 DKK.

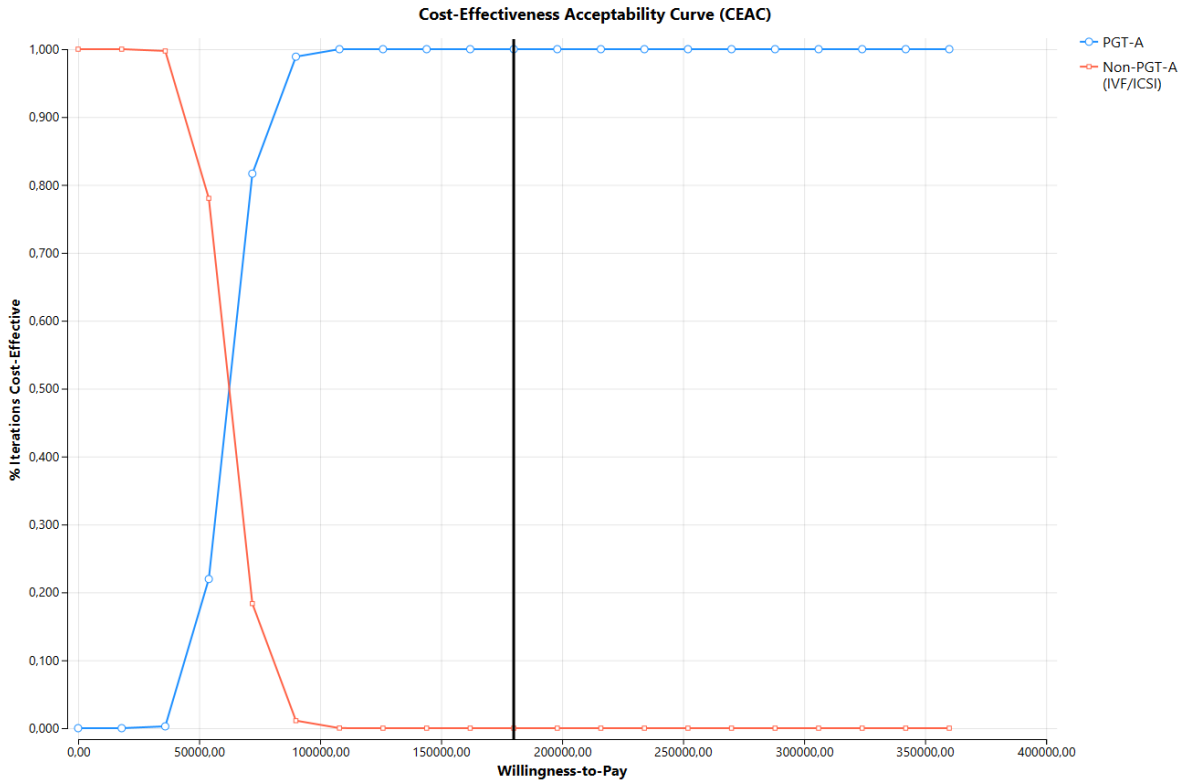

Figure 3.3: *Visualization of the Cost-Effectiveness Acceptability Curve (Cost-Effectiveness Acceptability Curve), showing the percentage of iterations which are cost-effective at a given WTP threshold. The chosen WTP threshold of 180,000 DKK/QALY is represented with the black line.*

3.3 Cost-Consequence Analysis

The cost-consequence analysis was developed to account for outcomes not captured through the cost-utility analysis. The analysis presents health outcomes and patient centred beyond-health outcomes for PGT-A compared to non-PGT-A (IVF/ICSI) to support decision-makers in making the most optimal strategy based on all relevant and crucial outcomes.

3.3.1 Clinical and Pregnancy Outcomes

In a recent systematic review and meta-analysis by Simopoulou et al. 2020, which strictly included only RCT studies, the clinical value of PGT-A was investigated [18]. The results of the meta-analysis, comparing PGT-A to non-PGT-A, were reported as a relative risk ratio (RR). Ratios above one translate to a higher probability of an event occurring in the PGT-A group, and a ratio below one translates to a lower probability of an event occurring in the PGT-A group. Relative risk ratios extracted from the meta-analysis are presented to the far right in the table 3.4 below with extracted relevant clinical outcomes from three RCT studies [26], [27], [28]. Clinical outcomes were only extracted if the biopsy were performed on five-day blastocysts and NGS was the

reported procedure for genetic testing, ensuring the technical procedures applied in the studies aligned with the PGT-A RCT protocol [Appendix 7.3]. Furtheremore, the increase in ongoing pregnancy rate reported by Munné et al. 2019 was significant for the subgroup aged 35-40. The study even reported a improvement in LBR of 14% in the PGT-A group, which is similar to the expected 10% improvement of the PGT-A RCT study [28]. This emphasizes the dispute in efficiency in regards to PGT-A, since the relative risk ratio (RR) of 1.37 (1.03-1.82) similarly indicates and improvement of the LBR in the PGT-A group, however this was not reported in the study by Ozgur et al. 2019 [18], [26].

Clinical outcome:	**PGT-A**	**Non-PGT-A**	**RR** (Simopoulou,2020)
Live birth rate:	56.3% (Ozgur, 2019	58.6% (Ozgur, 2019)	1.37 (1.03–1.82)
Cumulative live birth rate:	77.2% (Yan,2021)	81.8% (Yan,2021)	1.36 (1.13-1.64) (Per patient)
Positive β-hCG test:	72.1% (Munné,2019)	59.3% (Munné,2019)	n/a
Ongoing pregnancy rate:	50.8% (Munné,2019)	37.2% (Munné,2019)	1.36 (1.03-1.79)
Miscarriage rate:	6.1% (Ozgur, 2019) 8.2% (Munné,2019)	14.5% (Ozgur, 2019) 11% (Munné)	0.37(0.12-1.17) (Per clinical pregnancy)
Clinical pregnancy:	61.3% (Ozgur, 2019)	68.5% (Ozgur, 2019)	1.07 (0.89-1.28) (Per patient >35 years)
Time-to-pregnancy (months):	12.5 (Yan,2021) (Per patient)	12.4 (Yan,2021) (Per patient)	n/a
Congenital anomality at birth:	1.9% (Yan,2021) (Per patient)	2.3% (Yan,2021) (Per patient)	n/a

Figure 3.4: *A presentation of clinical outcomes of PGT-A compared to non-PGT-A (IVF/ICSI). Each outcome is presented with the study of extraction. On the far right column relative risk ratios (RR) extracted from the meta-analysis by Simopoulou et al. 2020 are presented [18]. If not otherwise described parameters were extracted as per embryo transfer.*

Moreover, clinical outcomes were if applicable extracted as per embryo transfer, thus relative risk ratios (RR) for cumulative live birth rate and clinical pregnancy were extracted as per patient, and relative risk ratio (RR) for miscarriage rate was extracted per clinical pregnancy. Moreover, time-to-pregnancy and the likelihood of congenital abnormalities at birth were also extracted per patient. PGT-A has the potential to improve time-to-pregnancy due to an improved implantation potential of the embryos. The time-to-pregnancy reported by Yan et al. 2021 however is quite similar between the two strategies [27]. However, in a study by Neal et al. 2018 time in treatment were reduced with three months in the PGT-A group compared to conventional IVF [38]. Moreover, clinical outcome shows great variation between studies complicating the basis for comparison. The variation can be explained by several factors, for one the characteristics of the study population. The study by Ozgur et al. 2019 investigated a study population below the age of 35, the study by Yan et al. 2021 a study population

between the ages 20-42, and Munné et al. 2019 investigated a study population between the ages 25-40[26], [28], [27]. Thus, Munné et al. 2019 aggregated data into age subgroups, and extracted data shown in the table of this study are of the 35-40 age subgroup [28].

In addition, to the reported clinical outcomes it is important to be attentive to other factors besides age, which could potentially be confounders and explain the heterogeneity of outcomes between studies. In the meta-analysis by Simopoulou et al. 2020 they compared fresh versus frozen embryo transfer and found that PGT-A only improves LBR when utilizing frozen embryo transfer (RR: 1.39 (1.09–1.78)) for women 35 years or older [18]. Moreover, RCT studies fail to capture the accuracy of a given PGT-A assay, and the predictive values of the intervention are vital to underline the certainty of PGT-A´s clinical value. Especially, in the light of all three RCT studies used for outcome extraction have only included transfer of fully euploid embryos, meaning embryos with mosaicism and segmental aneuploidy were not transferred [26], [28], [27]. This approach is contrary to the PGT-A RCT protocol where all euploid embryos with a mosaicism degree $\geq$ 80% will be transferred [Appendix 7.3].

In a PGT-A non-selection study by Tiegs et al. 2020 NGS was employed, and the negative predictive value of PGT-A was 100%, meaning that the clinical error of an aneuploid diagnosis was 0% [39]. However, the study appointed a likely variation between 0-2.43% due to the unlikelihood of the clinical error being 0% [39]. Another PGT-A non-selection study by Scott et al. 2012 uncovered a negative predictive value of 93.5% for when performed a blastocysts stage trophectoderm biopsy [40].

3.3.2 Patient Centred Outcomes

To capture the full picture of the beneficial and decremental effects of PGT-A patient preferences, concerns, and motivations should be explored, meaning broader outcomes beyond health. In a systematic review by Bracewell-Milnes et al. 2020 attitudes towards PGT-A were investigated [41]. The review found that studies have proven a need for improved patient education, since couples do not understand the complexity of PGT-A and the techniques limitations [41]. Moreover, studies have shown that women selecting PGT-A in their decision primarily do so to reduce the risk of birth abnormalities, the risk of miscarriages, and to reduce time-to pregnancy [41]. In addition, a cross-sectional survey by Jones et al. 2020 on a UK population found similar results with the highest motivation for PGT-A being a healthy child. Moreover, 44.1% of the cohort viewed time-to-pregnancy as a significant motivator [42]. When it comes to concerns towards PGT-A the most significant in the survey was the possibility of not having any embryos to transfer after the biopsy, damage of the embryos, and the costs associated with PGT-A [42]. Other concerns causing patients not to undergo or select PGT-A are previous single gene screening of the parents, underlining the need to educate patients on the difference between genetic disorders and assessment of embryos ploidy status. It is important for patients to understand that congenital as well as structural abnormalities can arise due to a number of factors [41].

A proportion of patients also reported declining PGT-A due to religious beliefs, and other patients declared that they would not terminate a pregnancy under any circumstances [41]. Although, the additional costs are reported as one of the major concerns of PGT-A, other studies have not identified it as significant in decision making of patients [42]. A study by Goldman et al. 2019 found a negative correlation between the number of available embryos after the biopsy and regretting ones decision of selecting PGT-A [43]. 39% of patients expressed some degree of regret in the decision of choosing PGT-A, where euploidy status of the embryo was associated with some degree of regret, while the number of eligible embryos after biopsy where associated with higher degree of regret. Accordingly, Jones et al. 2020 found that women who achieved live birth or were pregnant during the questionnaire had a more positive perception of PGT-A compared to women with unsuccessful outcomes [42].

In a French study by Courbiere et al. 2020 a study population of both women and men currently experiencing infertility and going throug fertility treatment, were investigated. Patients had to evaluate their experience, and self-reported the impact of fertility treatment on affective life as 5.7 on a scale from 1-10, with no significant variation between men and women. However, unsurprisingly women experienced a significant higher physical impact [44]. The self-experience of infertility treatment is described as a burdensome life under stressful conditions, which does not only affect patients physical and mental well-being, but also their work. Other studies have investigated QoL, which reported quality of life of women to be lower in compared to men and fertile couples [44]. Although the study did not investigate PGT-A separately from other types of fertility treatments the outcomes should be taken into account. Infertility treatment have a high impact of patients physical and mental well being, and time-to pregnancy becomes crucial to minimize the time spent in fertility treatment. Moreover, the study reported that 63% of the patients thought fertility treatment had an impact on how they organized their work time, and 51% reported that they had experienced a decrease in work motivation due to reduced job well-being [44]. In comparability with this, it is intended in the PGT-A RCT to ask patients and their partner about their QoL including missed work days. The productivity loss for each of the two interventions, and a potential improvement in days of absence would contribute with a impact of PGT-A on a society level.

A comprehensive analysis as this preliminary economic evaluation of PGT-A should be seen as a support and a decision tool for future decision makers. However, the large variance in the literature makes international comparison and transferability of outcomes difficult. The true magnitude of PGT-A´s benefit and clinical value cannot be determined before multiple trails have been conducted with a standardized protocol, which underlines the necessity of conducting the prognostic cohort study and RCT of PGT-A in a Danish setting.

4 Discussion

4.1 Summary of Evidence

This preliminary economic evaluation aimed to investigate the cost-effectiveness of PGT-A compared to non-PGT-A (IVF/ICSI), the current standard of care in a Danish clinical setting. This objective was relevant to examine due to the clinical value of PGT-A being a highly disputed topic. The magnitude of PGT-A´s effect is a matter of controversy due to methodological variations between studies, how contextualized the procedures is, and the fact that no standardized protocol exists yet. Moreover, the cost-effectiveness of PGT-A has never, to the knowledge of this study, been explored through a cost-utility analysis supplemented by a cost-consequence analysis.

The cost-utility analysis was performed through the generation of a hybrid model including both a Markov model and a decision tree. The goal of the model was to imitate the patient pathway as described in the PGT-A RCT study protocol [Appendix 7.3]. Input parameters were extracted from studies with the best transferability and feasibility, but the live birth rate for both strategies applied was extracted from the PGT-A RCT study. The results of the calculated ICER showed that both strategies were undominated, PGT-A was more effective but also more costly. The ICER was 62,262.34 DKK/QALY, which means that PGT-A is cost-effective at the adopted WTP threshold.

Since, PGT-A has not previously been economically assessed with a cost-utility analysis comparison of the results to cost-effectiveness studies must be done with caution. Cost-effectiveness studies comparing PGT-A to non-PGT-A have found that the cost-effectiveness were highly dependent on the age of the patients, the number of blastocysts and the perspective applied in the economic assessment [37], [45], [21]. In a cost-effectiveness study of Lee et al. 2021 based on national data of women from the United states PGT-A was similarly to the results of this study cost-effective from a payer perspective. Thus, from a patient perspective PGT-A was not favoured before the age of 39 [37]. This is in concordance with the results of a study by Lee et al. 2019 investigating real world data of Australian women aged ≥ 37, which showed a 80% probability of PGT-A being cost-effective from a healthcare perspective with the WTP threshold of (213,000 DKK)QALY [45]. Thus, with this threshold PGT-A was not cost-effective from a patient perspective, and whether PGT-A is cost-effective is ultimately dependent on societies- or the individuals willingness-to-pay [45]. The results of the cost-effectiveness acceptability curve of this study showed a 100% probability of PGT-A being cost-effective at the adopted WTP threshold. Furthermore, a cost-effectiveness study by Somigliana et al. 2019 based on a theoretical model the cost-effectiveness of PGT-A was investigated at different ages. PGT-A became more cost-effective with increased age, and showed superiority in women above the age of 36 [21]. Moreover, the number of eligible blastocysts after biopsy had an impact, and in the case of three eligible blastocysts, PGT-A became cost-effective for patients at the age of 35 [21]. Furtheremore, the results of the Tornado diagram showed that the cost of PGT-A was the input parameter with the greatest impact on the model. This is in concordance with a sensitivity analyses performed by the study of Somigliana et al. 2020 where variations in the cost of PGT-A showed prominent differences, and altered the

age of which PGT-A would be favoured [21]. Similarly, results of a sensitivity analysis exploring a 10% reduction of PGT-A costs performed by Lee et al. 2021, where the model was found to be sensitive to the costs of PGT-A [45]. This study have not investigated the cost-effectiveness of PGT-A by age, which could potentially alter the results, and for a future economic assessment age could advantageously be incorporated in the model.

The cost-consequence analysis is a comprehensive analysis of outcomes to supplement the results of the cost-utility analysis. When comparing clinical outcomes from RCT studies it is of importance which procedures were employed in regard to PGT-A, which effect outcomes were chosen, and whether they were extracted per transfer, per ART cycle or per patient. The clinical outcomes extracted from the three RCT studies showed that PGT-A improved the probability of a positive hCG test, the ongoing pregnancy rate, and slightly improved the time-to-pregnancy. Moreover, a decrease in the risk of miscarriage was associated with PGT-A, which was supported by the relative risk ratio (RR) reported by Simopoulou et al. 2020 [18]. Overall, it is important to note the limited improvement of the clinical pregnancy rate reported by the study, thus the true effect of PGT-A should be seen in the light of radically decreasing the risk of a miscarriage and thereby the probability of sustaining a pregnancy is improved leading to a live-birth for the age group above 35 [18]. Moreover, a study by Robertson et al. 2022 of UK register data showed an improved LBR for PGT-A compared to conventional IVF (36.9% vs. 27.6%), which is relative more in concordance with relative risk ratio reported and the expected LBR of the Danish RCT study. Moreover, another outcomes of a study by Yang et al. 2017 found that PGT-A improved both clinical pregnancy (69.1% vs. 49.4% (IVF)) and ongoing pregnancy rate (67.9% vs. 44.6% (IVF)), however these results were not reported as extracted outcomes due to the study only being accessible as an abstract [46].

PGT-A has the potential to increase implantation rate and time-to-pregnancy which would minimize the time spent in fertility treatment. Fertility treatment has a toll on physical and psychological health of both women and men, and by reducing time spent within fertility treatment it could potentially enhance the well-being of the prospective parents. Patients´ preferences, motivations and even regrets towards PGT-A indicates that the primary reasons of selecting PGT-A is the reduced risk of having a child with abnormalities, a reduced risk of miscarriage, and the probability of reducing the time-to-pregnancy. In the case of fertility treatment especially, which are known as burdensome for both individuals and couples it is important to incorporate patients´ preferences and concerns in the decision process. Future economic assessment would benefit from incorporating a cost-consequence analysis with real world data of the study population in question, including the potential change in QoL of going through fertility treatment.

4.2 Strengths and Limitations

It is of importance to discuss strengths and limitations of this study, to assess assumptions of the economic evaluation including the decision analytic model, evaluate uncertainties, and thereby enhance the transferability of this studies methods and results. Simple economic evaluations can appear callous when only focusing on one metric, underscoring the strength of this economic evaluation. First of all, this preliminary economic evaluation

of PGT-A included the combination of a cost-utility analysis supplemented by a cost-consequence analysis. The cost-utility analysis provided the accumulated effect in the generic metricQALY that in comparison to LBR and other clinical outcomes, which often have been used as effect measure for cost-effectiveness studies, encapsulates both quality and quantity of life. Moreover, the chosen time horizon of 24 months was similar to recent cost-effectiveness studies with a time horizon of 12 months [23]. The time horizon had to align with the PGT-A RCT protocol of 18 months, and the model was elongated with an additional cycle, equal to 6 months, to capture the accumulated effects and costs [Appendix 7.3]. This economic evaluation was carried out with a hospital perspective only including costs only including costs in relation to hospital expenditures. To assess a broader impact of PGT-A it would be an advantage to perform an economic assessment with a societal perspective, where the costs of productivity loss, person-time, salary, and overhead costs should be incorporated. The study by Somigliana et al. 2019 reported additional costs in relation to PGT-A, which included transportation costs and the costs of genetic counselling [21]. However, the hospital perspective was applicable in this study, since the DRG tariffs included an average of costs, which for PGT-A included the cost of genetic counselling. The costs of miscarriages was extracted from the study by Somigliana et al. 2019, which divivded miscarriages into medical and surgical miscarriages, and it was assumed that miscarriages before week 13 incurred the costs of a medical miscarriages [21]. Thus, this assumption being controversial, since other studies have reported much higher costs in relation to a miscarriages [37].There is a great differentiation in the costs of a miscarriage utilized in cost-effectiveness studies. The study by Somigliana et al. 2019 divided miscarriages into medical and surgical, while a study by Lee et al. 2021 provided a cost of a clinical miscarriage with a much higher [21], [37]. A higher miscarriage cost could potentially alter the decision, however the cost of a miscarriage did not show any notable impact on the model.

Another strength is the construction of the hybrid decision analytic model incorporating both a Markov model and decision tree. Other cost-effectiveness studies of PGT-A have developed a decision tree or have not mentioned the methodological considerations behind their model [23]. The hybrid model accounted for all the accumulated effects incurred to the cohort after a total of three embryo transfers, a live birth or 18 months after randomization. The study by Lee et al. 2021 performed a simple decision tree, but still accounted for the total number of embryo transfers, miscarriage rate, and whether the patient became pregnant or not after a transfer. The study also included if no blastocysts where eligible for transfer [37]. Due to this study being a preliminary study data was not available from the non-selection nor the RCT PGT-A study currently ongoing in Denmark, although the expected LBR of both strategies were included in the model. The decision after an embryo transfer was limited to either a live birth, a miscarriage or no pregnancy, where the latter two health states would result in a new embryo transfer. This does not accurately mimic the true clinical setting, which would include drop-out rate, the chance of no eligible embryos after biopsy, and even the chance of no applicable blastocysts after fertilization. To mimic the clinical setting fully it would improve the model if probabilities for a miscarriage were applicable after a biochemical pregnancy and a clinical pregnancy. For the definitive economic evaluation it would be favourable to extract probabilities for each blastocyst and not only per embryo transfer. In the cost-consequence analysis clinical most outcomes were reported in the RCT studies as per embryo transfer, which according to Viville et

al. 2025 is highly problematic due to this reference point excluding a large number of attempts [13]. According to Viville et al. 2025 it is critical that the studies showing a beneficial effect of PGT-A are the ones reporting an effect per embryo transfer, while studies reporting outcomes per cycle, per patient or with an intention-to-treat purpose find similar outcomes between PGT-A and non-PGT-A with no significant difference in outcomes [13].

Economic evaluations are ultimately dependent on quality of evidence of the studies included for input parameter extraction. In retrieval of input parameters through the systematic literature search a broad search was conducted, however resulting in very few applicable studies due to a lack in consensus of terminology within the research field. Applied literature was found through reference search and a more unsystematic approach to ensure all relevant literature within the research field was included. A strength of this study is that the PGT-A procedures performed was of priority, only including studies which had performed a trophectoderm biopsy, used NGS for genetic analysis, and preferably had mentioned utilization of single embryo transfer. The miscarriage rate utilized in the cost-utility analysis were extracted from a multi-centre RCT study investigating patients from centres of the United states, Canada, Australia, and the UK, which strengthens the utilization of these miscarriage rates in the model, since the study population to a degree resemble the Danish population [28]. Thus, the health cares systems between countries are very different, all countries are high-income countries, further strengthening the application. The two other RCT studies by Ozgur et al. 2019 and Yan et al. 2021 utilized in the cost-consequence analysis for reporting clinical outcomes investigated a Turkish and a Chinese population respectively, thus the chosen PGT-A procedures weighed higher in the selection of input parameters [26], [27].

Evaluation of fertility treatments adds a level of complexity and requires a different approach compared to other health and medical areas. Even though, cost-utility analysis have become the standard when economically evaluating other medical interventions, this approach might not fully capture the true value of fertility treatment [47]. Utilizing QALY to measure utility is as mentioned uncommon and have in other fertility studies not been done in a structured manner. The unique situation with fertility treatment is that it is evaluated on its ability to create a new life. QALYs on the other hand are generated to capture advantageous or detrimental effects on quality of life [47]. Guidelines therefore propose only to include QALYs of future live if these lives would exist regardless of the intervention [48]. Utilities of potential lives were for this reason not included in the cost-utility analysis. A strength of this study is the application of a parental perspective, incorporating effects for both the patients and their partners. Utilities for different health states originated expert opinions, which may not truly reflect the patient´s and their partners preferences for given health states. Moreover, utilities were extracted per month and from baseline utility of one, thus converted into disutilities for utilization in the decision analytic model. Utilities were extracted as maternal, but as 1:50 ratio were assumed to be relevant to account utilities of partners. A more accurate ratio on the disutilities the partners inquire within fertility treatment is needed. QALYs of the prospective parents capture the impact on quality of life related to certain health states of fertility treatment, but most effects of fertility treatment are not health related. Consequences of fertility treatment include impact on couples well-being, life goals, and dreams i relation to making a families. Therefore, initiatives towards extending the well known QALY elicitation tool EQ-5D to EQ-Health and Well being (EQ-HWB) have

started [47]. Initiatives like this wanting to include a broader perspective into the assessment of fertility treatments aligns perfectly with the aim of this economic evaluation.

Moreover, a study by Keller and Chambers 2022 argues that the use of QALY is inadequate, and a cost-effectiveness study within the framework of a cost-benefit analysis would be more advantageous when assessing value for money of fertility treatments [47]. A cost-benefit analysis can be seen as a supplementary analysis, which offers all outcomes in a monetary value. The analysis offers an alternative perspective, but the conclusion depends heavily on the monetary values assigned to the benefits. Even though, analyses with a one metric conclusion offer a simpler reference for comparison for decision-makers, constituting the results of the cost-utility analysis with the results of the cost-consequence analysis offers a unique insight into the cost-effectiveness of PGT-A. Even, so due to the complexity if assessing fertility treatments a bolder approach might be the solution to adequately support decision-making. The MRC (Medial Research Council)- framework is a structured approach developed as a guide to researcher and stakeholders in the development, evaluation, implementation and assessment of health interventions with complex interacting components [49]. Research on complex interventions such as ART treatments should not be limited by a single perspective, but should be scrutinized for its complex components, which requires the implementation- and decision context to be considered early on in the process. By applying the MRC-framework factors as feasibility and patients outcomes are considered, and support real-world application of the intervention, which potentially would be beneficial if PGT-A were to be implemented.

The WTP threshold adopted in this study is employed by NICE and applied in the UK, since no fixed WTP threshold is employed in Denmark [33]. In a review by Fenwick et al. 2023 the WTP threshold of infertility treatment studies was investigated. The review identified no standard WTP threshold for a given outcome or fertility treatment, and no justification for the chosen threshold were often not given. This underlines a need for establishing a standardized threshold which can be applied to fertility treatments [50]. It has been established that ART treatment is costly to the patient, but in the case of PGT-A proving to be adequate for implementation in a Danish setting after conduction of the PGT-A non-selection- and RCT study, it is essential to look into the acceptable cost for society as well. In a study by Chambers et al. 2013 the cost from society´s perspective of a given ART treatment does not only relate to the cost per cycle or per embryo transfer, but also to the proportion of treatments in demand, and the percentage of the total health care costs this demand allocates [51].

4.3 Ethical considerations

In the controversy around the effect of PGT-A ethical considerations were important to clarify. According to Viville et al. 2025 one of the cornerstones in regard to PGT-A is the principle of proportionality which insists on the benefits of an intervention must outweigh the harms [13]. In terms of benefits the true clinical value of PGT-A is still very disputed. Thus, the results of this study indicate a higher accumulated QALYs, as well as PGT-A being advantageous in several clinical outcomes and results show PGT-A was cost-effective. In terms of burdens assessment of the PGT-As predictive value is essential, since the risk of discarding viable embryos

must be kept at a minimum. Before it was established that embryos with mosaicism could lead to a healthy live birth, many mosaic embryos were discarded. The purpose of PGT-A is to select embryos with the best chance of implantation and pregnancy, which is why embryos are now selected with a ranking system. However, it is a misconception that aneuploidy and mosaicism can be correctly predicted with PGT-A, which can potentially lead to embryo waste due to false positives [13].

The broad adoption of PGT-A without establishment of the true clinical value in countries outside of Denmark can be explained by ´technological imperative´, where a technological interventions are implemented and used unreflectively, without the necessary knowledge of the technology [52]. This societal pressure might disseminate as a pressure onto the patients as ´internalized technological imperative´. Patients and their partners will try anything available to them to conceive a child, which ultimately affect their autonomy negatively [52]. Patients autonomy may also be inflicted by the additional costs in relation with PGT-A due to it being offered commercially in many countries, leading to unequal access due to heterogeneity of costs inflicted on patients and couples [52]. Whether fertility treatment is entirely subsidized or comes with high out-of-pocket payments is highly country dependent, leading to inequality in access to reproductive treatment. Variations in access are impacted by inequalities as class, gender, age, ethnicity and ability [52]. Moreover, inequality in accessibility in combination with variations in legislations across countries can to some degree cause reproductive tourism, which is when patients or couples seek the treatment in demand in another country were it is available [52].

In a study by Siermann et al. 2024 investigating health care professionals´ attitudes towards preimplantation genetic testing, it was described how sociocultural norms of what a desirable life is, are based on views impacted by sexist, racist or ableist ideas [52]. It is argued that with reproductive selection techniques available the standard for what is seen as an ´acceptable child´ have enhanced. On the opposite side the controversial principle of procreative beneficence see it as a moral obligation of prospective parents and society to select the embryo or child which could have the best possible life of all embryos available [52]

In the economic assessment of a ART treatments and PGT-A treatment the discussion on the value of a live birth and the value of a child can not be avoided. In conventional economic evaluations conceived children are valued as an indirect benefit from fertility treatment. Due to limited resources in the health care sector, allocation of future funds must be based on ´opportunity cost´, meaning if services are allocated to one area they can not be applied elsewhere. In a study by Martins et al. 2022 it was reported that children bring a range of benefits to prospective parents as well as society, and economically all individuals can be valued based on their human capital contributions, hence the future absent productivity and economical losses can be measured [53]. Since children are seen as indirect benefits it can be questioned whether the societal benefits and consequences of fertility treatment are excluded in a majority of conventional economic evaluations [53]. The value of a future life to society must be seen in the light of the current negative population momentum and the huge number of countries worldwide experiencing a TFR below the replacement level. Despite the small amount of children born within fertility treatment, they could be an important contribution to invert the tendency. As in Denmark,

governments of countries countries have continuously prioritized funding towards fertility treatment with the aim of increasing the birth rate. However, the true value of a child to society is dependent on whether infertility is seen as the individuals or a society problem. In the case where infertility is recognised as a problem for both parties, and the true cost of what society is willing to pay is still to be established [53].

Lastly, to avert potential harms of PGT-A in relation to the trophectoderm biopsy´s impact on implantation potential, less invasive techniques are being developed. One less invasive technique is non invasive PGT-A (niPGT-A) which is a tehcnique still at at a experimental level. Cell-free DNA is isolated from the embryo spent culture media, which should accordingly reflect the genetic status of the embryo. In this way the embryos are not impacted in any way by a biopsy. However, results are inconsistent, but the results of the PGT-A RCT study will be compared to a subsequent analysis performed of niPGT-A [Appendix 7.3].

4.4 For Future Researchers & Decision-makers

Decision makers within healthcare systems must prioritize allocation of resources in accordance with opportunity cost due to resource constraints. Prioritization must be based both on clinical and cost efficiency. Fertility treatments and especially ART treatments are important to investigate as it involves the well-being of the prospective parents, but also incurres large additional costs, and pose a potential value to broader society with the value of future lives. The findings of this study contribute as a framework for which costs and effects should be considered when assessing PGT-A in a Danish clinical setting. However, decision makers should consider several factors including the decision context when opting for the most optimal strategy.

Firstly, this study is a preliminary economic evaluation of PGT-A, which must be considered when interpreting results. Yet, the findings of the economic evaluation and the generation of the hybrid decision analytic model can be utilized by future researchers performing the definitive economic evaluation to guarantee inclusion of all relevant outcomes. The utilization of a cost-utility analysis captures decrements in utility of prospective parents, however Danish utilities elicited from specific for PGT-A and non-PGT-A performed with a recognized tool such as EQ-5D would be preferred.

Secondly, it is urged that a common understanding of the concept of PGT-A is generated, and alongside a standardized recommendations on how to carry out economic evaluations on interventions within fertility treatment in the best methodological manner. Recommendations should be based on local clinical setting, real world costs, and country specific reimbursement programs. Additionally, future decision makers should consider the results of the PGT-A non-selection and RCT studies as real-world data more adequately inform about the effects of PGT-A in a Danish clinical setting. Moreover, decision makers should account for possible capacity increase if future evidence indicates that PGT-A has a positive effect of time-to-pregnancy and thereby time-in-treatment. Nevertheless, PGT-A remains a complex decision influenced by a multitude of factors, and the exact magnitude of PGT-As benefit can not be established be before multiple trails with a standardized protocol have

been conducted. The ultimate goal of future studies must be to ensure the benefits outweigh the harms, and implementation does not happen without this being backed up by consistent evidence.

5 Conclusion

In conclusion, this preliminary economic evaluation incorporating both a cost-utility analysis and a cost-consequence analysis showed the potential of PGT-A being cost-effective. The cost-utility analysis found PGT-A had a higher accumulated QALYs, but were more costly. PGT-A were found to be cost-effective at the employed WTP threshold of 180,000 DKK/QALY with an ICER of 62,262.34 DKK/QALY. The input parameters with the biggest impact on the model were the cost of PGT-A and the cost of conventional IVF. The cost-effectiveness acceptability curves showed the probability of PGT-A being cost-effective was a 100% at approximately 110,000 DKKQALY.

The results of the cost-consequence analysis similarly points towards PGT-A improving several clinical outcomes such as LBR, positive hCG test rate, ongoing pregnancy rate, and reduction of the risk of miscarriage. Potentially, improving these outcomes could contribute to improved implantation rate of embryos, and overall shorten the time-to-pregnancy. The primary reason for selecting PGT-A was to reduce the risk of a child with abnormalities, the risk of miscarriages, and the time-to-pregnancy, which are all events of fertility treatment affecting the well-being of individuals and couples. Although, the true value of a new life to the prospective parents and the broader society are yet to be established.

This study is the first to investigate the cost-effectiveness of PGT-A within a Danish clinical setting through a cost-utility analysis and a cost-consequence analysis. This study provides a foundation for future researchers and decision-makers, and deliver a framework for relevant costs, probabilities, and utilities to include in the generation of the definitive economic evaluation of the PGT-A RCT study when real-world data are available.

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7 Appendix

7.1 Systematic Literature Search

7.1.1 Search strategy Embase

	AND			
OR	Population	Intervention	Comparison	Outcome
	Emtree: Infertility/exp Infertility therapy/exp **Free text:** ´Assisted reproductive technology´/ti;ab ´ART´/ti;ab	**Emtree:** Preimplantation genetic screening/exp In vitro fertilization/exp **Free text:** IVF/exp ´PGT-A´/ti;ab ´Preimplantation genetic testing aneuploidy´/ti;ab		**Emtree:** Quality adjusted life year/exp Quality of life/exp Utility value/exp Disease burden/exp **Free text:** ´qaly´/ti;ab ´Utilit*´/ti;ab ´Disutilit*´/ti;ab ´Burden of illness´/exp

7.1.2 Search string Embase

Search: ('infertility'/exp OR 'infertility therapy'/exp OR ''assisted reproductive technology'':ti,ab OR ''art'':ti,ab) AND ('preimplantation genetic screening'/exp OR 'in vitro fertilization'/exp OR 'ivf'/exp OR ''pgt-a'':ti,ab OR ''preimplantation genetic testing - aneuploidy'':ti,ab OR 'preimplantation genetic diagnosis'/exp) AND ('quality adjusted life year'/exp OR 'utility value'/exp OR 'quality of life'/exp OR 'disease burden'/exp OR ''qaly'':ti,ab OR ''utilit'':ti,ab OR ''disutilit'':ti,ab OR 'burden of illness'/exp)

7.1.3 Search strategy PubMed

	AND			
	Population	Intervention	Comparison	Outcome
OR	**MeSH term:** Infertility/exp Assisted reproductive technics/exp Assisted reproductive technologies/exp **Free text:** ´Infertile therapy´/ti;ab ´ART´/ti;ab	**MeSH term:** Preimplantation genetic diagnoses/exp In vitro fertilization/exp **Free text:** ´Preimplantation genetic testing aneuploidy´/ti;ab ´PGT-A´/ti;ab ´IVF´/ti;ab		**MeSH term:** quality adjusted life year/exp quality of Life/exp cost of illness/exp **Free text:** ´quality-adjusted life year*´/ti;ab ´qaly´/ti:ab ´Utilit*´/ti;ab ´Disutilit*´/ti;ab

7.1.4 Search string PubMed

Search: ((infertility[MeSH Terms]) OR (assisted reproductive technics[MeSH Terms]) OR (assisted reproductive technologies[MeSH Terms]) OR (Infertility therapy [Title/Abstract]) OR (ART [Title/Abstract])) AND ((preimplantation genetic diagnosis[MeSH Terms]) OR (preimplantation genetic testing aneuploidy [Title/Abstract]) OR (PGT-A [Title/Abstract]) OR (in vitro fertilization[MeSH Terms]) OR (IVF [Title/Abstract])) AND ((quality adjusted life year[MeSH Terms]) OR (quality of life[MeSH Terms]) OR (quality adjusted life year* [Title/Abstract]) OR (qaly [Title/Abstract]) OR (utilit* [Title/Abstract]) OR (disutilit* [Title/Abstract]) OR (cost of illness[MeSH Terms]))

7.2 Assumptions of the Decision Analytic Model

Assumptions of the Decision Analytical Model:
1. PGT-A is assumed to have a relative increase of 10% on the live birth rate (LBR) compared to non-PGT-A (30% vs. 20%).
2. If a live birth is achieved patients do not continue in the model but proceed to the absorbing health state `Given birth´ in accordance with the PGT-A RCT protocol.
3. It was assumed that all patients had three eligible blastocysts, and went through three embryo transfer if they did not achieve a live birth.
4. All PGT-A embryo transfers were performed with FET. The first embryo transfer of the non-PGT-A arm was fresh. Thus, the following two embryo transfers was FETs.
5. It was assumed that all patients went through the model with a partner.
6. Utilities were applied with a parental perspective, where a 1:0.5 ratio of the maternal utilities was found relevant to account for the magnitude of the partners utilities.
7. The probability of a late miscarriage of the general population was assumed to be similar to the late miscarriage rate in the study population.
8. The probability of a live birth was assumed to be constant regardless of age.
9. The probability of a miscarriage was assumed to be constant regardless of age.
10. The dropout rate was assumed to be of 0%.

7.3 PGT-A RCT Study Protocol

Project title

Preimplantation Genetic Testing for Aneuploidy (PGT-A) in women aged 37-41 years – a randomized controlled multicenter trial

Dansk titel: Præimplantationsgenetisk test for aneuploidi (PGT-A) hos kvinder i alderen 37-41 år – et randomiseret, kontrolleret, multicenter studie.

Research group (The PGT-A consortium research group)

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Aim

To assess the efficacy and safety of preimplantation genetic testing for aneuploidy (PGT-A) in 37-41-year-old women in a multinational, multi-centre randomized controlled trial (RCT).

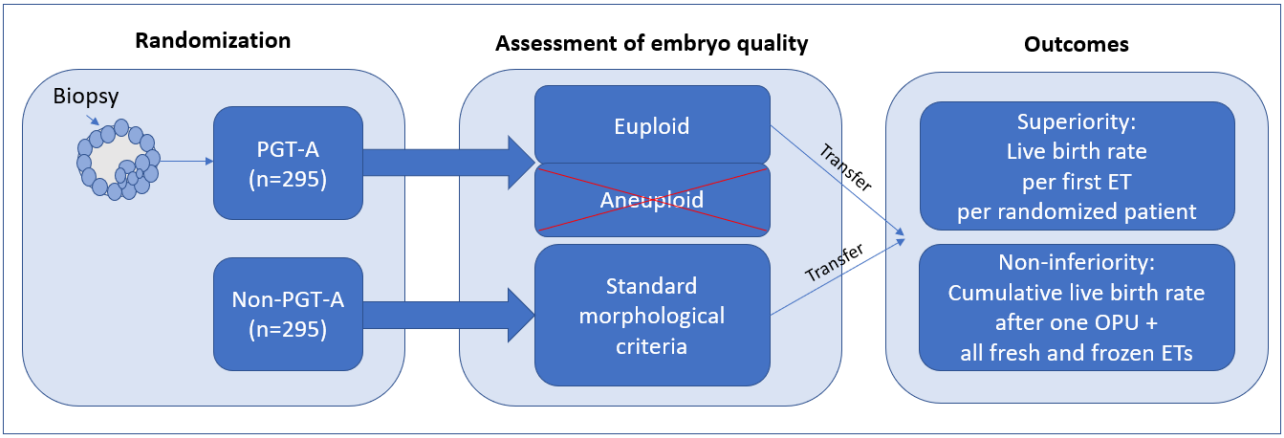

Fig. 1. Overview of the RCT assessing the efficacy of PGT-A. Patients will be included and randomized to PGT-A or standard treatment with morphological evaluation of embryos (non-PGT-A). ET=embryo transfer. OPU=oocyte pick up.

Introduction

Techniques that involve the manipulation and fertilization of oocytes outside the body are referred to as assisted reproductive technologies (ART) with in vitro fertilization (IVF) as the most common form. ART treatments are used increasingly worldwide and contribute to 2-9% of deliveries in Europe (Wyns et al., 2022). The aim of an ART treatment is to establish a healthy ongoing pregnancy that leads to the delivery of a healthy child. To achieve this goal, the selection of embryos with the highest possible sustained implantation potential is important. For many years, a morphological characterization of embryos based on light microscopy has been used to choose embryos predicted to have the highest chance of implantation. However, the morphological evaluation of human embryos is an inefficient marker for ploidy as it fails to identify which embryos are euploid (with all cells containing the correct chromosome copy number), aneuploid (with all cells containing an incorrect chromosome copy number), or mosaic (the appearance of two or more cell lines with a different karyotype within the embryo).

PGT-A is a relatively new technique that allows for the prediction of embryo ploidy status through analysis of an embryo biopsy conducted prior to embryo transfer (ET). A previous study has indicated that PGT-A is not efficient in women ≤37 years of age (Yan et al., 2021) perhaps because of a relatively low aneuploidy rate in this age group, and perhaps because mosaic embryos were not transferred in that study. The aneuploidy rate of human embryos increases with increasing female age, with an aneuploidy rate of ~25% in women aged 25-30 years increasing to ~70% in women aged 41 years (Franasiak et al. 2014). Further, in women of advanced reproductive age, time-to-live birth matters as the ovarian reserve declines fast. PGT-A has the potential to avoid aneuploid ETs, decrease the miscarriage rate, and shorten the time-to-pregnancy in women of advanced reproductive age. Therefore, it is essential to investigate whether PGT-A can improve the live birth rate (LBR) per first

transfer after oocyte pick-up (OPU), without compromising the cumulative LBR in women ≥37 years of age.

In the past, PGT-A biopsies were performed at the cleavage stage (on day three after OPU); however, biopsies are now conducted at the blastocyst stage, five to six days after OPU. The biopsy at the blastocyst stage is taken from the trophectoderm cell layer (TE), which forms the future placenta. The genetic analysis of these cells is used to infer the genetic status of the inner cell mass (ICM) that will develop into the foetus. Mosaicism is frequently observed in early human preimplantation embryos and while the extent of mosaicism and the concepts of self-correction and preferential allocation of aneuploid cells to the TE are still under debate, it is widely acknowledged that the ICM and TE cannot be assumed to be genetically identical. Therefore, as the ICM is not directly tested, it is crucial to consider the predictive values of the PGT-A analysis. Two rather large PGT-A non-selection studies have shown negative predictive values (failure of delivery per aneuploid embryo transferred) of 93.5% and 100%, respectively (Scott et al., 2012; Tiegs et al., 2021). The largest and most recent study showing a negative predictive value of 100% applied a next-generation sequencing (NGS)-based assay on blastocyst TE biopsies (Tiegs et al., 2021), and although results cannot be directly inferred to NGS-based PGT-A assays in other centres, they seem reassuring. Further, other studies have found a high concordance between whole chromosome aneuploidy in the TE biopsy and inner cell mass (Victor et al. 2019).

Non-invasive PGT-A (niPGT-A) is a developing technique that utilizes cell-free DNA isolated from the spent embryo culture medium (SCM), as it is suggested to reflect the genetic status of the embryo. However, the consistency of results between TE and SCM samples has shown considerable variation across studies (Liu et al., 2017; Ho et al., 2018, Xu et al., 2023), and a significant challenge in niPGT-A is the high risk of maternal contamination (Leaver et al., 2020). The niPGT-A technique is still highly experimental and must be developed and tested appropriately before it can be used in a clinical setting, but if it is shown to be effective, it might lower the cost and potential risks related to PGT-A.

Definitions

Pregnancy is defined as a positive hCG > 3 IU/L.
Pregnancy loss is defined as the outcome of any pregnancy that does not result in at least one live birth.
Clinical pregnancy is defined as the ultrasonic visualization of a fetal heartbeat at gestational week seven to eight.
One complete ART treatment is defined as the use of all blastocysts (fresh + frozen) derived from one OPU until live birth, or until 18 months after the date of study randomization, whichever comes first.
The cumulative LBR is defined as the number of live births after one complete ART treatment.

Endpoints

Primary endpoints

1. To assess if PGT-A is *superior* to standard non-PGT-A treatment regarding the LBR per first ET (or no ET if only aneuploid embryo(s) in the PGT-A group) per randomized woman.

2. To assess if PGT-A is *non-inferior* compared to standard treatment regarding the cumulative LBR after one complete ART treatment per randomized woman.

Secondary endpoints

1. Pregnancy loss rate per randomized woman after one complete ART treatment.
2. Number of embryo transfers *per live birth* per randomized woman until live birth *or* until use of all blastocysts after the OPU (fresh + frozen) or until 18 months after study randomization (whatever comes first).
3. Time from randomization until pregnancy per woman with delivery.
4. Time from randomisation until a new IVF/ICSI treatment can be initiated (no more blastocysts left) in women not achieving a delivery.
5. Positive hCG rate, clinical pregnancy rate and pregnancy loss rate after the first ET (or no ET if only aneuploid embryo(s) in the PGT-A group) per randomized woman.
6. Quality of life (QOL) / patient satisfaction measured by QOL questionnaires administered three times during the study period in both the PGT-A and control group.
7. Obstetric (preterm delivery, gestational diabetes mellitus (GDM), Hypertensive disorder of pregnancy (HDP), small for gestational age (SGA), large for gestational age (LGA), birth weight) and neonatal outcomes (congenital anomalies).
8. Health of children up to 5 years of age born after PGT-A and standard treatment.
9. Cost-effectiveness analysis.
10. Concordance between TE biopsies and TE and ICM biopsies in blastocyst with aneuploidies in the initial TE biopsy.
11. Concordance between PGT-A and niPGT-A results.

As only women with at least one good quality blastocyst will be randomized, the main analyses will be performed as per randomized woman. We choose, however, to include women at cycle day two to five before initiation of the ovarian stimulation as we aim to report the cycle cancellation rates after patient inclusion due to i) no blastocyst development or ii) no blastocyst available for biopsy.

Methods

Study design

The study is designed as a multinational multi-centre, randomized, controlled non-blinded trial with participation of three fertility clinics in Denmark (Rigshospitalet, Herlev Hospital and Aalborg University Hospital), and one in Spain (Dexeus Mujer, Barcelona). The fertility clinics at Rigshospitalet and Aalborg University Hospital perform PGT for structural rearrangements (PGT-SR) and monogenic disorders (PGT-M), and the fertility clinics at Herlev Hospital and Dexeus Mujer, Barcelona already perform PGT-A in a research and clinical setting. Therefore, all the clinics have the framework to perform PGT-A. Patient enrolment is expected to begin in 2024 and continue until 2028 (four years).

Inclusion and exclusion criteria

Inclusion criteria:

- Women aged 37-41 years with a male partner, a female partner og undergoing fertility with no partner.
- Anti Müllerian Hormone (AMH) ≥6.28 pmol/L (AMH should be measured no more than one year prior to study inclusion). The optimal is to use the Elecsys® Assay. If other assays are used this should be reported to the investigator and the AMH cut-off level may appropriately be changed so that it corresponds to the cut-off used in the Elecsys® Assay.
- IVF/ICSI cycle number 1-5 (previous IVF/ICSI cycles will not count if the woman is recruited after an IVF/ICSI/FET-delivery).

Exclusion criteria:

- PGT-SR or PGT-M.
- Testicular sperm aspiration (TESA), testicular sperm extraction (TESE), micro-TESE (or cryopreserved sperm from these procedures).
- Males with severely compromised semen quality (<1 million progressively motile sperm cells following gradient centrifugation).
- Endometriosis stage three or four.
- Women with severe thyroid disease (women can be included if they have normal thyroid levels on relevant medication).
- Severe co-morbidity; diabetes mellitus type 1 (DM1), Mb Crohn or Colitis ulcerosa, systemic lupus erythematosus (SLE), HIV, Hepatitis B/C, or dysregulated thyroid disease.
- ≥2 previous ART treatment without blastocyst formation.

Study population and recruitment

The study population will consist of patients with an indication for treatment with IVF or intra-cytoplasmic sperm injection (ICSI). Eligible patients will be recruited if they fulfil the inclusion criteria and none of the exclusion criteria. Each patient will be included and randomized only once, and for one complete ART treatment only. Eligible patients who have been referred to the clinic for fertility treatment will be informed about the study by a nurse or a medical doctor. Patients who wish to receive more information about the project will be invited to an in-person consultation at the clinic. The consultations will be managed by a medical doctor (primarily Nathalie Friis Wang) or one of the research nurses at the fertility clinic. Privacy and discretion will be ensured by planning the consultation in a private room, and patients will be informed of their right to bring an assessor to the appointment. Written patient information will be handed out or sent by e-Boks (patients in DK) or e-mail. Patients will be offered at least 24 hours of consideration before signing the informed consent. The informed consent form can be signed via an electronic link sent to their e-Boks (patients in DK) or in person.

Enrolled patients have the freedom to withdraw from the study at any point, for any reason, without any negative consequences. Additionally, the treating or non-treating doctor has the authority to interrupt participation if either (i) the patient's overall health condition contradicts their involvement in the study, or (ii) a protocol violation takes place that, in the investigator's judgment, could impact

the study's results. In the event of withdrawal from the study, patients will still receive standard treatment at the fertility clinic.

Inclusion and randomization

Inclusion is performed on cycle day two to five around the initiation of ovarian stimulation. Randomization will be performed five, six or seven days after OPU by a member of the research team using an electronic randomization program if the following criterion is fulfilled: Minimum one blastocyst suitable for biopsying. Patients are randomized 1:1 by simple randomization.

Treatment and interventions

Ovarian stimulation with gonadotrophins and ovulation trigger according to the standard treatment in each clinic. GnRH-agonist trigger is allowed in the GnRH antagonist protocol in case of OHSS risk and elective freeze-all. Fertilization by ICSI. If minimum one blastocyst suitable for biopsying develops five, six, or seven days after OPU, the woman is randomized 1:1 to one of the following two groups:

A. **PGT-A and freeze-all** (by vitrification) of day 5 and/or day 6 and/or day 7 blastocyst(s) and subsequent transfer of euploid or mosaic (≤80%) blastocysts in FET cycles. Luteal phase supplementation (LPS) will be administered according to the participating clinics standard practice.

B. **Non-PGT-A and fresh blastocyst transfer**. In the non-PGT-A group, fresh day 5 single blastocyst transfer and/or FET of day 6 and/or day 7 blastocysts is used. LPS will be administered according to the participating clinics standard practice. All surplus day 5,day 6, or day 7 blastocysts will be vitrified. If there is a risk of OHSS, elective freeze-all will be performed. None of the blastocysts will be PGT-A tested.

Biopsy procedure

The TE biopsy is performed on day five,six or seven after OPU and the biopsied blastocysts will be vitrified after the procedure.

Figure 1. Illustration of the PGT-A procedure.
1. Blastocyst ready for biopsy. 2. Biopsy is taken. 3. Blastocyst following biopsy.

Blastocyst selection procedure

Ranking according to ploidy (expected chance of implantation):

1) Euploid and ≤50% mosaicism
2) >50-80% mosaicism
3) >80% mosaicism and fully aneuploid

Blastocysts showing euploidy and ≤80% mosaicism will be transferred. Blastocysts showing aneuploidy or >80% mosaicism will not be transferred.

Genetic counselling
The written and oral study information emphasize the possibility for genetic counselling before and after the PGT-A analysis. In case of blastocysts with mosaicism >50%, the patients will receive genetic counselling including recommendation for follow up analysis in pregnancy.

Concordance study
Blastocyst with chromosome aneuploidy or >80% mosaicism not suitable for transfer will be biopsied again from the TE and inner cell mass. The additional biopsies will be analysed for concordance with the initial TE biopsy result.

Spent culture medium
In parallel to the biopsy, the SCM from blastocysts (day 5-6-7) will be frozen and stored in a -80°C freezer for later niPGT-A analysis.

Genetic platform
A whole genome amplification (WGA)-NGS platform with a sequencing depth of 0.01x will be used to carry out the PGT-A analyses in the study. It is not possible to detect genetic variants at a sequencing depth of 0.1x.

Sample size calculations
The sample size calculations are based on the following assumptions: an average of two good quality blastocysts per oocyte retrieval in this age group, an aneuploidy rate of 55% in the study population (women 37-41 years old), and a LBR of 45% per euploid blastocyst transfer.

For superiority regarding the LBR after first (or no) ET in the PGT-A compared to the first ET in the non-PGT-A group per randomized woman, a total of 590 randomized patients are required (295 *in each group*) to have an 80% chance of detecting, at a significance level of 5%, an increase in LBR from 20% per randomized woman in the non-PGT-A group to 30% per randomized woman in the PGT-A group.

For non-inferiority, we predict a cumulative LBR of 35% in both the PGT-A and the non-PGT-A group. If there is truly no difference in cumulative LBR between the PGT-A and the non-PGT-A group, and if the cumulative LBR is 35% in both groups, then 566 randomized patients (*283 in each group*) are required to be 80% sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favour of the non-PGT-A group of more than 10%.

The trial will be based on both the superiority and the non-inferiority principle, the former requiring the highest number of randomized patients (https://www.sealedenvelope.com).

Data collection and management

A common redcap database will be used to store the relevant data from all the trial sites.

Questionnaire

A validated questionnaire regarding quality of life (QOF) and patient satisfaction will be handed out three times during the study period to the patient and her partner (the partner questionnaire will be omitted if no partner is present). The questionnaire takes approximately 5-10 minutes to fill out. The purpose of the questionnaire is to monitor patient satisfaction and QOL during the treatment, and to compare the patient wellbeing during the new project treatment compared with the patient wellbeing in the past (from previously filled out questionnaires in other studies).

WGA product

The WGA product obtained in the project will be used to carry out the PGT-A analysis.

Spent culture medium

Spent culture medium that would have otherwise been discarded will be kept in a -80°C freezer for later niPGT-A analysis.

Biobank

The leftover WGA product and spent culture medium will be transferred to a research biobank (forskningsbiobank). The research biobank will be kept until the last patient has been enrolled in the study and the last analysis has been carried out (expected 01-01-2034). Following this, the material will be transferred to a biobank for future research The material will be kept until 01-01-2044 after which any remaining biological material will be destroyed. If we wish to use the biological samples in a new research project, it will require a new approval from the Scientific Ethics Committee. All data protection laws (databeskyttelsesregler) will be followed (overholdt).

Ethical considerations

The risk of discarding viable embryos by deselecting aneuploid embryos is considered low (Tiegs et al. 2021). PGT-A is widely used around the world in patients of all age groups including patients of advanced maternal age with few blastocysts. It is relevant to address whether PGT-A can increase the chance of a live birth per transfer without negatively impacting the cumulative LBR. All the patients will be informed about the lack of evidence with regards to PGT-A prior to entry in the study including a potential decrease in the cumulative LBR. By examining this research question, the time to live birth and overall efficacy of IVF/ICSI may be improved.

Other risks and adverse effects

All clinical examinations performed in the study are according to conventional IVF/ICSI procedures. The most common side-effects to standard medications of IVF/ICSI treatments are fatigue, gastro-intestinal discomfort, headache and rarely OHSS. When drawing blood, the patient may experience pain and discomfort during puncture of the skin and in rare occasions a smaller bruise will appear. Furthermore, there is an unknown but expected small risk of discarding viable embryos in the study.

Patient insurance

The study is covered by Patienterstatningen.

Information from patient journals and handling of confidential patient data

Prior to informed consent, patient journals and referrals will be screened to identify eligible patients. Age, AMH value, allergies, and pre-existing medical conditions will be passed on to the research personnel by the treating doctor. The information will be obtained from the journal entry written at the first visit to the fertility clinic ("ambulatorienotat") or one of the subsequent entries if this is more up to date. The obtained data is expected to be a maximum of 1-2 years old. We expect to screen approximately 1800 patient journals, as only approximately 30 % of the invited patients are expected to agree to participate and make it to randomisation. After randomisation, the following treatment-related data will be collected from patient journals.: number and type of fertility treatments after randomisation and until live birth, information about the first pregnancy after randomisation; biochemical pregnancy (yes/no), pregnancy ultrasound findings during pregnancy (1^{st}, 2^{nd} and 3^{rd} trimester) and gestational age and weight/height at birth, and the health of the neonate. If the parents provide consent on a separate consent form, the health records of children born following PGT-A and standard treatment will be reviewed for short- and long-term health information for up to five years after birth. These data will be obtained because they are needed to clarify the primary and secondary hypotheses (outcomes) of the study.

Informed consent and inclusion in this study will allow the principal investigator, sponsor and sponsor's representatives as well as relevant authorities direct access to patient journals (paper journals, electronic patient records, laboratory systems etc.), in order to gain information about the participants health status, which is necessary as a result of the implementation of the research project as well as for control purposes, including self-control, quality control and monitoring, which these authorities might be obliged to perform.

Data are transferred to an online electronic case report form (eCRF); REDCap. The REDCap database has a complete audit trail and is based on anonymous subject ID numbers used in the trial. Data are backed up daily and stored on a server located in a locked facility in Denmark. No data or biological material will be sent abroad and databeskyttelsesforordningen and databeskyttelsesloven will be obeyed.

Funding

Professor Anja Pinborg, consultant Kristine Løssl and post.doc. Nathalie Friis Wang from the Fertility Clinic Rigshospitalet, are the initiators of the study. The study is funded by an independent grant from

Danmarks Frie Forskningsfond (DFF) of 4.5 million DKK. The grant will be paid out to a public research fund managed by Rigshospitalet. The funding covers salary costs for study coordinators Nathalie Friis Wang and Kristine Løssl as well as other support staff and costs related to the PGT-A analyses. The initiators and researchers have no affiliation with Danmarks Frie Forskningsfond (DFF), which is a public, independent fund under Uddannelses- og forskningsministeriet.

The pharmaceutical company Gedeon Richter will sponsor research meetings related to the project during the project period. They have no influence on the trial design or the progression of the trial and will not be present at the research meetings. No member of the research group has any personal affiliation with Gedeon Richter.

Publication

We aim to publish relevant data as soon as possible. First results might be published as soon as the last patient has finished the study, with a follow up publication of all data related to the cumulative LBR. Positive, negative, and inconclusive results will be published in international scientific journals and at clinicaltrials.gov. The results of this study will be presented at national as well as international scientific congresses and published in high impact peer-reviewed international scientific journals targeting reproductive medicine. Results of public interest will be reported in the lay press and in press releases at relevant media sources.

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7.4 CASP Checklist Assessment - Example

Example for reference of the study by Munné et al. 2019 [28].

Critical Appraisal Skills Programme

CASP Checklist:
For Randomised Controlled Trials (RCTs)

Reviewer Name:	E.M.E
Paper Title:	"Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial".
Author:	Santiago Munne, Ph.D.,a,b Brian Kaplan, M.D.,c John L. Frattarelli, M.D., H.C.L.D.,d Tim Child, M.D.,e Gary Nakhuda, M.D.,f F. Nicholas Shamma, M.D.,g Kaylen Silverberg, M.D.,h,i Tasha Kalista, M.A.,j Alan H. Handyside, Ph.D.,k Mandy Katz-Jaffe, M.D.,l Dagan Wells, Ph.D.,m Tony Gordon, Ph.D.,n Sharyn Stock-Myer, Ph.D.,o and Susan Willman, M.D.,p on behalf of the STAR Study Group
Web Link:	*Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial
Appraisal Date:	21.05.2025

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Section A Is the basic study design valid for a randomised controlled trial?	
1. Did the study address a clearly formulated research question?	☒ Yes ☐ No ☐ Can't Tell
CONSIDER: *Was the study designed to assess the outcomes of an intervention?* *Is the research question 'formulated' in terms of:* • *Population studied* • *Intervention given* • *Comparator chosen* • *Outcomes measured?*	
2. Was the assignment of participants to interventions randomised?	☒ Yes ☐ No ☐ Can't Tell
CONSIDER: • *How was randomisation carried out? Was the method appropriate?* Providers were blinded until embryo transfer, patients were blinded until a pregnancy, and laboratory personnel were blinded until study completion. • *Was randomisation sufficient to eliminate systematic bias?* • *Was the allocation sequence concealed from investigators and participants?*	
3. Were all participants who entered the study accounted for at its conclusion?	☒ Yes ☐ No ☐ Can't Tell
CONSIDER: • *Were losses to follow-up and exclusions after randomisation accounted for?* Primary reason for exclusion were not being able to reach 2 eligible blastocysts. • *Were participants analysed in the study groups to which they were randomised (intention-to-treat analysis)?* • *Was the study stopped early? If so, what was the reason?* No, it was not.	
Section B Was the study methodologically sound?	
4. (a) Were the participants 'blind' to intervention they were given?	☒ Yes ☐ No ☐ Can't Tell
(b) Were the investigators 'blind' to the intervention they were giving to participants?	☒ Yes ☐ No ☐ Can't Tell
(c) Were the people assessing/analysing outcome/s 'blinded'?	☒ Yes ☐ No ☐ Can't Tell
5. Were the study groups similar at the start of the randomised controlled trial?	☒ Yes ☐ No ☐ Can't Tell
CONSIDER: • *Were the baseline characteristics of each study group (e.g. age, sex, socio-economic group) clearly set out?* Mean age and reason for infertility were similar between the two arms. • *Were there any differences between the study groups that could affect the outcome/s?*	
6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	☒ Yes ☐ No ☐ Can't Tell
CONSIDER: • *Was there a clearly defined study protocol?* Yes, a clinical study protocol • *If any additional interventions were given (e.g. tests or treatments), were they similar between the study groups?* Yes. • *Were the follow-up intervals the same for each study group?* Yes, clear randomization and end of follow-up dates.	

Section C: What are the results?	
7. Were the effects of intervention reported comprehensively?	☒Yes ☐ No ☐ Can't Tell
CONSIDER: • *Was a power calculation undertaken?* Yes, above 300 in each arm would provide a 85%. • *What outcomes were measured, and were they clearly specified?* • *How were the results expressed? For binary outcomes, were relative and absolute effects reported?* • *Were the results reported for each outcome in each study group at each follow-up interval?* • *Was there any missing or incomplete data? No.* • *Was there differential drop-out between the study groups that could affect the results?* No. • *Were potential sources of bias identified?* • *Which statistical tests were used?* Fisher exact test and an ad hoc test. • *Were p values reported?* P-values for all outcomes were reported.	
8. Was the precision of the estimate of the intervention or treatment effect reported? For some outcomes and characteristics.	☒Yes ☐ No ☐ Can't Tell
CONSIDER: • *Were confidence intervals (CIs) reported?*	
9. Do the benefits of the experimental intervention outweigh the harms and costs? Yes, however only a beneficial effect is seen for the subgroup 35-40 with improved LBR and ongoing pregnancy.	☒Yes ☐ No ☐ Can't Tell
CONSIDER: • *What was the size of the intervention or treatment effect?* • *Were harms or unintended effects reported for each study group?* • *Was a cost-effectiveness analysis undertaken? (Cost-effectiveness analysis allows a comparison to be made between different interventions used in the care of the same condition or problem.)*	
Section D: Will the results help locally?	
10. Can the results be applied to your local population/in your context?	☒Yes ☐ No ☐ Can't Tell
CONSIDER: • *Are the study participants similar to the people in your care?* Yes. • *Would any differences between your population and the study participants alter the outcomes reported in the study?* • *Are the outcomes important to your population?* Yes. • *Are there any outcomes you would have wanted information on that have not been studied or reported?* • *Are there any limitations of the study that would affect your decision?*	
11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	☒Yes ☐ No ☐ Can't Tell
CONSIDER: • *What resources are needed to introduce this intervention taking into account time, finances, and skills development or training needs?*	

- *Are you able to disinvest resources in one or more existing interventions in order to be able to re-invest in the new intervention?*

APPRAISAL SUMMARY: *List key points from your critical appraisal that need to be considered when assessing the validity of the results and their usefulness in decision-making.*		
Positive/Methodologically sound	**Negative/Relatively poor methodology**	**Unknowns**
PGT-A vs. IVF. - Trophectoderm biopsy - Single embryo transfer - Next generation sequencing (NGS) -Patients, clinicians, and laboratory staff blinded. -Aggregation of data performed in age subgroups.	-No control of demographics of patients, and the mean age was 33.7, plus over half of the study population was below 35. This is a different picture from what is often seen in clinic. -Small number of patients enrolled per clinic, meaning no in between clinic comparison.	**-**Mosaic embryos were excluded for transfer.

7.5 AI-declaration

AALBORG UNIVERSITY
DENMARK

Disclosure – Use of Artificial-Intelligence (AI) Generated Content

Students must acknowledge all use of AI

Select all applicable statements and complete the text if applicable.

1. Disclosure: No AI use

☐ I acknowledge that no AI tools/technologies (Grammarly, ChatGPT, Bard, Quillbot, OpenAI etc.) were used in the completion of this assessment.

2. Disclosure: Formulate research question

☐ I acknowledge the use of XYZ, version, Month, Year (web URL) to formulate the following research question what was formulated. I uploaded the text, and I entered the following prompts on Date, Month, Year:.

3. Disclosure: Literature search

■ I acknowledge the use of Rayyan (Rayyan: AI-Powered Systematic Review Management Platform) to systematically screen identified records of the literature search. Furthermore, copilot (https://copilot.microsoft.com) was used to check if additional grey literature within the research field had been overlooked. Data/Month/Year was not recorded.

4. Disclosure: Critical literature assessment

☐ I acknowledge the use of XYZ, version, Month, Year (web URL) to assess my literature. I entered the following prompts on Date, Month, Year:

5. Disclosure: Synthesize literature

☐ I acknowledge the use of XYZ, version, Month, Year (web URL) to synthesize the literature. I entered the following prompts on Date, Month, Year:

6. Disclosure: Generated/manipulated code – list each occurrence

■ I acknowledge the use Copilot (https://copilot.microsoft.com) to generate code to generate layout and bibliography in Overleaf (Latex). Date/Month/year was not recorded.

7. Disclosure: Generated/manipulated image – list each occurrence

☐ I acknowledge the use of XYZ, version, Month, Year (web URL) to explain what you used AI for. I entered the following prompt on Date, Month, Year:

8. Disclosure: Data analysis

☐ I acknowledge the use of XYZ, version, Month, Year (web URL) to analyze data. I entered the following prompts on Date, Month, Year:

9. Disclosure: Generate or rephrase text incl. edit/refine grammar, spelling, or formatting – list each occurrence

■ I acknowledge the use of suggestions from Writefull, an AI assist in Overleaf (Latex). Moreover, copilot (https://copilot.microsoft.com) was utilized to translate words and phrases. Date/month/year was not recorded.

10. Disclosure: Create presentations

☐ I acknowledge the use of XYZ, version, Month, Year (web URL) to explain what you used AI for. I entered the following prompts on Date, Month, Year:

11. Disclosure: Communicate to laymen/non-specialists

☐ I acknowledge the use of XYZ, version, Month, Year (web URL) to explain what you used AI for. I entered the following prompts on Date, Month, Year:

■ ***I declare that the disclosure is complete and truthful.***

Student number: 20196829

Course: Master Thesis

Date: 27.05.2025