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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

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ABSTRACT

Background The randomized ESTEEM trial reported that preimplantation 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 [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 steigert, jedoch die Anzahl von Behandlungszyklen mit Embryoübertragung und das Abortrisiko verringert.

Methode Es wurde ein entscheidungsanalytisches Modell basierend auf Daten der ESTEEM-Studie erstellt, und drei Kostenszenarien einer assistierten Reproduktion in Deutschland aus Patientenperspektive (gesetzlich versichert [GKV] = Selbstbehalt 50 % der EBM-Kosten; privat versichert [PKV] = Abrechnung basierend auf Gebührenordnung für Ärzte [GOÄ]; privat versichert [einfacher GOÄ-Faktor] Abrechnung GOÄ mit einfachem Faktor) auf Kosteneffektivität (Kosten pro Lebendgeburt), Kosten- und Effektschwellenwerte und Kosten pro verhindertem Abort untersucht.

Ergebnisse Eine PKD erhöht die Kosten pro Lebendgeburt in allen Szenarien (GKV: + 208 %; PKV: + 49 %; einfacher GOÄ-Faktor: + 89 %). Eine Schwellenwertanalyse zeigt eine erhebliche Diskrepanz zwischen den Kosten einer aCGH-Polkörperdiagnostik von im Mittel 5801 € und den für eine Kosteneffektivität theoretisch maximal zulässigen Kosten für die genetische Diagnostik (GKV: 561 €, PKV: 1037 €, einfacher GOÄ-Faktor: 743 €). Die inkrementellen Kosten pro verhindertem Abort betragen rund 70 000–75 000 € in allen Kostenszenarien.

Schlussfolgerung Die Aneuploidieuntersuchung von Eizellen durch PKD und aCGH im Rahmen einer assistierten Reproduktion ist unter Kosten-Wirksamkeits-Aspekten nicht empfehlenswert.

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 genetic 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].

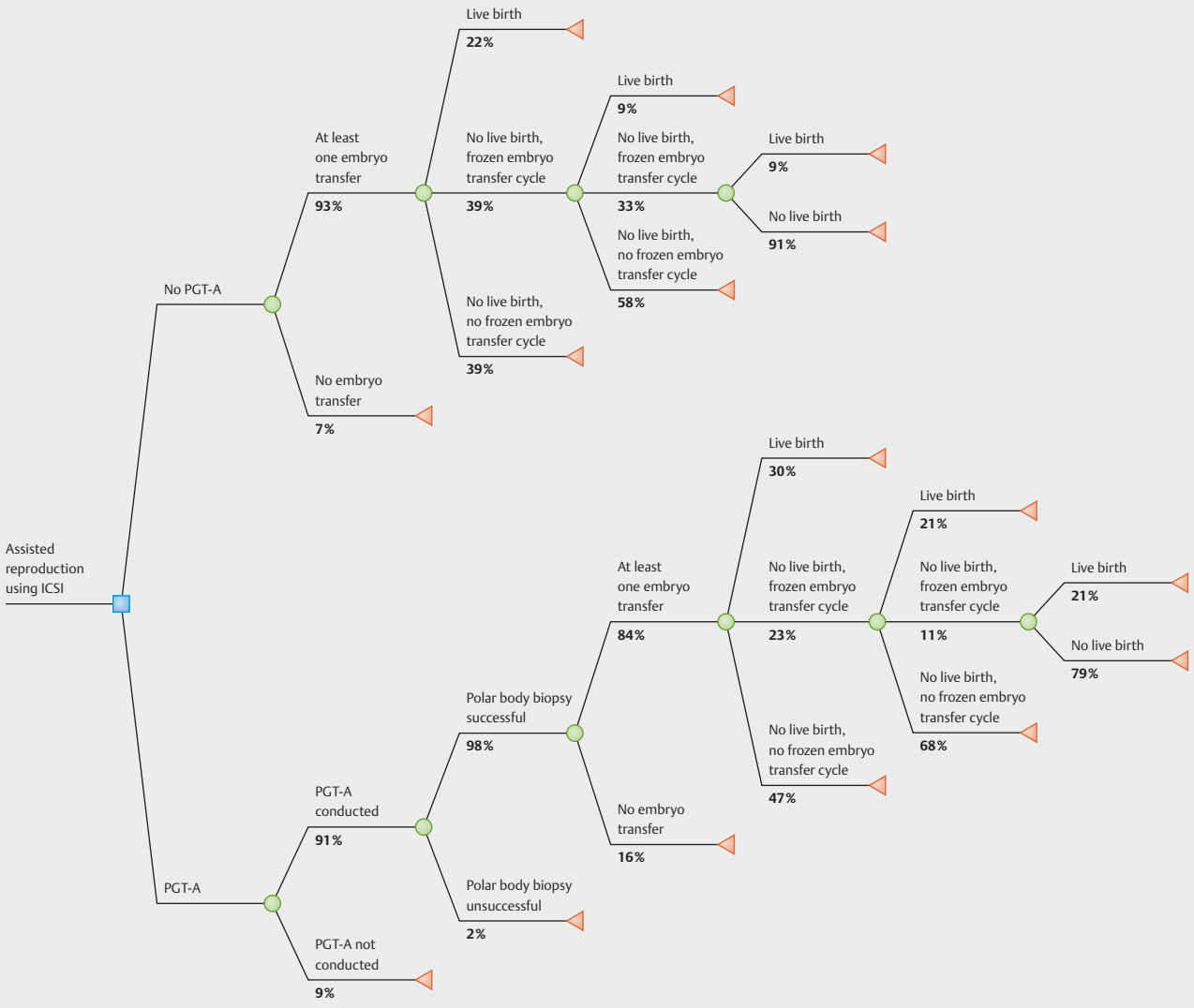
From the patient's point of view, reducing the number of embryo transfer cycles necessary to achieve live birth does not only have implications in terms of the physical stress but also in terms of financial costs. This means that calculating the cost implications for specific treatment scenarios using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

Since 2004, patients with statutory health insurance are required to bear 50 % of the costs of assisted reproductive treatments themselves. Treatment of "self-payers", for example unmarried couples, will not be funded by an insurance company, and these patients will be charged according to the German medical fee schedule (GOÄ). Couples with private insurance are likewise charged by GOÄ, with the base rate multiplied by an additional factor. Couples undergoing ART often request adjunctive treatments such as aneuploidy screening using PBB, in the hope of increasing the efficacy of the assisted reproductive treatment. Of note, neither couples with statutory health insurance nor self-payers or couples with private health insurance are reimbursed for the costs of such additional measures, and these additional costs must be added either pro rata or in their entirety to the actual cost of treatment born by the couple. This economic analysis therefore examines the cost implications of PGT-A (aneuploidy screening based on PBB) with array comparative genomic hybridization (aCGH) from the patient perspective, using cost-effectiveness under the current social and legal conditions in Germany as a primary endpoint.

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) (▶ **Fig. 1**) [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.



▶ **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.

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

▶ **Table 1** Distributions of the probabilistic sensitivity analysis. Beta distribution was assumed for effects and log-normal distribution for costs. These figures are not the same as the probabilities and costs calculated for the basic scenarios.

Parameter	Distribution	Parameter 1	Parameter 2	Expected value	Reference
PGT-A carried out	beta	180	17	0.91	Verpoest et al. 2018 [11]
PGT-A successful	beta	1006	17	0.98	
At least one embryo transfer, PGT-A	beta	149	30	0.83	
At least one embryo transfer, control group	beta	171	13	0.93	
Live births, PGT-A (first embryo transfer)	beta	44	105	0.29	
Live births, PGT-A (additional embryo transfers)	beta	6	22	0.21	
Live births, control group (first embryo transfer)	beta	38	133	0.22	
Live births, control group (additional embryo transfers)	beta	7	71	0.9	
First frozen embryo transfer cycle, PGT-A	beta	25	80	0.24	
Second frozen embryo transfer cycle, PGT-A	beta	2	18	0.1	
First frozen embryo transfer cycle, control group	beta	55	78	0.41	
Second frozen embryo transfer cycle, control group	beta	15	35	0.3	
Costs	**Distribution**		**Standard deviation**	**€**	
At least one embryo transfer	log-normal				
▪ GKV		7.3	0.32	1558	
▪ PKV		8.9		7717	
▪ Simple GOÄ factor		8.4		4680	
No embryo transfer					
▪ GKV		7.3	0.32	1558	
▪ PKV		8.9		7717	
▪ Simple GOÄ factor		8.3		4235	
First frozen embryo transfer cycle		6.7	0.32	855	
Additional frozen embryo transfer cycle		6.2	0.32	518	
PGT-A		8.6	0.32	5717	

this deductible herself. The individual cost items are discussed in detail in a previous study [15].

2. Private health insurance (PKV): Invoicing is based on the German medical fee schedule for physicians (*Gebührenordnung für Ärzte*, GOÄ), often with increases to the simple GOÄ rates (= € 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 (= € 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 = € 396, frozen embryo transfer cycle = € 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.

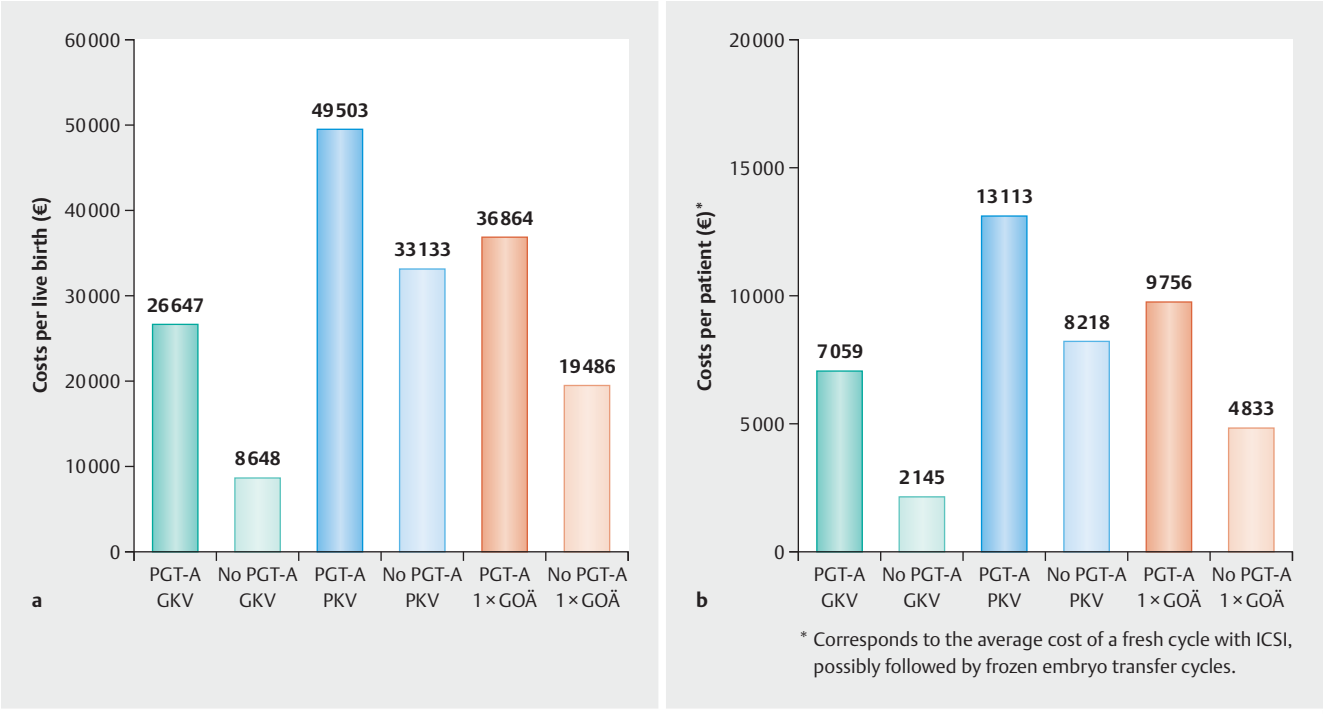
Threshold value analysis

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:

Δ 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: € 689), the cost of a human geneticist to examine the polar body, and the material costs of aCGH (= € 900 per oocyte). The main costs are related to the material cost of the aCGH



▶ **Fig. 2** Carrying out PTG-A results in higher costs per live birth (**a**) and per patient (**b**) in all cost combinations in the base-case scenarios.

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 PTG-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.

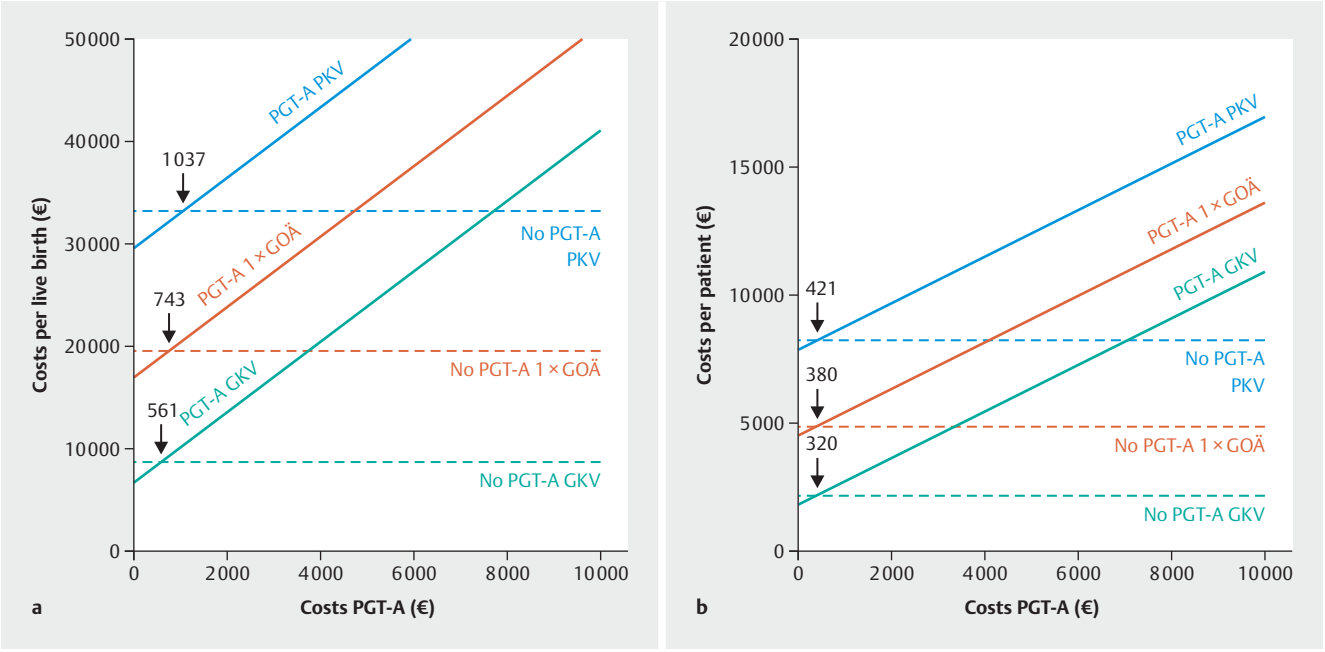
Incremental cost for preventing one miscarriage

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-



▶ **Fig. 3** Sensitivity analysis for the dependence of the cost per live birth (**a**) and per patient on the cost of PGT-A (**b**). The points of intersection define the threshold values for cost-effectiveness of PGT-A.

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 GÖA 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 genetic 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.

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