An Economic Analysis of Aneuploidy Screening of Oocytes in Assisted Reproduction in Germany

Eine Kostenanalyse zur Aneuploidieuntersuchung von Eizellen im Kontext der assistierten Reproduktion in Deutschland

Authors
Kay Neumann1, 2, Georg Griesinger1, 2

Affiliations
1 Sektion für gynäkologische Endokrinologie und Reproduktionsmedizin, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Lübeck, Germany
2 Universitäres Kinderwunschzentrum Lübeck und Manhagen & PID Zentrum Lübeck, Lübeck, Germany

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ABSTRACT
Background The randomized ESTEEM trial reported that pre-implantation genetic aneuploidy testing of oocytes by polar body biopsy (PGT-A) with array comparative genomic hybridization (aCGH) in women aged 36–40 years undergoing assisted reproduction treatment reduces the number of embryo transfers and the risk of miscarriage while not impacting the live birth rate.

Method A decision tree model based on data from the ESTEEM trial was created and analyzed, using three cost scenarios for assisted reproduction treatment in Germany (statutory health insurance [GKV] = the deductible is 50% of the standard medical costs; private medical insurance [PKV] = invoicing is based on the German medical fee schedule [GOÄ]; private medical insurance with a simple GOÄ factor = invoicing is based on the standard medical fees multiplied by a linear GOÄ factor). The scenarios were compared for cost-effectiveness (cost per live birth), cost per prevented miscarriage and the threshold values for cost and effectiveness.

Results PGT-A increased the costs per live birth in all scenarios (GKV: + 208%; PKV: + 49%; simple GOÄ factor: + 89%). A threshold analysis showed a substantial cost discrepancy between the actual cost of the intervention based on GOÄ (€ 5801) vs. the theoretically tolerable PGT-A cost (GKV: € 561, PKV: € 1037, single GOÄ-factor: € 743). The incremental cost per one prevented miscarriage was approximately € 70 000 – 75 000 for all cost scenarios.

Conclusion The use of PGT-A with aCGH in assisted reproduction cannot be recommended from a cost-effectiveness perspective.

ZUSAMMENFASSUNG
Hintergrund Die ESTEEM-Studie zeigte, dass eine Aneuploidieuntersuchung von Eizellen durch Polkörperbiopsie (PKD) und array comparative genomic hybridization (aCGH) Diagnostik im Rahmen einer assistierten Reproduktion bei Frauen im Alter von 36 bis 40 Jahren die Lebendgeburtsrate nicht stiegt, jedoch die Anzahl von Behandlungszyklen mit Embryoübertragung und das Abortrisiko verringert.

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Introduction

In 2017, around 63,000 women in Germany underwent assisted reproductive treatment (ART) for infertility [1]. The mean age of these women at the time of assisted reproductive treatment was 35.7 years, implying that a relevant percentage of these women were between the age of 35–40 years, which is considered to be an advanced maternal age (AMA). Studies have reported a higher incidence of numerical chromosomal aberrations for this age group in embryos created by assisted reproductive techniques, and this is considered to be the main cause of the increasing risk of miscarriage and the decreasing likelihood of a live birth in this age group [2, 3]. Chromosomal aberrations can develop at different stages of parental meiosis, fertilization and early embryonic development, respectively, with female meiosis considered to be the most common cause of numerical chromosomal anomalies [4–8]. It was therefore postulated that aneuploidy screening in the context of preimplantation diagnostic testing during ART could increase the live birth rate (LBR) through negative selection of genetically abnormal, non-viable oocytes, and thereby reduce the time to pregnancy [9, 10]. One method used for aneuploidy screening is based on the biopsy of polar bodies (PBB) which are extruded by the oocyte during fertilization. Screening of polar bodies is not subject to the restrictions of the German Embryo Protection Law, meaning that no special requirements or permits are necessary to carry out PBB in contrast to the genetic screening of human embryos.

A recently published multicenter study (ESTEEM trial), the largest randomized clinical study of aneuploidy screening using PBB, was unable to find an increase in LBR for women of AMA (36–40 years). However, fewer embryo transfers were required following aneuploidy screening, and fewer miscarriages occurred to achieve the same LBR as the control group. Of note, 24% of patients in the PBB group had no fresh embryo transfer after ART while in the control group this figure was only 7% [11].

From the patient’s point of view, reducing the number of embryo transfer cycles necessary to achieve live birth does not only have implications in terms of the physical stress but also in terms of financial costs. This means that calculating the cost implications for specific treatment scenarios using the available data from the ESTEEM trial is useful and appropriate.

Material and Methods

A decision tree model from the patients’ perspective based on data from the ESTEEM trial was developed using the TreeAge Pro Suite 2018 software (TreeAge Software, Inc., Williamstown, MA, USA) [12]. As no actual patients were involved in this theoretical study, no ethics commission was consulted prior to carrying out this analysis.

In this model, patients undergo assisted reproduction treatment with intracytoplasmic sperm injection (ICSI) analogously to the ESTEEM trial. ICSI is then either followed by PTG-A with aneuploidy screening of both polar bodies using aCGH and the subsequent transfer of maximally two embryos (PGT-A group), or embryo transfer is carried out directly after ICSI with no genetic screening (control group). Surplus fertilized oocytes are cryopreserved (=frozen) and then transferred after thawing in a later cycle if the first embryo transfer does not result in pregnancy. In the ESTEEM trial, frozen embryo transfer cycles were evaluated over a period of one year from the start of assisted reproductive treatment.
Effectivity

The probability of a live birth was calculated as a live birth from the first embryo transfer and possible further transfers after a frozen embryo transfer cycle. The probability of a first and second frozen embryo transfer cycle for embryo transfer purposes was calculated based on the percentage of patients with a frozen embryo transfer cycle in both treatment arms. Patients with >3 embryo transfers or an embryo transfer outside the period of observation of one year after randomization were not included in this analysis as these data are not available from the ESTEEM trial.

The probability of a successful PGT-A was calculated for the total number of PGT-A procedures carried out. All probabilities used in the study are shown in ▶ Fig. 1.

Cost scenarios

To depict the different billing scenarios for fertility treatment in the German healthcare system, the direct costs of assisted reproductive treatment with ICSI were simulated using three different cost scenarios from the patients’ perspective:

1. Statutory health insurance (GKV): The costs of treatment are born by a statutory health insurance company based on the “uniform assessment scale” for medical fees in Germany (Einheitlicher Bewertungsmaßstab, EBM), but patients are required to pay a 50% deductible. Treatment includes hormone treatment, monitoring, follicular puncture, ICSI and embryo transfer. This corresponds to invoicing under treatment plan 10.5 according to the guideline of the Joint Federal Committee of Physicians and Health Insurance Funds in Germany (50% deductible = €1601) [13, 14]. The patient must bear the cost of

▶ Fig. 1 Decision tree model based on the ESTEEM trial. Nodes within the model are marked by green circles, percentages show the patient flow analogously to the ESTEEM trial. Red triangles define endpoints.
Private health insurance (PKV): Invoicing is based on the German medical fee schedule for physicians (\textit{Gebührenordnung für Ärzte, GOÄ}), often with increases to the simple GOÄ rates (\(\text{€ 7681}\)) [16]. Depending on their private health insurance contract, patients with private health insurance may be reimbursed for these costs.

3. Simple GOÄ factor: Invoicing is based on the GOÄ multiplied by a simple linear factor (\(\text{€ 4328.94}\)). Depending on their private health insurance contract, patients with private health insurance will be reimbursed for these costs.

The costs incurred for cryopreservation and a subsequent frozen embryo transfer cycle are not born by the GKV and typically also not by a private insurance, and were therefore integrated into all of the scenarios, using the German medical fee schedule for physicians (GOÄ) (cryopreservation \(\text{€ 396}\), frozen embryo transfer cycle \(\text{€ 577}\)). The costs of a miscarriage were disregarded in all three cost scenarios, as the incidental costs of a miscarriage are born by health insurance companies irrespective of the insurance status of the affected woman.

### Threshold value analysis

A threshold value analysis for the maximum tolerable costs for the cost-effectiveness of PGT-A was calculated for all base-case scenarios. The threshold values are therefore the costs of PGT-A above which additional costs for PGT-A are compensated by the effect. The necessary live birth rate which would be theoretically required for cost-effectiveness in the PGT-A group was simulated.

This corresponds to the theoretically necessary live birth rate which would compensate for the costs of PGT-A. The cost per prevented miscarriage was calculated as follows:

\[\Delta \text{treatment cost per patient with vs. without PGT-A multiplied by the "number needed to treat (= 15) to reduce the incidence of miscarriage by one".}\]

### Cost of PGT-A and sensitivity analysis

Carrying out PGT-A to screen for aneuploidy is self-funded by patients in all three cost scenarios, and invoicing of patients is based on the GOÄ. Calculation of the costs incurred for PGT-A include the cost of performing polar body biopsy (mean cost according to the GOÄ: \(\text{€ 689}\)), the cost of a human geneticist to examine the polar body, and the material costs of aCGH (\(\text{€ 900 per oocyte}\)). The main costs are related to the material cost of the aCGH.
chips used and the reagents (on average, 4 chips are necessary for 10 available polar bodies). A one-way sensitivity analysis for the range € 0–10 000 was carried out for PGT-A aneuploidy screening with the endpoints “costs per live birth” and “mean cost per patient”.

Probabilistic sensitivity analysis
A probabilistic sensitivity analysis (PSA) was carried out to test for uncertainties in the assumptions of the base-case scenarios. To do this, effects were replaced by beta distributions and costs by log-normal distributions. 1000 calculations with different costs and effects were analyzed, which corresponds to the recommended requirements for economic analysis [17].

All distributions used are shown in ►Table 1. Beta distributions were assumed for probabilities, and their parameters were based on the figures observed in the ESTEEM trial. Log-normal distributions were assumed for costs, with assumed median values based on the specifications for the respective base-case scenarios. For PGT-A costs of € 5801 and a maximum cost of € 14 000 in 396 cases in the ESTEEM trial, 0.5 and 0.99937 quantiles and a log-normal distribution were assumed. This resulted in a standard deviation of the logarithm of 0.32 (variation coefficient 33%), which represents a realistic range for 95% of the values for the remaining costs (►Table 1).

The incremental costs to avoid a miscarriage were calculated by multiplying Δ treatment costs per patient with the “number needed to treat to benefit” in 1000 simulated scenarios.

Results
Costs per live birth and average costs per patient for the base-case scenarios
Carrying out PGT-A aneuploidy screening significantly increased the cost per live birth in all three cost scenarios. Thus, the costs per live birth increased by € 17 999 (GKV), € 16 370 (PKV) and € 17 378 (simple GOÄ factor) in the group which had PGT-A.

The average cost per patient was also significantly higher if PGT-A was carried out. The increase in the cost per patient in the PGT-A group was € 4914 (GKV), € 4895 (PKV) and € 4923 (simple GOÄ factor), respectively.► Fig. 2 shows the costs per live birth and the costs per patient for the respective cost scenarios.

Incremental cost for preventing one miscarriage
Using the assumptions of the base-case scenarios, the incremental costs of preventing a single miscarriage by additionally carrying out PGT-A were € 73 708 (GKV), € 73 434 (PKV) and € 73 980 (simple GOÄ factor), respectively.

Sensitivity analysis and threshold value analysis
A one-way sensitivity analysis of the cost of PGT-A ranging from € 0 to € 10 000 with the endpoints “cost per live birth” and “average cost per patient” showed a linear correlation for the costs per live birth and the costs per patient, depending on the cost of PGT-A (► Fig. 3).

A threshold value analysis of the cost of PGT-A with the endpoint “cost per live birth” showed that for the GKV and the simple GOÄ factor scenarios, the amount at which PGT-A became cost-
effective was significantly less than € 1000 (GKV: € 561, simple GOÄ factor: € 743). In contrast, in the PKV cost scenario, PGT-A becomes cost-effective when the cost of PGT-A is € 1037 or less.

▶ Fig. 3 shows the point of intersection between the cost of PGT-A and the group which did not have PGT-A as the threshold value for cost-effectiveness (i.e., PGT-A costs above which the additionally accruing cost of PGT-A is compensated by the effect) for the respective cost scenarios.

A simulation of the increase in the LBR required in the PGT-A group which would result in PGT-A being cost-effective and thus compensate for the additional cost of PGT-A showed a theoretically necessary increase in the LBR of > 47% per embryo transfer (the exact LBR cannot be calculated for this model as the ramifications of the decision tree model would add up to > 100%) for GKV, and an increase of + 14% for PKV and + 26% for simple GOÄ factor for the figures above which PGT-A would become cost-effective.

Probabilistic sensitivity analysis (PSA)

PSA showed no cost-effectiveness in the PGT-A group across 1000 calculations for all three cost scenarios.

The median incremental costs to prevent one miscarriage based on 1000 calculations were € 63 686 (GKV: 95% confidence interval [CI]: € 60 030–67 587), € 64 504 (PKV: 95% CI: € 61 983–68 549) and € 66 117 (simple GOÄ factor: 95% CI: € 63 150–69 334).

Discussion

This study shows that patients of AMA with fertility problems who are entitled to have 50% of the costs of an assisted reproductive treatment cycle with ICSI reimbursed (if needed, with cryopreservation and subsequent frozen embryo transfer cycles) contribute an average of € 8600 of their own money per live birth. The LBR observed in the ESTEEM trial compares well with the documented treatment outcomes recorded in the German IVF Register for this age group. The addition of PGT-A with aCGH significantly increases these costs. This cost-effectiveness analysis from the patients’ point of view showed significantly higher costs per live birth for aneuploidy screening using PGT-A with aCGH for all three cost scenarios. A threshold analysis of the maximum costs of a PGT-A which would result in the same costs per live birth as in the control group showed results (€ 561, € 1037 and € 743, respectively) which were significantly below the costs incurred under GOÄ for 5 oocytes (= average number of investigated oocytes in the ESTEEM trial) for aCGH. Recent technological developments have already led to a reduction in the costs of genetic diagnostics. This study explores the costs of a cost-neutral PGT-A by threshold analysis. It should be mentioned that polar body biopsy is only possible in the context of ICSI treatment. ICSI is not only more expensive than IVF treatment but should additionally be reserved for couples with severe male subfertility. The study also highlighted the enormous cost discrepancy between GKV and PKV cost scenarios which is caused by the fundamentally different payment terms for patients with GKV (= statutory health insurance) and patients with PKV (= private health insurance; invoicing is based on the GOÄ). This discrepancy is a frequently criticized issue of the German healthcare system [18].

The decision tree mode was modelled from the point of view of patients and does not take account of the costs incurred if a miscarriage occurs (relative risk PGT-A: 0.48) or the costs of a twin pregnancy (relative risk PGT-A: 0.54), which introduces bias against PGT-A. However, another cost analysis we carried out...
using four different international cost scenarios which took the costs of miscarriage into account also did not find that PGT-A was cost-effective [19].

A calculation of the incremental incurred cost of PGT-A to prevent a single miscarriage showed a cost dimension (at least €73,434), which makes using PGT-A to reduce the rate of miscarriages unrealistic from an economic perspective.

In summary, in view of the high costs of testing, aneuploidy screening using PGT-A with aCGH is not suitable for routine applications from the perspective of cost-effectiveness. The limitations of this cost analysis are the fact that indirect medical costs (for example, the costs of having to miss work because of miscarriage, etc.) were not incorporated in the model because such costs vary significantly and are difficult to calculate. However, because of the big discrepancy in costs between the PGT-A and the control group, it is unlikely that the results of this cost analysis would change even if indirect medical costs were also taken into account.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Deutsches IVF-Register. Jahrbuch 2017. Online: https://www.deutsches-ivf-register.de/perch/resources/dir-jahrbuch-2017-deutsch-final-4.pdf; last access: 28.07.2019
[2] Macklon NS, Geraedts JPM, Fauser BCJM. Conception to ongoing pregnancy: The “black box” of early pregnancy loss. Hum Reprod Update 2002; 8: 333–343
[3] Fransasiak JM, Forman EJ, Hong KH et al. The nature of aneuploidy with increasing age of the female partner: A review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. Fertil Steril 2014; 101: 656–663.e1
[4] Johnson DS, Cinnioglu C, Ross R et al. Comprehensive analysis of karyotypic mosaicism between trophectoderm and inner cell mass. Mol Hum Reprod 2010; 16: 944–949. doi:10.1093/molehr/gaq062
[5] Mertzanidou A, Wilton L, Cheng J et al. Microarray analysis reveals abnormal chromosomal complements in over 70% of 14 normally developing human embryos. Hum Reprod 2013; 28: 256–264. doi:10.1093/humrep/des362
[6] Chow JF, Yeung WS, Lau EV et al. Array comparative genomic hybridization analyses of all blastomeres of a cohort of embryos from young IVF patients revealed significant contribution of mitotic errors to embryo mosaicism at the cleavage stage. Reprod Biol Endocrinol 2014; 12: 105. doi:10.1186/1477-7827-12-105
[7] Northrop LE, Treff NR, Levy B et al. SNP microarray-based 24 chromosome aneuploidy screening demonstrates that cleavage-stage FISH poorly predicts aneuploidy in embryos that develop to morphologically normal blastocysts. Mol Hum Reprod 2010; 16: 590–600
[8] Fragouli E, Alfarawati S, Spath K et al. The origin and impact of embryonic aneuploidy. Hum Genet 2013; 132: 1001–1013
[9] Feichtinger M, Stopp T, Goebel C et al. Increasing Live Birth Rate by Pre-implantation Genetic Screening of Pooled Polar Bodies Using Array Comparative Genomic Hybridization. PLoS One 2015; 10: e0128317. doi:10.1371/journal.pone.0128317
[10] Sermon K. Novel technologies emerging for preimplantation genetic diagnosis and preimplantation genetic testing for aneuploidy. Expert Rev Mol Diagn 2017; 17: 71–82
[11] Verpoot W, Stassen C, Bossuyt PM et al. Preimplantation genetic testing for aneuploidy by microarray analysis of polar bodies in advanced maternal age: a randomized clinical trial. Hum Reprod 2018; 33: 1767–1776. doi:10.1093/humrep/dey262
[12] Drummond M, Sculpher M, Torrance G et al. Methods for the economic Evaluation of Health Care Programmes. 3rd ed. Oxford: Oxford Medical Publications, Oxford University Press; 2005
[13] Kinderwunschrecht. Rechtsanwalt Philipp Alexander Wagner. Online: http://ra-kinderwunschrecht.de; last access: 28.07.2019
[14] Gemeinsamer Bundesausschuss. Richtlinien über künstliche Befruchtung. Online: https://www.g-ba.de/richtlinien/1/; last access: 30.07.2019
[15] Hildebrandt T, Oversohl N, Dittrich R et al. Can a University Reproductive Medicine Centre Be Financed Under the Pre-Existing General Conditions in Germany? Geburtsh Frauenheilk 2019; 79: 63–71
[16] Bundesverband Reproduktionsmedizinischer Zentren Deutschlands e. V. Online: https://repromed.de; last access: 30.07.2019
[17] Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford, UK: Oxford University Press; 2006
[18] Friedrich Ebert Stiftung. Gesprächskreis Sozialpolitik. Neuordnung der Versorgung im deutschen Gesundheitswesen. Online: http://library.fes.de/pdf-files/wiso/09893.pdf; last access: 29.10.2019
[19] Neumann K, Sermon K, Bossuyt P et al. An economic analysis of preimplantation genetic testing for aneuploidy (PGT-A) by polar body biopsy in advanced maternal age. BJOG 2020. doi:10.1111/1471-0528.16089