National Institute for Health and Care Excellence

Draft for consultation

Fertility problems: assessment and treatment

[N] Evidence report for pre-implantation genetic testing for aneuploidy as a fertility treatment add-on

NICE guideline number NGXXX

Evidence report underpinning recommendations 1.10.25 in the NICE guideline

September 2025

Draft for consultation

This evidence review was developed by NICE

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Review question

What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

Introduction

Fertility treatment add-ons to core treatments such as in-vitro fertilisation (IVF) and intrauterine insemination (IUI) are sometimes offered to patients to improve their chances of a live birth or to reduce the risk of adverse events during or after treatment, such as ovarian hyperstimulation syndrome (OHSS). However, the effects of fertility treatment add-ons on these outcomes are often unclear.

PGT-A involves testing the DNA of some cells removed from an embryo for chromosomal abnormalities to determine if an embryo should be excluded from transfer. The aim is to select embryos with a higher potential for implantation, and the technique is sometimes offered to people with previous IVF attempts that did not result in a live birth. However, PGT-A may reduce the number of embryos available for transfer and overall it is unclear is this add-on improves the chances of a live birth.

The aim of this review is to determine the effectiveness of PGT-A with blastocyst stage biopsy and genome-wide analysis as a fertility-treatment add-on.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Inclusion: • People undergoing IVF for a health-related fertility problem. In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. Exclusion: Studies that restrict analysis to those reaching a euploid embryo transfer, or where PGT-A was not performed on full cohort of embryos, will not be included.
Intervention	• IVF with preimplantation genetic testing for aneuploidies (PGT-A), previously known as preimplantation genetic screening (PGS) Exclusion: Only studies that use PGT-A with blastocyst biopsy will be included, studies where the timing of biopsy is at polar body or cleavage stage will be excluded. Only studies that use genome-wide analysis will be included. Studies using fluorescence in situ hybridisation (FISH) will be excluded.

Comparison	• IVF without PGT-A
Outcome	**Critical** • Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one fetal heart rate) The primary unit of analysis will be cumulative rates (of each outcome) per woman randomised **Important** • Miscarriage (loss of a baby before 24 weeks gestational age) • Multiple gestation (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least 2 fetal heartbeats) • Time to pregnancy • Number of cycles without an embryo transfer • Chromosomal abnormalities in the baby

IVF: in-vitro fertilisation

Methods and process

During the development of the guideline, the fertility treatment add-ons rating system developed by the Human Fertilisation and Embryology Authority (HFEA) was identified as relevant to the effectiveness of PGT-A. Given the potential for efficiencies to the guideline development process and the applicability of the HFEA's work to the UK setting, the committee took the pragmatic decision to draft recommendations relevant to this review question based on the evidence identified by the HFEA, and the HFEA ratings and as such no new systematic review of evidence was conducted for this review question. This approach is consistent with the principles outlined in Appendix N of Developing NICE guidelines: the manual.

The quality of the HFEA evidence statements were assessed independently by 2 reviewers using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool. This instrument is intended for assessing the quality of systematically developed clinical practice guidelines, including assessments of methodological rigour, transparency, and applicability. The AGREE II instrument is an internationally validated tool that is used to assess the methodological rigour and transparency of clinical practice guidelines. The evidence statements considered by the committee have all been produced with the intention of helping practitioners and service users make informed treatment decisions based on the available evidence for fertility treatment add-ons and in this sense were considered by the committee as being appropriate for inclusion in the evidence base and assessed using AGREE II. However, the fact that the quality of these documents has been assessed by an instrument designed for use on guidelines should be borne in mind. For example, some of the terminology used in AGREE II is based on the assumption that specific recommendations have been made, and therefore domains such as 'Clarity of presentation' and 'Applicability' include questions directly related to the quality of guidance given and its relevance to clinical practice. The HFEA evidence statements were assessed as the AGREE II tool sets out because all domains are important and form part of this validated instrument, but it is important to acknowledge that some of the low ratings are due to the applicability of the tool to the statements and not necessarily a reflection of the quality of the statements themselves.

The HFEA ratings are available at the treatment add-ons page of the HFEA website.

During the development of this guideline, a published Cochrane review was identified which matched the committee's intended PICO and which was referred to by the HFEA, comparing

the effectiveness of IVF with PGT-A versus IVF without PGT-A (Cornelisse 2020). The Cochrane protocol differed from the committee's intended intervention in that the effectiveness of both PGT-A using genome-wide analyses (including polar body and blastocyst stage biopsy) and PGT-A using fluorescence in situ hybridisation (FISH) was investigated, however in order to be consistent with the HFEA's approach and the intended approach as specified by the committee for this guideline, only the comparison of IVF with PGT-A using genome-wide analyses with blastocyst-stage biopsy versus IVF without PGT-A was considered by the committee.

Cochrane's methods are closely aligned to standard NICE methods, minor deviations (the use of the original Cochrane risk of bias tool, summary of findings tables instead of full GRADE tables, defining primary and secondary outcomes as opposed to critical and important, differences between outcomes as further discussed in the committee's discussion and interpretation of the evidence below) relevant to the topic area were highlighted to the committee and taken into account in discussions of the evidence.

The HFEA work was conducted in 2023 and the Cochrane review was conducted in 2020, so the guideline committee were consulted as to whether further important evidence had been published since the completion of the external reviews that could affect decision-making. However, the guideline committee were not aware of any such evidence.

Full details of the HFEA review methods are available through the HFEA website, and the Scientific and Clinical Advances Advisory Committee (SCAAC) decision tree for rating add-ons is available in the document "SCAAC Meeting Papers July 2023" (p17).

Further description of the methods used in this and other similar reviews are available from the methods document (supplement 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

HFEA ratings

The HFEA ratings for PGT-A are available from the relevant page of the HFEA website, as linked. The evidence review commissioned by the HFEA which underpins these ratings is available from the HFEA SCAAC website, under heading 'Meeting minutes and papers' from July 2023, in the document "SCAAC Meeting Papers July 2023" (pp12-13, 21-22 and PDF pp46-48 for PGT-A evidence). The SCAAC decision making on the ratings is described in the document "SCAAC Minutes July 2023 - Treatment Add-Ons" (pp7-8).

Summaries of the HFEA ratings and evidence on which the ratings were based are presented in Table 2.

Table 2: Summary of HFEA ratings

Treatment add-on	HFEA ratings
Pre-implantation genetic testing for aneuploidy (PGT-A)	Rated red for increasing chances of having a baby for most fertility patients: • There are potential safety concerns and/or, on balance, the findings from moderate/high quality evidence shows that this add-on may reduce treatment effectiveness Rated green for reducing the chances of miscarriage for most fertility patients: • On balance, findings from high quality evidence shows this add-on is effective at improving the treatment outcome Rated grey for reducing the chances of miscarriage for older women and for improving chances of having a baby for older women:

Treatment add-on	HFEA ratings
	• Effectiveness cannot be rated due to insufficient moderate/high quality evidence of effectiveness

HFEA: Human Fertilisation and Embryology Authority

HFEA treatment ratings

PGT-A was overall given a red rating, indicating there are potential safety concerns and/or, on balance, findings from moderate/high quality evidence shows that this add-on may reduce treatment effectiveness; this is because PGT-A often reduces the number of embryos available for transfer, without necessarily improving live birth or pregnancy rates.

Contributing to this overall rating, PGT-A was rated red for increasing the chances of having a baby for most fertility patients primarily based on findings from 1 randomised controlled trial (RCT: Yan 2021), which showed that, although live birth was higher from the first transfer, cumulative live birth was lower in the PGT-A arm. It also showed that time to conception resulting in live birth was significantly longer in the PGT-A arm. The HFEA noted that for some patients, PGT-A may shorten the time to pregnancy (by avoiding a series of embryo transfers), but the evidence from this RCT showed that the time to achieving pregnancy for most patients may be longer due to the additional time taken to carry out this test. The HFEA also noted safety concerns related to using PGT-A despite it not carrying any additional known risks for the person undergoing fertility treatment. These concerns were regarding an association between PGT-A and risks for the embryo, for example: the potential for healthy embryos to be discarded if a test result is not accurate; the potential for viable embryos to be discarded if they are not suitable for biopsy or are reported as mosaic (which have a lower chance of pregnancy but can still result in live birth); the potential for an embryo to be damaged by having cells removed and therefore being prevented from successfully developing.

PGT-A was given a green rating for reducing the chances of miscarriage in most fertility patients, based on multiple studies the HFEA considered moderate or high quality which the HFEA interpreted as showing that the miscarriage rate is lower in participants who received PGT-A. However, the HFEA note that PGT-A does not remove the chance of having a miscarriage entirely, and the potential reduction in miscarriage rates may not increase patients' chances of having a baby.

PGT-A was given a grey rating both for reducing the chances of miscarriage and improving the chances of having a baby for older women. One RCT was identified and showed PGT-A reduced miscarriage rates compared to standard IVF in older women, however this study was investigating PGT-A using polar stage biopsy, which the HFEA overall considered a different class of intervention and which is out of scope of the original review protocol as defined by the NICE committee. Therefore, only 1 non-randomised study was found for this population, which the HFEA did not consider to be of sufficient quality to aid decision-making.

Further information about the HFEA rating for PGT-A can be found on the relevant page of the HFEA website.

Further information about the HFEA's rating system can be found on the treatment add-ons page of the HFEA website.

Cochrane review

One Cochrane review comparing the effectiveness of IVF with PGT-A versus IVF without PGT-A (Cornelisse 2020), including 1 RCT which used blastocyst stage biopsy with next-generation sequencing in the comparison between IVF with PGT-A and IVF without (Munné 2019) was considered in this report. This Cochrane review had a different protocol to the HFEA's review, with stricter inclusion criteria (for example restricting included studies to

RCTs only) and implementation of data synthesis. There was overlap between Cochrane and the HFEA, as the study included in the Cochrane review was also included in the HFEA's. The Cochrane review was considered sufficiently relevant, high quality and up to date, and therefore was additionally considered by the committee to ensure all evidence had been reviewed, and used to supplement the HFEA evidence statements to guide recommendation making by the committee. See the benefits and harms section for the committee's discussion of the Cochrane evidence.

Full details of the Cochrane review (Munné 2019) including methods are available, as linked.

Economic evidence

A total of 3,908 studies were identified for this review question. After duplicates were removed, 2,679 studies were screened on tittle and abstract. Of these studies, 16 were screened on full text, and 3 of these studies were identified as being potentially applicable to this review question. Of the 3 studies that were formally checklisted, two were included and one was excluded.

Included studies

Two economic studies were identified that were relevant to this question (Scriven 2017, Scriven 2022).

See the literature search strategy in appendix H and economic study selection flow chart in appendix C.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix F.

Summary of included economic evidence

See Table 3 for the economic evidence profile of the included studies.

Table 3: Economic evidence profile of a systematic review of economic evaluations of PGT-A as a treatment add-on for people undergoing fertility treatment

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Scriven 2017	Potentially serious limitations[1,2,3,4]	Partially applicable[5,6]	Decision analytic model	*PGS1 v No testing:* £1,540 *PGS2 v PGS1:* *£519*	***Live Birth*** *PGS1 v No testing:* -0.015 *PGS2 v PGS1:* *0.015* ***Miscarriage*** *PGS1 v No testing:* *-0.019* *PGS2 v PGS1:* *0.009*	***Live Birth*** No testing dominates for live births ***Miscarriage*** *PGS1 v No testing* £81,013 per miscarriage avoided *PGS2 v PGS1* PGS1 dominates PGS2	No sensitivity analysis Data based on a prospective non-selection study where the clinical miscarriage rate per clinical pregnancy was calculated to be 8.5% (5/59) without genetic testing and 5.1% (3/59) following aneuploidy screening. Small numbers and wide confidence intervals for these data.
Scriven 2022	Potentially serious limitations[1,2,3,4]	Partially applicable[5,6]	Decision analytic model	***Costs[5]*** *PGT-A2 v PGT-A1* £542	***Live Birth[5]*** *PGT-A2 v PGT-A1* 0.005	***Live Birth[5]*** *PGT-A2 v PGT-A1* *£33,867 per live birth*	The 5% detriment threshold is arbitrary. No probabilistic sensitivity analysis was undertaken and only limited deterministic sensitivity analysis was undertaken

Study	Limitations	Applicability	Other	Incremental			Uncertainty
				PGT-A3 v PGT-A2 £508 *No testing v PGT-A3* £2,264	*PGT-A3 v PGT-A2* 0.004 *PGT-A3 v No testing* 0.000 ***Miscarriage*** *PGT-A2 v PGT-A1* 0.002 *PGT-A3 v PGT-A2* 0.003 *PGT-A3 v No testing* 0.021	*PGT-A3 v PGT-A2* *£128,640 per live birth* *No testing v PGT-A3* *£5,180,778 per live birth* ***Miscarriage*** PGT-A1 dominates other strategies for miscarriages	

[1] *Estimates of live birth and miscarriage rates were not obtained from randomised studies*
[2] *A full incremental analysis was not presented although could be calculated*
[3] *Time horizon and discounting was not explicitly discussed*
[4] *Probabilistic sensitivity analysis was not used to assess uncertainty in model inputs*
[5] *QALYs are not used to assess benefits and the presentation of 2 alternative measures of cost-effectiveness using different outcomes poses difficulties for a cost-effective threshold for either outcome*
[6] *Costs are not derived from NHS sources*
[7] *Multiple scenarios are presented by treatment, maternal age and number of blastocysts. For ease of exposition results are just presented for women aged 41-42 years, having IVF with ICSI and with 10 blastocysts*

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Originally, the committee prioritised live birth and clinical pregnancy as critical outcomes for decision making because they are the most important outcomes for people with fertility problems, and the committee agreed they should be prioritised above other outcomes to reflect their comparative importance. Of these outcomes, the HFEA only stated that live birth would be given specific consideration in the review and when creating the evidence ratings, but the review did also report information on pregnancy rates when reported in included studies. Both live birth and clinical pregnancy were reported in the Cochrane review.

The committee originally considered miscarriage, multiple gestation, time to pregnancy, number of cycles without an embryo transfer, and chromosomal abnormalities in the baby as important outcomes. The HFEA review reported on miscarriage and time to pregnancy or live birth, but did not report on multiple gestation, number of cycles without an embryo transfer, or chromosomal abnormalities in the baby. The Cochrane review reported on miscarriage, multiple pregnancy rate, and proportion of women reaching an embryo transfer but not time to pregnancy or chromosomal abnormalities in the baby.

The quality of the evidence statements

The quality of the HFEA evidence statements were assessed independently by 2 reviewers using the AGREE II tool and scored between 4% and 61% in all domains. Although the HFEA statements received low scores in some of the domains, the committee was confident this was primarily due to the purpose of the AGREE II tool to assess guidelines, and therefore did not reflect on the quality of the work conducted. Please see the Methods and process section for further information on the use of the AGREE II tool.

The evidence statements scored 50% for scope and purpose. The overall scope of the evidence statements, the health questions covered, and intended population are generally described. However, specific information including the expected benefits/ outcomes of the evidence statements and protocols are not reported.

The evidence statements scored 61% for stakeholder involvement. The SCAAC included a range of individuals from relevant professional groups, and detailed information about the specific professions of the members is linked. A patient representative was a part of the SCAAC, but there is no other information on whether views were sought from the target population/stakeholders or considered during the development of the evidence statements. The target users of the guideline are not well-defined but the intention of the evidence statements (to ensure patients are fully informed about whether add-ons are likely to be effective and to inform clinical decision-making) is made clear.

The score for rigour of development was 40%. A literature search was performed but there is no publicly available information on the search strategy and searches which are therefore not replicable. The committee also noted the review was not systematic and only one database was searched for relevant studies, although they agreed it was unlikely that any critical evidence was missed. The criteria for selecting the evidence are partially described including detailed information about study selection, but an explicit list of inclusion/exclusion criteria, excluded studies lists and protocols are not reported. Detailed descriptions of the evidence are provided narratively but GRADE tables were not reported. There was also no synthesis

of the evidence reported. The committee therefore agreed to use the Cochrane reviews to supplement their understanding of the evidence base, and to ensure any synthesised evidence was considered where possible. The risk of bias domains assessed are described but it is unclear whether an appropriate, certified checklist was used for each study type. Details on the methodology used by the HFEA to arrive at each evidence rating are provided, including a decision tree and descriptions of each rating. There is detailed information about specific discussions the committee had about the evidence, benefits, harms, risks, and, where appropriate, costs of each add-on. There are limited descriptions of how the evidence was interpreted to influence the statements, though it is usually unclear what evidence contributes to each statement and there is some inconsistency in how the evidence has been used to inform evidence statements between add-ons. There is no information about an external review of the evidence statements prior to publication, but an explicit statement of intent to update the evidence statements is provided with a review date. Information about the HFEA's methods for evidence surveillance and updating the statements is provided.

The evidence statements scored 17% for clarity of presentation. The evidence statements themselves are clearly defined and provided along with a description of each rating. However, the ratings themselves are not recommendations for practice and are therefore usually non-specific and ambiguous. Recommended actions are not provided, and it is rare that advice for how the evidence statements should be interpreted and applied is given.

The score for applicability was 6%. There is no discussion of barriers and facilitators of application and no information is given about feedback from key stakeholders, or whether this type of feedback was sought. There is no advice on how the evidence statements can be put into practice because the intention of the evidence statements is not to provide advice on how practice should be influenced. The cost of each add-on and resource implications are described for add-ons in order to aid decision-making. No monitoring and/ or auditing criteria have been reported.

The evidence statements also scored low for editorial independence at 4%. There is very little information reported about funding. An independent reviewer carried out the reviews of the evidence but there is no statement that the funding body did not influence the content of the evidence statements themselves. There is no information about the competing interests of the SCAAC, including no declarations of interest section.

See Appendix B for the AGREE II reviewer scoring tables.

Benefits and harms

The committee discussed the HFEA treatment ratings for PGT-A and the evidence underpinning them and agreed there was insufficient evidence of effectiveness on live birth rates to justify its use when also considering the potential risks associated with it. In particular, the committee noted that that PGT-A often reduces the number of embryos available for transfer and can therefore lower the likelihood of a fertility patient undergoing embryo transfer at all, lowering their chances of having a baby. There were additional concerns raised by the HFEA relating to an association between PGT-A and risks for the embryo. In the Cochrane review, under the comparison of IVF with PGT-A using genome-wide analyses with blastocyst-stage biopsy versus IVF without PGT-A, only 1 study was included, in part because studies that only reported results on participants reaching a euploid embryo transfer were excluded due to bias by design in favour of PGT-A. The evidence was of low certainty. However, the included study found that PGT-A reduced the proportion of participants reaching embryo transfer and had no effect on live birth rates. The authors of the Cochrane review concluded that it is uncertain whether PGT-A improves live birth rate after first embryo transfer.

The HFEA gave PGT-A a green rating for reducing the chances of miscarriage for most fertility patients. However the HFEA also stated that reducing the chance of miscarriage still

might not translate to an increased chance of having a baby due to the evidence showing no benefit of PGT-A for live birth rates as well as the potential risks associated with PGT-A, as noted above. An additional risk of PGT-A was the chance for no embryos to be deemed suitable for transfer if chromosomal abnormalities were detected in all embryos. Although this might reduce the chances of miscarriage, again, the reduction in available embryos may not translate to an increased chance of having a baby. Additionally, although the point estimate reported in the studies considered by the HFEA favoured PGT-A, the 95% confidence intervals all crossed the line of no effect, which would usually (according to standard NICE methodology) be interpreted as showing no important difference between interventions for the outcome miscarriage rates. The Cochrane review also concluded that it is uncertain whether PGT-A with blastocyst-stage biopsy improves miscarriage rate. The committee agreed that based on the available evidence it was uncertain whether PGT-A reduced miscarriage rates. The committee acknowledged that there could be the potential for people with recurrent miscarriage to benefit from PGT-A, but this group is outside the scope of this guideline.

The HFEA also considered the effectiveness of PGT-A in a sub-group of older women but gave PGT-A a grey rating because there was insufficient relevant evidence considered to be of moderate or high quality for this cohort. The committee noted that the study included in the Cochrane review did a subgroup analysis in older participants and did find an improvement in live birth rates exclusively in older women who had at least 2 embryos available for transfer, but this effect was not sustained in the intention to treat analysis. Therefore, the committee agreed there was insufficient evidence that PGT-A was effective in older women.

The committee's recommendation not to offer PGT-A to fertility patients was based on the HFEA treatment rating and the Cochrane review which showed that PGT-A can reduce the number of embryos available for transfer, without necessarily improving live birth rates.

Cost effectiveness and resource use

Two UK economic evaluations (Scriven 2017, Scriven 2022) were included for this review question. The committee noted that both were based on a hypothetical cohort of patients and that the author notes that, whilst the analysis can provide insights into the cost-effectiveness of PGT-A, it is not a substitute for randomised trials. The committee also reflected that the analysis presented incremental cost-effectiveness ratios for both live birth and miscarriage. Furthermore, in the absence of a particular strategy being cost-effective for both outcomes, cost-effectiveness would seem to require a qualitative trade-off between them.

Scriven (2017) found that whilst PGT-A strategies had higher costs than no testing, it was also characterised by lower birth rates and so on those grounds was dominated by not testing. However, PGT-A strategies did lead to lower miscarriage rates. Scriven (2022) also concluded that PGT-A is effective in reducing the rate of miscarriage but also that a strategy which excludes embryos with intermediate copy number results from transfer can reduce the chance of a first live birth from a full cycle. The study suggested that a strategy of only transferring embryos with a 'uniform' euploid test result had the potential to be cost-effective in women aged over 40 years as the ability of the test to detect non-viable embryos increases in older women.

The committee noted that both studies had serious limitations and were only intended to give insights into the cost-effectiveness. No strong conclusion was made with respect to the cost-effectiveness of PGT-A although the earlier paper suggested that PGT-A was unlikely to be beneficial to most women. The committee agreed that neither study provided evidence that would support a cost-effective recommendation to offer PGT-A.

Other factors the committee took into account

The committee were also aware of the recommendation made on PGT-A by the European Society of Human Reproduction and Embryology (ESHRE; Good practice recommendations on add-ons in reproductive medicine). This recommendation was based on existing RCTs and systematic reviews (including the Cochrane review referred to by the HFEA: Cornelisse 2020), as well as consideration of the cost of PGT-A and any safety concerns (ESHRE Add-ons working group 2023). Some additional safety concerns associated with PGT-A that were highlighted by ESHRE included a potential increased risk of intrauterine growth restriction, hypertensive disorders of pregnancy compared to IVF/ICSI, and hypertensive disorder in pregnancy, large for-gestational age, and macrosomia due to the freeze-all strategy usually used for PGT-A cycles. The committee agreed the NICE recommendation aligns with ESHRE's findings that PGT-A could not be recommended for routine clinical use.

The full guideline can be found on ESHRE's website: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Addons

Recommendations supported by this evidence review

This evidence review supports recommendation 1.10.25.

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023451157
1.	Review title	Clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment
2.	Review question	What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?
3.	Objective	To determine the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment
4.	Searches	The following databases will be searched (with no date limit): Clinical searches • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Searches will be restricted by:

		• English language • Human studies The guideline committee will decide whether and when to re-run the searches before final submission of the review to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Fertility treatment add-ons
6.	Population	Inclusion: • People undergoing IVF for a health-related fertility problem. In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. Exclusion: Studies that restrict analysis to those reaching a euploid embryo transfer, or where PGT-A was not performed on full cohort of embryos, will not be included.
7.	Interventions	• IVF with preimplantation genetic testing for aneuploidies (PGT-A), previously known as preimplantation genetic screening (PGS) Exclusion: Only studies that use PGT-A with blastocyst biopsy will be included, studies where the timing of biopsy is at polar body or cleavage stage will be excluded. Only studies that use genome-wide analysis will be included. Studies using fluorescence in situ hybridisation (FISH) will be excluded.
8.	Comparators	IVF without PGT-A
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs (individual or cluster) • If no RCT evidence:

		○ Quasi-randomised controlled trials (experimental studies using a non-randomly assigned control group design with matched comparison or another method of controlling for confounding variables)
10.	Other exclusion criteria	Other exclusion criteria: • Language limitations: non-English-language papers will be excluded (unless data can be obtained, and risk of bias assessed, from an existing systematic review) • Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted (and risk of bias assessed) from elsewhere (for instance, from an existing systematic review)
11.	Context	This guidance will fully update the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156)
12.	Primary outcomes (critical outcomes)	• Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one fetal heart rate) The primary unit of analysis will be cumulative rates (of each outcome) per woman randomised
13.	Secondary outcomes (important outcomes)	• Miscarriage (loss of a baby before 24 weeks gestational age) • Multiple gestation (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least 2 fetal heartbeats) • Time to pregnancy • Number of cycles without an embryo transfer • Chromosomal abnormalities in the baby
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies included after full-text review. The following data will be extracted: study details, participant characteristics, inclusion and exclusion criteria, details of the interventions, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.

15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs (and quasi-RCTs, if no RCT evidence identified) The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where there is available data, meta-analyses will be conducted using Cochrane Review Manager software, and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. It is considered likely that a fixed-effects model will be used for pairwise meta-analyses (based on the assumption that studies will be similar in terms of populations and interventions). Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using pre-specified subgroup analysis. Where heterogeneity cannot be accounted for by subgroup analysis, a random effects meta-analysis will be conducted (and both random effects and fixed effects analyses will be presented). If the fixed and random effect estimates differ, sensitivity analyses excluding small studies will be considered. If very significant heterogeneity remains, data will not be pooled across studies, and results will be summarised narratively. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: • Live birth: statistical significance • Continuous outcomes: +/- 0.5x pooled control group SD for mean difference and SMD -0.5/0.5 for standardised mean difference • Dichotomous outcomes (other than live birth): 0.8 and 1.25 for all relative dichotomous outcomes
17.	Analysis of sub-groups	Evidence will be sub-grouped by the following: • Female age (based on the mean age in the study): ○ <35 years ○ 35-39 years ○ ≥39 years Where evidence is sub grouped the committee will consider on a case-by-case basis if separate recommendations

		should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	July 2023			
22.	Anticipated completion date	November 2024			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☐
		Piloting of the study selection process		☐	☐
		Formal screening of search results against eligibility criteria		☐	☐
		Data extraction		☐	☐
		Risk of bias (quality) assessment		☐	☐
		Data analysis		☐	☐
24.	Named contact	5a. Named contact Guideline development team A			

		5b. Named contact e-mail FertilityProblems@nice.org.uk 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
25.	Review team members	Senior Technical Analyst Technical Analyst
26.	Funding sources/sponsor	This systematic review is being completed by NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10263
29.	Other registration details	None
30.	URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023451157
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Fertility treatment add-on, infertility, pre-implantation genetic testing for aneuploidy, PGT-A
33.	Details of existing review of	None

	same topic by same authors		
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☒	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Quality assessment (AGREE II)

AGREE II reviewer scoring tables for review question: What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

Table 5: AGREE II quality assessment of HFEA evidence statements

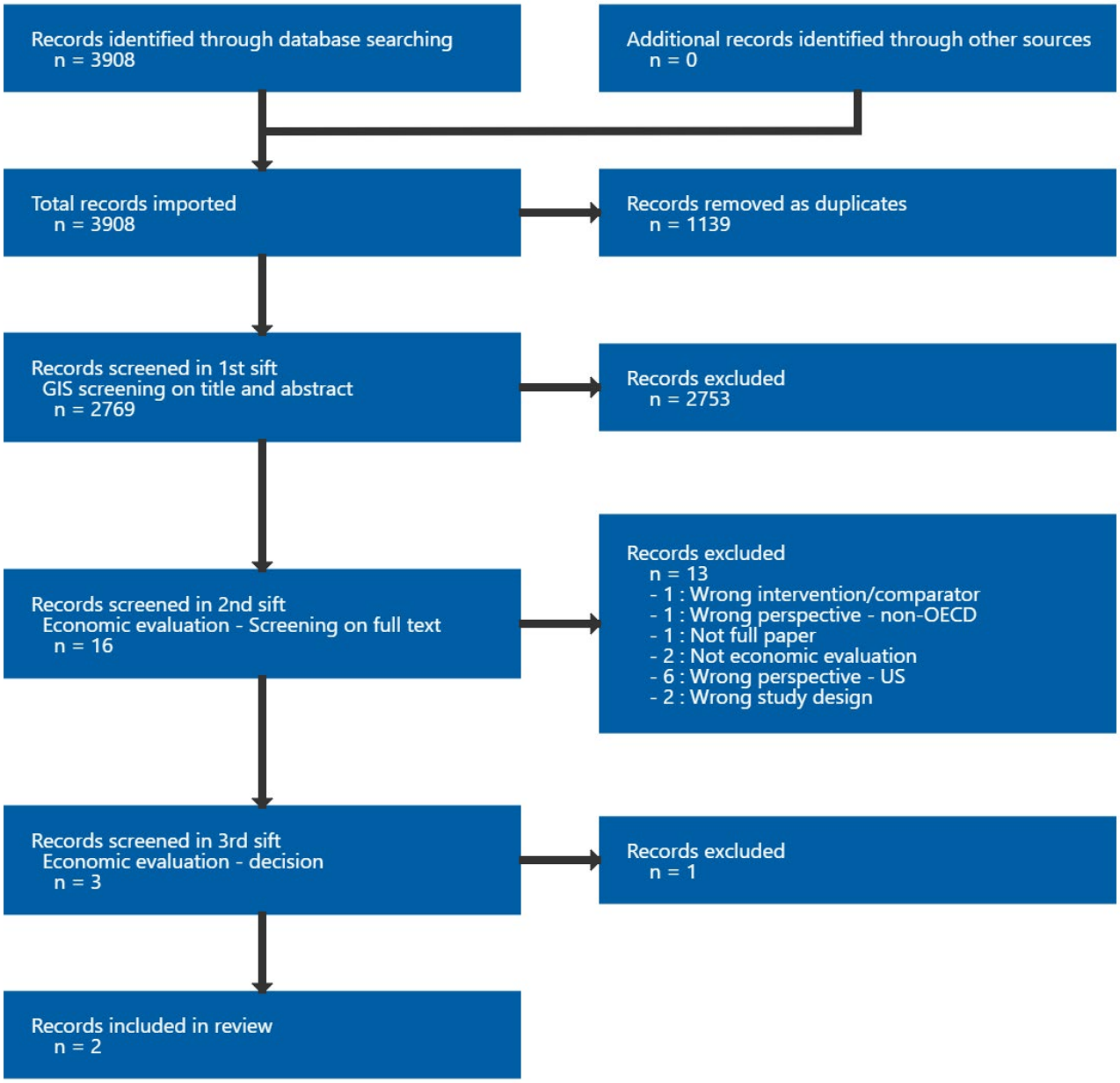
	1. Scope and purpose				2. Stakeholder involvement				3. Rigour of development									4. Clarity of presentation				5. Applicability					6. Editorial independence		
Reviewer	Objectives	Question	Population	Totals and **scores%**	Group membership	Target population	Target users	Totals and **scores%**	Search methods	Evidence selection criteria	Evidence strengths and limitations	Formulation of recs	Consideration of benefits/harms	Link between recommendations and evidence	External review	Updating procedure	Totals and **scores%**	Specific and unambiguous recs	Management options	Identifiable key recs	Totals and **scores%**	Facilitators and barriers to implementation	Implementation advice/tools	Resource implications	Monitoring/auditing criteria	Totals and **scores%**	Funding body	Competing interests	Totals and **scores%**
R1	5	5	6	16	7	4	5	16	3	4	6	7	7	5	1	6	39	2	1	5	8	1	1	4	1	7	2	1	3
R2	2	3	3	8	7	3	2	12	3	2	3	1	2	2	1	1	15	2	1	1	4	1	1	1	1	4	1	1	2
Score%				**50%**				**61%**									**40%**				**17%**					**6%**			**4%**

Appendix C Economic evidence study selection

Study selection for review question: What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

Two economic evaluations were included for this review question.

Figure 1: Study selection flow chart



Appendix D Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

Table 6: Economic evidence tables for PGT-A as a treatment add-on for people undergoing fertility treatment

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Scriven 2017 **Country:** UK **Type of economic analysis:** CEA **Source of funding:** No funding received for this study	**Intervention:** For embryos with an abnormal test result: 1. Exclude from transfer (PGS1) 2. Available for transfer but ranked below those with a normal test result (PGS2) **Comparator:** No testing	**Population:** People undergoing IVF **Modelling approach:** Decision analytic model **Source of baseline data:** Franasiak 2014 Used to estimate aneuploid and euploid genetic test result probabilities **Source of effectiveness data:** Scott 2012 Used to estimate the probability that aneuploid and euploid	**Costs:** Healthcare perspective **Mean cost:** *No testing:* £7,547 *PGS1:* £9,087 *PGS2:* £9,606 **Primary measure of outcome:** Live births Miscarriage **Mean outcome:**	**ICERs:** ***Live Birth*** No testing dominates for live births ***Miscarriage*** *PGS1 v No testing* £81,013 per miscarriage avoided *PGS2 v PGS1* PGS1 dominates PGS2	**Currency:** GBP **Cost year:** 2016 **Time horizon:** 2-year 'virtual' trial **Discounting:** None **Applicability:** Partially applicable **Limitations:** Serious limitations **Other comments:** No PSA but effect estimates are highly uncertain Data based on a prospective

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		embryos would result in clinical pregnancy, implantation failure, live birth or miscarriage **Source of cost data:** Expert opinion **Source of unit cost data:** Guy's and St Thomas' Assisted Conception Unit Private Healthcare self-funding costs and Private Healthcare UK	***Live Birth*** *No testing:* 0.648 *PGS1:* 0.633 *PGS2:* 0.648 ***Miscarriage*** *No testing:* 0.056 *PGS1:* 0.037 *PGS2:* 0.046		non-selection study where the clinical miscarriage rate per clinical pregnancy was calculated to be 8.5% (5/59) without genetic testing and 5.1% (3/59) following aneuploidy screening. Small numbers and wide confidence intervals for these data. The authors note, adding PGS universally to a first treatment cycle is likely to be an expensive way of reducing the risk of clinical miscarriage and shortening treatment time without a substantial reduction in the cost of genetic testing. Costs of assisted conception based on a single private UK clinic. Difficult to envisage a decision rule to appraise ICERs for 2 different outcomes
Author and year: Scriven 2022 **Country:** UK	**Intervention:** 1. PGT-A1: only embryos with a uniform euploid test result are	**Population:** Women undergoing IVF using their own eggs. **Modelling approach:**	**Costs:** Healthcare perspective Multiple scenarios are presented by treatment,	Multiple scenarios are presented by treatment, maternal age and number of blastocysts. For ease of exposition results are presented for women	**Currency: GBP** **Cost year:** 2022 **Time horizon:**

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Type of economic analysis: CEA **Source of funding:** NR	transferred 2. PGT-A2: only embrtyos with a uniform euploid or low-grade aneuploid/diploid are transferred without ranking 3. PGT-A3: transfers all embryos without ranking except those with a uniform aneuploid test result **Comparator:** No testing	Decision analytic modelling **Source of baseline data:** Scriven 2017 **Source of effectiveness data:** Viotti 2021 and Armstrong 2022 **Source of cost data:** NR **Source of unit cost data:** Publicly available UK private treatment prices in from a provider in London and Nottingham before a scheduled update on 1 July 2022	maternal age and number of blastocysts. For ease of exposition results are just presented for women aged 41-42 years, having IVF with ICSI and with 10 blastocysts **Mean cost:** *No testing:* £16,657 *PGT-A1:* £13,538 *PGT-A2:* *£13,885* *PGT-A3:* £14,393 **Mean outcome:** ***Live Birth*** *No testing:* 0.085 *PGT-A1:*	aged 41-42 years, having IVF with ICSI and with 10 blastocysts **ICERs:** ***Live Birth*** *PGT-A2 v PGT-A1* *£33,867 per live birth* *PGT-A3 v PGT-A2* *£128,640 per live birth* *No testing v PGT-A3* *£5,180,778 per live birth* ***Miscarriage*** PGT-A1 dominates other strategies for miscarriages	Not stated **Discounting:** None **Applicability:** Partially applicable **Limitations:** **Other comments:** Sensitivity analysis explored the impact of reducing PGT-A costs by 50% Full incremental analysis not presented but can be calculated Costs based on private clinic costs single private UK clinic. Difficult to envisage a decision rule to appraise ICERs for 2 different outcomes

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			0.076 *PGT-A2:* 0.081 *PGT-A3:* 0.085 ***Miscarriage*** *No testing:* *0.032* *PGT-A1:* *0.007* *PGT-A2:* *0.009* *PGT-A3:* 0.012		

ICER: Incremental cost-effectiveness ratio; NR: Not reported; PGS: Preimplantation genetic screening; PGT-A: Preimplantation generic testing - aneuploidy

Appendix E Economic model

Economic model for review question: What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

No economic analysis was conducted for this review question.

Appendix F Excluded studies

Excluded studies for review question: What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

Excluded effectiveness studies

No effectiveness evidence review was conducted, therefore there are no excluded studies.

Excluded economic studies

Table 7: Excluded health economic studies

Study	Code [Reason]
Somigliana, Edgardo; Busnelli, Andrea; Paffoni, Alessio et al. (2019) Cost-effectiveness of preimplantation genetic testing for aneuploidies. Fertility and sterility; vol. 111 (no. 6); 1169-1176	- Excluded at check listing stage
Lee, Evelyn; Zhang, Jinhu (2022) Which assisted reproductive technology (ART) treatment strategy is the most clinically and cost-effective for women of advanced maternal age: a Markov model. BMC health services research vol. 22 (no. 1); 1197	- Wrong intervention / comparator
Mersereau, Jennifer E; Plunkett, Beth A; Cedars, Marcelle I (2008) Preimplantation genetic screening in older women: a cost-effectiveness analysis. Fertility and sterility; vol. 90 (no. 3); 592-8	- Wrong perspective – US
Lee, Malinda; Lofgren, Katherine T; Thomas, Ann; Lanes, Andrea et al. (2021) The cost-effectiveness of preimplantation genetic testing for aneuploidy in the United States: an analysis of cost and birth outcomes from 158,665 in vitro fertilization cycles. American journal of obstetrics and gynecology; vol. 225 (no. 1); 55e1-55e17	- Wrong perspective – US
Collins, Stephen C; Xu, Xiao; Mak, Winifred (2017) Cost-effectiveness of preimplantation genetic screening for women older than 37 undergoing in vitro fertilization. Journal of assisted reproduction and genetics; vol. 34 (no. 11); 1515-1522	- Wrong perspective – US
Neal, Shelby A; Morin, Scott J; Franasiak, Jason M; Goodman, Linnea R et al. (2018) Preimplantation genetic testing for aneuploidy is cost-effective, shortens treatment time, and reduces the risk of failed embryo transfer and clinical miscarriage.	- Wrong perspective – US

Study	Code [Reason]
Vaiarelli, Alberto; Cimadomo, Danilo; Gennarelli, Gianluca et al. (2022) Second stimulation in the same ovarian cycle: an option to fully-personalize the treatment in poor prognosis patients undergoing PGT-A. Journal of assisted reproduction and genetics; vol. 39 (no. 3); 663-673	- Wrong study design
Lee, Evelyn; Costello, Michael F; Botha, Willings C; Illingworth, Peter; Chambers, Georgina M (2019) A cost-effectiveness analysis of preimplantation genetic testing for aneuploidy (PGT-A) for up to three complete assisted reproductive technology cycles in women of advanced maternal age. The Australian & New Zealand journal of obstetrics & gynaecology; vol. 59 (no. 4); 573-579	- Wrong study design
He, Xuan; Wang, Xiao; Shen, Jiaojie; Wan, Bin; Wang, Yingpeng et al. (2023) Cost-effectiveness of preimplantation genetic testing for aneuploidy for women with subfertility in China: an economic evaluation using evidence from the CESE-PGS trial. BMC pregnancy and childbirth; vol. 23 (no. 1); 254	- Wrong perspective – non-OECD
Facadio Antero, Maria; Singh, Bhuchitra; Pradhan, Apoorva; Gornet, Megan et al. (2021) Cost-effectiveness of preimplantation genetic testing for aneuploidy for fresh donor oocyte cycles. F&S reports; vol. 2 (no. 1); 36-42	- Wrong perspective – US
Khorshid, Arian; Bavan, Brindha; Chung, Esther H; Lathi, Ruth B (2024) Mosaic embryo transfer versus additional IVF with PGT-A Cycle: a decision model comparing live birth rate and cost. Journal of assisted reproduction and genetics; vol. 41 (no. 3); 635-641	- Wrong perspective – US
Ledger, William (2019) Preimplantation genetic screening should be used in all in vitro fertilisation cycles in women over the age of 35 years: AGAINST: Pre-implantation genetic screening should not be used in all IVF cycles in women over the age of 35 years. BJOG : an international journal of obstetrics and gynaecology; vol. 126 (no. 13); 1555	- Not an economic evaluation
Ben Nagi, Jara; Serhal, Paul; Wells, Dagan; Jones, Benjamin P (2019) Preimplantation genetic screening should be used in all in vitro fertilisation cycles in women over the age of 35 years: FOR: Optimising reproductive outcomes is cost-effective and minimises adverse sequelae. BJOG : an international journal of obstetrics and gynaecology; vol. 126 (no. 13); 1554	- Not a full paper
McIntyre, L (2001) Pre-implantation diagnosis; London: Bazian Ltd (Editors), Wessex Institute for Health Research and Development, University of Southampton	- Not economic evaluation

Appendix G Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

No research recommendations were made for this review question.

Appendix H Health economic literature search strategies

Health economic literature search strategies for review question: What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

Database: Ovid MEDLINE(R) ALL <1946 to May 08, 2024>

Date of last search: 09/05/2024

#	Searches
1	exp Fertilization in Vitro/
2	exp Embryo Transfer/ or Embryo Implantation/
3	Blastocyst/
4	(embryo* or blastocyst* or blastomer*).tw.
5	vitro fertili?ation.tw.
6	(ivf or ICSI).tw.
7	((intracytoplas* or intra-cytoplas*) adj2 (sperm or injection*)).tw.
8	exp Reproductive Techniques, Assisted/
9	(assisted adj1 (reproduct* or conception)).tw.
10	live birth*.tw.
11	abortion, spontaneous/ or abortion, habitual/ or embryo loss/
12	(implant* adj2 (poor or fail*)).tw.
13	(pregnan* adj3 (fail* or loss*)).tw.
14	(abortion* adj2 (habitual or recurr* or threaten* or spontaneous*)).tw.
15	miscarriage*.tw.
16	(older adj2 (wom?n or female* or maternal* or reproductive*)).tw.
17	(advanced adj2 age*).tw.
18	("35 year*" or "age 35*" or "39 year*" or "age 39*" or "4* year" or "age 4*").tw.
19	or/1-18
20	exp Chromosome Aberrations/
21	Preimplantation Diagnosis/
22	Genetic Testing/
23	chromosom*.tw.
24	aneuploid*.tw.
25	((Preimplant* or pre-implant*) adj3 (gene* or diagnos* or test* or screen*)).tw.
26	(gene* adj3 screen*).tw.
27	(PGS or PGD or PGTA or PGT).tw.
28	Comparative Genomic Hybridization/
29	(genom* adj2 hybrid*).tw.
30	(CGH or aCGH).tw.
31	exp Polymerase Chain Reaction/
32	(quantitative adj2 (polymerase or PCR)).tw.
33	qPCR.tw.
34	Polymorphism, Single Nucleotide/
35	(single nucleotide adj1 (polymorphism* or variant* or variation*)).tw.
36	(SNP or SNPs).tw.
37	Nucleic Acid Amplification Techniques/
38	((nucleic acid or rna or dna or whole-genome) adj2 amplification*).tw.
39	WGA.tw.
40	High-Throughput Nucleotide Sequencing/

#	Searches
41	(((high-through* or next-gen*) adj1 sequenc*) or NGS).tw.
42	((Trophectoderm* or troph-ectoderm* or blastocyst) adj4 (biops* or diagnos* or analys* or screen* or test*)).tw.
43	(spent adj1 culture medi*).tw.
44	or/20-43
45	19 and 44
46	letter/
47	editorial/
48	news/
49	exp historical article/
50	Anecdotes as topic/
51	comment/
52	case reports/
53	(letter or comment*).ti.
54	or/46-53
55	randomized controlled trial/ or random*.ti,ab.
56	54 not 55
57	animals/ not humans/
58	exp Animals, Laboratory/
59	exp Animal Experimentation/
60	exp Models, Animal/
61	exp Rodentia/
62	(rat or rats or rodent* or mouse or mice).ti.
63	or/56-62
64	45 not 63
65	limit 64 to english language
66	Economics/
67	Value of life/
68	exp "Costs and Cost Analysis"/
69	exp Economics, Hospital/
70	exp Economics, Medical/
71	exp Resource Allocation/
72	Economics, Nursing/
73	Economics, Pharmaceutical/
74	exp "Fees and Charges"/
75	exp Budgets/
76	budget*.ti,ab.
77	cost*.ti,ab.
78	(economic* or pharmaco?economic*).ti,ab.
79	(price* or pricing*).ti,ab.
80	(financ* or fee or fees or expenditure* or saving*).ti,ab.
81	(value adj2 (money or monetary)).ti,ab.
82	resourc* allocat*.ti,ab.
83	(fund or funds or funding* or funded).ti,ab.
84	(ration or rations or rationing* or rationed).ti,ab.
85	ec.fs.
86	or/66-85
87	quality-adjusted life years/
88	sickness impact profile/
89	(quality adj2 (wellbeing or well being)).ti,ab.
90	sickness impact profile.ti,ab.
91	disability adjusted life.ti,ab.
92	(qal* or qtime* or qwb* or daly*).ti,ab.
93	(euroqol* or eq5d* or eq 5*).ti,ab.

#	Searches
94	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
95	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
96	(hui or hui1 or hui2 or hui3).ti,ab.
97	(health* year* equivalent* or hye or hyes).ti,ab.
98	discrete choice*.ti,ab.
99	rosser.ti,ab.
100	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
101	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
102	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
103	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
104	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
105	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
106	or/87-105
107	65 and (86 or 106)

1 **Database: Embase <1974 to 2024 May 08>**

2 **Date of last search: 09/05/2024**

#	Searches
1	exp in vitro fertilization/
2	exp embryo transfer/ or nidation/
3	blastocyst/
4	(embryo* or blastocyst* or blastomer*).tw.
5	vitro fertili?ation.tw.
6	(ivf or ICSI).tw.
7	((intracytoplas* or intra-cytoplas*) adj2 (sperm or injection*)).tw.
8	exp infertility therapy/
9	(assisted adj1 (reproduct* or conception)).tw.
10	live birth*.tw.
11	spontaneous abortion/ or recurrent abortion/ or embryo death/
12	(implant* adj2 (poor or fail*)).tw.
13	(pregnan* adj3 (fail* or loss*)).tw.
14	(abortion* adj2 (habitual or recurr* or threaten* or spontaneous*)).tw.
15	miscarriage*.tw.
16	(older adj2 (wom?n or female* or maternal* or reproductive*)).tw.
17	(advanced adj2 age*).tw.
18	("35 year*" or "age 35*" or "39 year*" or "age 39*" or "4* year" or "age 4*").tw.
19	or/1-18
20	exp chromosome aberration/
21	prenatal diagnosis/ or exp preimplantation genetic screening/
22	genetic screening/
23	chromosom*.tw.
24	aneuploid*.tw.
25	((Preimplant* or pre-implant*) adj3 (gene* or diagnos* or test* or screen*)).tw.
26	(gene* adj3 screen*).tw.
27	(PGS or PGD or PGTA or PGT).tw.
28	comparative genomic hybridization/
29	(genom* adj2 hybrid*).tw.
30	(CGH or aCGH).tw.
31	exp polymerase chain reaction/
32	(quantitative adj2 (polymerase or PCR)).tw.
33	qPCR.tw.

#	Searches
34	single nucleotide polymorphism/
35	(single nucleotide adj1 (polymorphism* or variant* or variation*)).tw.
36	(SNP or SNPs).tw.
37	nucleic acid amplification techniques/
38	((nucleic acid or rna or dna or whole-genome) adj2 amplification*).tw.
39	WGA.tw.
40	high throughput sequencing/
41	(((high-through* or next-gen*) adj1 sequenc*) or NGS).tw.
42	trophectoderm biopsy/
43	((Trophectoderm* or troph-ectoderm* or blastocyst) adj4 (biops* or diagnos* or analys* or screen* or test*)).tw.
44	(spent adj1 culture medi*).tw.
45	or/20-44
46	19 and 45
47	letter.pt. or letter/
48	note.pt.
49	editorial.pt.
50	case report/ or case study/
51	(letter or comment*).ti.
52	or/47-51
53	randomized controlled trial/ or random*.ti,ab.
54	52 not 53
55	animal/ not human/
56	nonhuman/
57	exp Animal Experiment/
58	exp Experimental Animal/
59	animal model/
60	exp Rodent/
61	(rat or rats or rodent* or mouse or mice).ti.
62	or/54-61
63	46 not 62
64	limit 63 to english language
65	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
66	64 not 65
67	health economics/
68	exp economic evaluation/
69	exp health care cost/
70	exp fee/
71	budget/
72	funding/
73	resource allocation/
74	budget*.ti,ab.
75	cost*.ti,ab.
76	(economic* or pharmaco?economic*).ti,ab.
77	(price* or pricing*).ti,ab.
78	(financ* or fee or fees or expenditure* or saving*).ti,ab.
79	(value adj2 (money or monetary)).ti,ab.
80	resourc* allocat*.ti,ab.
81	(fund or funds or funding* or funded).ti,ab.
82	(ration or rations or rationing* or rationed).ti,ab.
83	or/67-82
84	quality adjusted life year/
85	"quality of life index"/
86	short form 12/ or short form 20/ or short form 36/ or short form 8/

#	Searches
87	sickness impact profile/
88	(quality adj2 (wellbeing or well being)).ti,ab.
89	sickness impact profile.ti,ab.
90	disability adjusted life.ti,ab.
91	(qal* or qtime* or qwb* or daly*).ti,ab.
92	(euroqol* or eq5d* or eq 5*).ti,ab.
93	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
94	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
95	(hui or hui1 or hui2 or hui3).ti,ab.
96	(health* year* equivalent* or hye or hyes).ti,ab.
97	discrete choice*.ti,ab.
98	rosser.ti,ab.
99	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
100	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
101	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
102	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
103	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
104	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
105	or/84-104
106	66 and (83 or 105)

1 **Database: HTA via CRD**

2 **Date of last search: 09/05/2024**

#	Searches
1	MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES
2	MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES
3	MESH DESCRIPTOR Embryo Implantation
4	MESH DESCRIPTOR Blastocyst
5	(embryo* or blastocyst* or blastomer*)
6	("vitro fertilisation" or "vitro fertilization")
7	(ivf or ICSI)
8	((intracytoplas* or (intra next cytoplas*)) near2 (sperm or injection*))
9	MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES
10	(assisted NEAR1 (reproduct* or conception))
11	(live next birth*)
12	MESH DESCRIPTOR Abortion, Spontaneous
13	MESH DESCRIPTOR Abortion, Habitual
14	MESH DESCRIPTOR Embryo Loss
15	(implant* near2 (poor or fail*))
16	(pregnan* near3 (fail* or loss*))
17	(abortion* near2 (habitual or recurr* or threaten* or spontaneous*))
18	miscarriage*
19	(older near2 (woman or women or female* or maternal* or reproductive*))
20	(advanced near2 age*)
21	((35 next year*) or (age next 35*) or (39 next year*) or (age next 39*) or (4* next year) or (age next 4*))
22	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
23	MESH DESCRIPTOR Chromosome Aberrations EXPLODE ALL TREES
24	MESH DESCRIPTOR Preimplantation Diagnosis
25	MESH DESCRIPTOR Genetic Testing
26	chromosom*
27	aneuploid*

#	Searches
28	((Preimplant* or (pre next implant*)) near3 (gene* or diagnos* or test* or screen*))
29	(gene* near3 screen*)
30	(PGS or PGD or PGTA or PGT)
31	MESH DESCRIPTOR Comparative Genomic Hybridization
32	(genom* near2 hybrid*)
33	(CGH or aCGH)
34	MESH DESCRIPTOR Polymerase Chain Reaction EXPLODE ALL TREES
35	(quantitative near2 (polymerase or PCR))
36	qPCR
37	MESH DESCRIPTOR Polymorphism, Single Nucleotide
38	("single nucleotide" near1 (polymorphism* or variant* or variation*))
39	(SNP or SNPs)
40	MESH DESCRIPTOR Nucleic Acid Amplification Techniques
41	(("nucleic acid" or rna or dna or "whole-genome" or "whole genome") near2 amplification*)
42	WGA
43	MESH DESCRIPTOR High-Throughput Nucleotide Sequencing
44	((high next through*) near1 sequenc*)
45	(("next gen" or "next generation" or "next-gen" or "next-generation") near1 sequenc*)
46	NGS
47	((Trophectoderm* or (troph next ectoderm*) or blastocyst) near4 (biops* or diagnos* or analys* or screen* or test*))
48	(spent near1 ("culture media" or "culture medium"))
49	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48
50	#22 AND #49
51	(#22 AND #49) IN HTA

1 **Database: INAHTA**

2 **Date of last search: 09/05/2024**

#	Searches
1	"Fertilization in Vitro"[mhe]
2	"Embryo Transfer"[mhe]
3	"Embryo Implantation"[mh]
4	"Blastocyst"[mh]
5	(embryo* or blastocyst* or blastomer*)
6	("vitro fertilisation" or "vitro fertilization")
7	(ivf or ICSI)
8	((intracytoplas* or "intra-cytoplasm" or "intra-cytoplasmic" or "intra cytoplasm" or "intra cytoplasmic") and (sperm or injection*))
9	"Reproductive Techniques, Assisted"[mhe]
10	(assisted and (reproduct* or conception))
11	("live birth" or "live births")
12	"Abortion, Spontaneous"[mh]
13	"Abortion, Habitual"[mh]
14	"Embryo Loss"[mh]
15	(implant* and (poor or fail*))
16	(pregnan* and (fail* or loss*))
17	(abortion* and (habitual or recurr* or threaten* or spontaneous*))
18	miscarriage*
19	(older and (woman or women or female* or maternal* or reproductive*))
20	("advanced age" or "advanced ages")
21	("35 year" or "35 years" or "age 35" or "39 year" or "39 years" or "age 39" or "40 year" or "40 years" or "age 40" or "41 year" or "41 years" or "age 41" or "42 year" or "42 years" or "age 42" or "43 year" or "43 years" or "age 43" or "44 year" or "44 years" or "age 44" or "45 year" or "45 years" or "age 45" or "46 year" or "46 years" or "age 46" or "47

#	Searches
	year" or "47 years" or "age 47" or "48 year" or "48 years" or "age 48" or "49 year" or "49 years" or "age 49")
22	#21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
23	"Chromosome Aberrations"[mhe]
24	"Preimplantation Diagnosis"[mh]
25	"Genetic Testing"[mh]
26	chromosom*
27	aneuploid*
28	((Preimplant* or "pre-implant" or "pre-implantation" or "pre implant" or "pre implantation") and (gene* or diagnos* or test* or screen*))
29	(gene* and screen*)
30	(PGS or PGD or PGTA or PGT)
31	"Comparative Genomic Hybridization"[mh]
32	(genom* and hybrid*)
33	(CGH or aCGH)
34	"Polymerase Chain Reaction"[mhe]
35	(quantitative and (polymerase or PCR))
36	qPCR
37	"Polymorphism, Single Nucleotide"[mh]
38	("single nucleotide" and (polymorphism* or variant* or variation*))
39	(SNP or SNPs)
40	"Nucleic Acid Amplification Techniques"[mh]
41	(("nucleic acid" or rna or dna or "whole-genome" or "whole genome") and amplification*)
42	WGA
43	"High-Throughput Nucleotide Sequencing"[mh]
44	((("high-through" or "high-throughput" or "high through" or "high throughput" or "next-gen" or "next-generation" or "next gen" or "next generation") and sequenc*) or NGS)
45	((Trophectoderm* or "troph-ectoderm" or "troph ectoderm" or blastocyst) and (biops* or diagnos* or analys* or screen* or test*))
46	(spent and ("culture media" or "culture medium"))
47	#46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23
48	#47 AND #22
49	Limit to English Language

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