Effective Health Care

Male Infertility

Results of Topic Selection Process & Next Steps

The nominator, the American Urological Association (AUA), is interested in a new AHRQ review examining the general health implications of underlying conditions associated with male infertility, the accuracy of tests in detecting these underlying conditions, the ability of tests to predict pregnancy outcomes, the effectiveness of surgical and medical treatments for male infertility, and the comparative effectiveness of sperm retrieval methods. They plan to use a new systematic review to inform the creation of a new guideline on male infertility.

Due to limited program resources, the program will not develop a review at this time. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Male Infertility

Topic #: 0683

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings:

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication: A new AHRQ review would not be duplicative of an existing product.
  - We identified 10 completed or in process systematic reviews pertinent to KQ 2-5. None of these reviews covered the full scope of the nomination. Reviews of note include a 2012 Cochrane review on surgery or embolization for varicoceles in subfertile men, a 2013 Cochrane review on gonadotropins for idiopathic male subfertility, and a 2014 Cochrane review on antioxidant vitamins and minerals for male subfertility. In addition, we identified an in-process AHRQ systematic review on the management of infertility; however, this did not provide sufficient detail on populations or outcomes for the AUA to develop guidelines.
  - We did not identify any reviews pertinent to KQ1.
- Feasibility: A new AHRQ review is feasible.
  - *Size/scope of review:* We identified 47 potentially relevant studies, including 4 studies on general health implications of conditions associated with male infertility

(KQ1), 10 studies on the accuracy of diagnostic and fertility prediction tests (KQ2), 17 studies on treatments for varicoceles (KQ3), 12 studies on interventions to improve fertility outcomes (KQ4), and 4 studies on sperm retrieval methods (KQ5) from our random sample of 200 studies.
    - *Clinicaltrials.gov:* We identified 14 ongoing or recently completed trials on ClinicalTrials.gov. The majority of these trials examined medical treatments for infertility (KQ4).
- Impact: A new AHRQ review may have moderate impact. The AUA last published best practice statements on the evaluation of the infertile male, evaluation of the azoospermic male, and management of azoospermia in 2011. The European Association of Urology last published guidelines on male infertility in 2012, although they provided a full-text update in 2015. A 2016 systematic review found inconsistencies between the recommendations of different urological groups on the evaluation of the infertile male, suggesting a need for a comprehensive evidence review by a separate organization.
- Value: The nomination has a high value potential, given that AUA will use an AHRQ systematic review to create new guidelines on male infertility. This organization has previously produced high-quality evidence-based guidelines, and is transparent about its methodology.

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Introduction

Approximately 15% of all couples are unable to conceive after 1 year of unprotected intercourse, and 20% of these cases can be attributed to male-only infertility.[1] Male infertility is caused by a variety of conditions, including genetic disorders, congenital absence of the vas deferens, testicular dysgenesis, and varicoceles. Male infertility can also be idiopathic. Treatments to improve male fertility depend on the underlying condition and can range from surgery or embolization of varicoceles, treatment with selective estrogen receptor modulators, aromatase inhibitors multivitamins, dietary supplements, or gonadotrophins. Sperm retrieval methods have also been used to extract sperm for use in assisted reproductive technology (ART).

Topic nomination *#0683 Male Infertility* was received on June 22, 2016. It was nominated by American Urological Association (AUA). We sent the nominator a draft of an in-process AHRQ review on management of infertility, and asked if it would potentially meet their needs. They commented that although the review partially addresses KQ3 and K4, it does not provide enough detail on populations (for ex, those with stage 0-3 varicoceles) or interventions (for ex, specific types of varicocelectomy). They also noted that although the review includes important outcomes such as pregnancy and live birth, it does not include relevant outcomes such as semen parameters that they would need to create a guideline. They did feel that the review addressed the effectiveness of assisted reproductive treatments (ART) for male infertility, so we removed this question from the nomination. Therefore, the questions for this nomination are:

Key Questions

Key Question 1. What are the general health implications for conditions associated with male infertility, including syndromes, varicoceles, CAVD, and testicular dysgenesis?

Key Question 2. What is the accuracy of tests to identify underlying conditions associated with male infertility and predict fertility outcomes (both spontaneous and through ART)?

a. " Semen analysis
b. " Chromosomal testing (among azoospermic/oligospermic males)
c. " Measures of FSH, LH, testosterone (for detecting primary testicular failure versus obstruction)
d. " Prolactin/pituitary MRI (detecting pituitary pathologies)
e. " DNA fragmentation index
f. " Other specialized testing (eg, sperm penetration assay and antisperm antibody testing)

Key Question 3. Among men of reproductive age with varicoceles, what is the effectiveness of treatments for each grade (0-3) of varicoceles in improving fertility outcomes?

a. " Varicocelectomy, including:
    i. Laparoscopic
    ii. Inguinal
    iii. Subinguinal
    iv. Macro/microscopic
b. " Embolization

Key Question 4. Among men of reproductive age with suspected or known infertility, what is the effectiveness of medical interventions in improving fertility outcomes?

a. " SERMs
b. " Aromatase inhibitors (including but not limited to anastrozole & letrozole)
c. " Multivitamins and nutritional supplements
d. " LH analogues
e. " FSH analogues

Key Question 5. Among men with azoospermia, what is the comparative effectiveness of sperm retrieval methods on pregnancy success rates?

a. Microsurgical epididymal sperm aspiration (MESA)
b. Percutaneous epididymal sperm aspiration (PESA)
c. Testicular sperm extraction (TSE or TESE)
d. Micro TSE
a. Percutaneous testicular sperm aspiration (TESA)

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes, (PICOs) of interest. See Table 1.

Table 1. Key Questions and PICOTs "

Key Questions	1. What are the general health implications for conditions associated with male infertility, including: a) Genetic Syndromes [Klinefelter's syndrome, cystic fibrosis, Kallmann's syndrome, Primary Ciliary Dyskinesias] b) Varicoceles c) CAVD d) Testicular dysgenesis e) Impact of abnormal semen analysis alone	2. What is the accuracy of tests to identify underlying conditions associated with male infertility and predict fertility outcomes (both spontaneous and through ART)?	3. Among men of reproductive age with varicoceles, what is the effectiveness of treatments for each grade of varicoceles in improving fertility outcomes? a) Grade 0 b) Grade 1 c) Grade 2 d) Grade 3	4. Among men of reproductive age with suspected or known infertility, what is the effectiveness of medical interventions in improving fertility outcomes?	5. Among men with azoospermia, what is the comparative effectiveness of sperm retrieval methods on pregnancy success rates?
Population	Men of reproductive age	Men of reproductive age	Men of reproductive age with varicoceles (Subgroups of idiopathic infertility, oligospermia, normospermia undergoing ART)	Men of reproductive age with suspected or known infertility	Men of reproductive age with azoospermia
Interventions	NA	a. Semen analysis b. Chromosomal testing (among azoospermic/oligospermic males) c. Measures of FSH, LH, testosterone (for detecting primary testicular failure versus obstruction) d. Prolactin/pituitary MRI (detecting pituitary pathologies) e. DNA fragmentation index f. Other specialized testing (eg, sperm penetration assay	a. Varicocelectomy, including: i. Laparoscopic ii. Inguinal iii. Subinguinal iv. Macro/microscopic v. Retroperitoneal b. Embolization	a. SERMs b. Aromatase inhibitors (including but not limited to anastrozole & letrozole) c. Multivitamins and nutritional supplements d. LH analogues e. FSH analogues	b. Microsurgical epididymal sperm aspiration (MESA) c. Percutaneous epididymal sperm aspiration (PESA) d. Testicular sperm extraction (TSE or TESE) e. Micro TSE f. Percutaneous testicular sperm aspiration (TESA)

		and antisperm antibody testing)			
Comparators	NA	NA	Control (no treatment)	Control (no treatment) or other medical therapies (SERMs, artificial insemination, Gonadotropins)	Other sperm retrieval methods
Outcomes	Malignancies, survival rates, other comorbid conditions	Sensitivity, specificity, yields, ability to predict spontaneous pregnancy and ART pregnancy outcomes [eg pregnancy, live birth]	Semen parameters [eg, volume, density, morphology and motility], spontaneous pregnancy and ART pregnancy outcomes [eg, pregnancy, live births], harms [eg, hydrocele, subsequent hypogonadism (low testosterone), recurrence, testicular loss, testicular atrophy, infection, hematoma, chronic pain]	Semen parameters[eg, volume, density, morphology and motility], spontaneous pregnancy and ART pregnancy outcomes [eg, pregnancy, live births], harms [eg, erythrocytosis, discontinuation due to any AE, elevated PSA, hair loss, acne, DVT, major adverse cardiovascular event]	Pregnancy success rates, harms [hydrocele, subsequent hypogonadism (low testosterone), recurrence, testicular loss, testicular atrophy, infection, hematoma, chronic pain]

Abbreviations: ART=Assisted Reproductive Technology; AE=adverse events; CAVD= Congenital Absence of the Vas Difference; DVT=Deep vein thrombosis; FSH= Follicle-stimulating hormone; LH= luteinizing hormone; SERMS= Selective estrogen receptor modulators; MRI= Magnetic Resonance Imaging; NA=Not applicable; PSA= Prostate Specific Antigen; TSE= Testicular sperm extraction

Methods

To assess topic nomination *#0683 Male Infertility* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

1. " Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. " Establish the overall *importance* of a potential topic as representing a health or " healthcare issue in the United States. "
3. " Determine the *desirability of new evidence review* by examining whether a new " systematic review or other AHRQ product would be duplicative. "
4. " Assess the *potential impact* a new systematic review or other AHRQ product.
5. " Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. " Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether a new review could influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.). See Appendix A.

Feasibility of New Evidence Review

We conducted a literature search in PubMed from July 2011 to July 2016.

Because a large number of articles were identified (n=721), we reviewed a random sample of 200 titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample. See Table 2, Feasibility Column, Size/Scope of Review Section for the citations of included studies.

We also searched Clinicaltrials.gov for recently completed or in-process unpublished studies. See Appendix B for the PubMed search strategy and links to the ClinicalTrials.gov search.

Value

We assessed the nomination for value (see Appendix A). We considered whether a partner organization could use the information from the proposed evidence review to facilitate evidence-based change; or the presence of clinical, consumer, or policymaking context that is amenable to evidence-based change.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. Approximately 15% of all couples are unable to conceive after 1 year of unprotected intercourse, and 20% of these cases can be attributed to male-only infertility.[1] Interventions to improve fertility, such as ART, can also be prohibitively expensive. In 1994, the cost of a successful live birth after one cycle of in vitro fertilization (IVF) was $66,667, and increased after each failed cycle.[2] Testing for and treating male infertility is one way to identify underlying causes of infertility, and can help predict the likelihood of a successful spontaneous pregnancy or pregnancy from ART.

Desirability of New Review/Duplication

A new AHRQ review would not be duplicative of an existing product. We identified 10 completed or in process systematic reviews[3-13] pertinent to KQ 2-5, but none pertinent to KQ1. No review covered the full scope of the nomination.

Reviews of note included a 2012 Cochrane review[4] on surgery or embolization for varicoceles in subfertile men, a 2013 Cochrane review[8] on gonadotropins for idiopathic male subfertility, and a 2014 Cochrane review[9] on antioxidant vitamins and minerals for male subfertility. We also identified an in-process AHRQ review[7] on the management of infertility which included one question on male-factor infertility. The nominator noted that this review would not provide sufficient detail on specific sub-populations, interventions, or outcomes for them to develop guidelines. These include outcomes such as semen parameters; interventions such as anastrozole and nutritional supplements in KQ 4; and details related to varicocelectomy, such as various surgical approaches and differences by grade of varicocele.

See Table 2, Duplication column for the systematic review citations that were determined to address the key questions.

Impact of a New Evidence Review

A new AHRQ review may have moderate impact. The AUA last published best practice statements on the evaluation of the infertile male,[14] evaluation of the azoospermic male,[15] and management of azoospermia[16] in 2011. The European Association of Urology last published guidelines on male infertility in 2012[17] and a full-text update in 2016. [18] A 2016 systematic review of guidelines[19] found inconsistencies between the methods and conclusions of guidelines on the evaluation of the infertile male, suggesting there is a need for a comprehensive examination of the evidence by a separate organization.

Feasibility of a New Evidence Review

A new AHRQ review is feasible.

We identified 47 studies from our random sample that were potentially relevant to the key questions in the nomination, including 4 observational studies[20-23] on general health implications of conditions associated with male infertility (KQ1); 10 observational studies[24-33] on the accuracy of diagnostic and fertility prediction tests (KQ2); 1 RCT[34], 1 nonrandomized study[35], and 15 observational studies[36-50] on treatments for varicoceles (KQ3); 3 RCTs,[51-53] 1 non-randomized study[54] and 8 observational studies[55-60] on interventions to improve fertility outcomes (KQ4); and 4 observational studies[60-63] on sperm retrieval methods (KQ5).

We also identified 14 ongoing or recently completed trials on ClinicalTrials.gov, including 1 study on a sex chromosome variants[64] (KQ1); 2 studies[65,66] on the accuracy of tests for predicting fertility and identifying underlying conditions (KQ2); 1 study[67] on varicocelectomy (KQ3); and 10 studies on treatments for improving fertility.[68-77]

We project there may be 169 relevant studies across all key questions. See Table 2, Feasibility column for the citations that were determined to address the key questions.

Table 2. Key questions with the identified corresponding evidence reviews and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews, 12/2011-12/2016)	Feasibility (Published and Ongoing Research, 12/2011-12/2016; Yield= 721)
KQ 1: What are the general health implications for conditions associated with male infertility, including: a) Genetic syndromes b) Varicoceles c) CAVD d) Testicular dysgenesis e) Abnormal Semen analysis alone	None identified.	Size/scope of review Total number of studies: 4 a) Genetic syndromes: 2 prospective cohort[20,21] b) Varioceles: 0 c) CAVD: 0 d) Testicular dysgenesis: 0 e) Abnormal semen analysis alone: 1 prospective cohort[22], 1 retrospective cohort[23] Projected number of studies: 14 ClinicalTrials.gov a) Genetic syndromes: 1 recruiting[64] b) Varioceles: 0 c) CAVD: 0 d) Testicular dysgenesis: 0 e) Semen analysis alone: 0
KQ 2. What is the accuracy of tests to identify underlying conditions associated with male infertility and predict fertility outcomes (both spontaneous and through ART), including: a) Semen analysis b) Chromosomal testing (among azoospermic/oligospermic males) c) Measures of FSH, LH, testosterone (for detecting primary testicular failure versus obstruction) d) Prolactin/pituitary MRI (detecting pituitary pathologies) e) DNA fragmentation index f) Other specialized testing (eg, sperm penetration assay and antisperm antibody testing)	Total number of completed in-process systematic reviews: • Other (In process)- 1[3]	Size/scope of review Total number of studies: 10 a) Semen analysis: 1 prospective non-randomized study[24], 1 case series[25] b) Chromosomal testing: 1 retrospective cohort,[26] 1 case-control[27], 1 case-series[28] c) Measures of FSH, LH, testosterone: 0 d) Prolactin/pituitary MRI: 0 e) DNA fragmentation index: 1 prospective cohort[30], 1 prospective case-control[31], 1 case-series,[28] 2 cross-sectional[32,33] f) Other specialized testing: 0 Projected number of studies: 36 ClinicalTrials.gov a) Semen analysis: 1 recruiting[65] b) Chromosomal testing: 1 active but not recruiting[66] c) Measures of FSH, LH, testosterone: 0 d) Prolactin/pituitary MRI: 0 e) DNA fragmentation index: 0

Key Question	Duplication (Completed or In-Process Evidence Reviews, 12/2011-12/2016)	Feasibility (Published and Ongoing Research, 12/2011-12/2016; Yield= 721)
		f) Other specialized testing: 0
KQ 3. What is the effectiveness of treatments for varicoceles (grade 0-3) in improving fertility outcomes? a.Varicocelectomy, including: i. Laparoscopic ii. Inguinal iii. Subinguinal iv. Macro/microscopic v. Retroperitoneal b. Embolization	Total number of completed in-process systematic reviews: • Cochrane- 1[4] • Other- 2[5,6] • AHRQ (in process): 1[7]	Size/scope of review Total number of studies: 17 a) Varicocelectomy: 1 RCT[34], 1 nonrandomized study[35], 3 prospective cohort[36-38,50] 2 case-series,[39,40] 8 retrospective cohort[42-48], 1 retrospective case-control[49] b) Embolization: 1 retrospective cohort[41] Projected number of studies: 61 ClinicalTrials.gov a) Varicocelectomy: 1 recruiting[67] b) Embolization: 0
KQ 4. What is the effectiveness of medical interventions in improving fertility outcomes? a. SERMs b. Aromatase inhibitors (including but not limited to anastrozole & letrozole) c. Multivitamins and nutritional supplements d. LH analogues e. FSH analogues	Total number of completed in-progress systematic reviews: • Cochrane: 2[8,9] • Other: 2[10,11] • Other (In process): 1[12] • AHRQ (in process): 1[7]	Size/scope of review Total number of studies: 12 a) SERMS: 0 b) Aromatase inhibitors: 1 non-randomized studies[54] c) Multivitamins and nutritional supplements:, 3 RCTs[51-53], 1 randomized trial[56], and 1 pre-post [57] d) LH analogues: 0 e) FSH analogues: 2 prospective cohort[58,59], 1 retrospective cohort[60], 1 case series[55] Projected number of studies: 43 ClinicalTrials.gov a) SERMS: 1 recruiting[68] b) Aromatase inhibitors: 1 recruiting[69] c) Multivitamins and nutritional supplements: 2 completed[70,71], 3 recruiting[72-74], 1 active but not recruiting[75] d) LH analogues: 0 e) FSH analogues: 2 recruiting[76,77]
KQ 5. Among men with azoospermia, what is the comparative effectiveness of sperm retrieval methods on pregnancy success rates?	Total number of completed in-progress systematic reviews: • AHRQ (in process): 1[7] • Other: 1[13]	Size/scope of review Total number of studies: 4 a) MESA: 0 b) PESA: 0 c) TSE/TESE: 1 retrospective cohort[61], 1 case-series[62]

Key Question	Duplication (Completed or In-Process Evidence Reviews, 12/2011-12/2016)	Feasibility (Published and Ongoing Research, 12/2011-12/2016; Yield= 721)
a. Microsurgical epididymal sperm aspiration (MESA) b. Percutaneous epididymal sperm aspiration (PESA) c. Testicular sperm extraction (TSE or TESE) d. Micro TSE e. Percutaneous testicular sperm aspiration (TESA)		d) Micro TSE: 2 retrospective cohort[60,63] e) TESA: 0 Projected number of studies:14 ClinicalTrials.gov None identified.

Abbreviations: CAVD= Congenital Absence of the Vas Difference; FSH= Follicle-stimulating hormone; LH= luteinizing hormone; SERMS= Selective estrogen receptor modulators; MRI= Magnetic Resonance Imaging; TSE= Testicular sperm extraction

Value

The potential for value for a new AHRQ review is high given that AUA will use an AHRQ systematic review to create new guidelines on male infertility. This organization has previously produced high-quality evidence-based guidelines, and is transparent about its methodology.

Summary of Findings

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication: A new AHRQ review would not be duplicative of an existing product.
  - We identified 10 completed or in process systematic reviews pertinent to KQ 2-5. None of these reviews covered the full scope of the nomination. Reviews of note include a 2012 Cochrane review on surgery or embolization for varicoceles in subfertile men, a 2013 Cochrane review on gonadotropins for idiopathic male subfertility, and a 2014 Cochrane review on antioxidant vitamins and minerals for male subfertility. In addition, we identified an in-process AHRQ systematic review on the management of infertility; however, this did not provide sufficient detail on populations or outcomes for the AUA to develop guidelines.
  - We did not identify any reviews pertinent to KQ1.
- Feasibility: A new AHRQ review is feasible.
  - *Size/scope of review:* We identified 47 potentially relevant studies, including 4 studies on general health implications of conditions associated with male infertility (KQ1), 10 studies on the accuracy of diagnostic and fertility prediction tests (KQ2), 17 studies on treatments for varicoceles (KQ3), 12 studies on interventions to improve fertility outcomes (KQ4), and 4 studies on sperm retrieval methods (KQ5) from our random sample of 200 studies.
  - *Clinicaltrials.gov:* We identified 14 ongoing or recently completed trials on ClinicalTrials.gov. The majority of these trials examined medical treatments for infertility (KQ4).
- Impact: A new AHRQ review may have moderate impact. The AUA last published best practice statements on the evaluation of the infertile male, evaluation of the azoospermic male, and management of azoospermia in 2011. The European Association of Urology last published guidelines on male infertility in 2012, although they provided a full-text update in 2015. A 2016 systematic review found inconsistencies between the recommendations of different urological groups on the evaluation of the infertile male, suggesting a need for a comprehensive evidence review by a separate organization.
- Value: The nomination has a high value potential, given that AUA will use an AHRQ systematic review to create new guidelines on male infertility. This organization has previously produced high-quality evidence-based guidelines, and is transparent about its methodology.

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Appendices

Appendix A: Selection Criteria Summary *

Appendix B: Search Strategy & Results (Feasibility)

Appendix A. Selection Criteria Summary (

1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents health care drugs and interventions available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on both effectiveness and comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. Approximately 15% of all couples are unable to conceive after 1 year of unprotected intercourse, and 20% of these cases can be attributed to male-only infertility.[1]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects heath care decisions for a large population.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of treatment of male infertility.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, the use of reproductive technology (ART) for conception is expensive. In 1994, the cost of a successful live birth after one cycle of in vitro fertilization (IVF) was $66,667, and increased after each failed cycle.[2] Testing for and treating male infertility is one way to identify underlying causes of infertility, and can help predict the likelihood of a successful spontaneous pregnancy or pregnancy from ART.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new AHRQ review would not be duplicative. We identified 10 completed or in process systematic reviews[3-13] pertinent to KQ 2-5, but none pertinent to KQ1. No review covered the full scope of the nomination.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the standard of care is unclear due to inconsistent guidance on the assessment and treatment of male infertility. The AUA last published best practice statements on this topic in 2011.[14-16] The European Association of Urology last published guidelines on male infertility in 2012[17] and a full-text update in 2015.[18] A 2016 systematic review of guidelines[19] found inconsistencies between the methods and conclusions of guidelines on

	the evaluation of the infertile male, suggesting there is a need for a comprehensive examination of the evidence by a separate organization.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation due to conflicting guidance.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	A new AHRQ review is feasible. Size/scope of the review: Out of the 200 random articles, we identified 47 studies potentially relevant to the key questions in the nomination. Based on an inclusion percentage of 23%, we project there may be 169 relevant studies across all key questions. From our sample, we identified 4 observational studies[20-23] pertinent to KQ1; 10 observational studies[24-33] pertinent to KQ2; 1 RCT[34], 1 nonrandomized study[35], and 15 observational studies[36-50] pertinent to KQ 3; 3 RCTs,[51-53] 1 non-randomized study[54] and 8 observational studies[55-60] pertinent to KQ 4; and 4 observational studies[60-63] pertinent to KQ 5. Clinicaltrials.gov: We identified 14 ongoing or recently completed trials on ClinicalTrials.gov. The majority of these trials examined medical treatments for infertility (KQ4).
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this topic exists within a clinical, consumer, and policy-making context that is amenable to evidence-based change.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, the AUA will use a new systematic review to create guidelines on male infertility.

Appendix B. Search Strategy & Results (Feasibility)

Topic: Male Infertility Date: December 19, 2016 Database Searched: MEDLINE (PubMed)	
Concept	Search String
Male Infertility	("Infertility, Male"[Majr]) OR ((infertility[Title]) AND male[Title])
OR	
Varicoceles CAVD (Congenital Absence of the Vas Deferens) Testicular dysgenesis	((((("Varicocele"[Majr]) OR "Congenital bilateral aplasia of vas deferens" [Supplementary Concept]) OR "Ovotesticular Disorders of Sex Development"[Mesh])) OR ((varicoceles[Title] OR CAVD[Title] OR "congenital absence"[Title] OR "testicular dysgenesis"[Title]))
AND	
Health Implications, Diagnosis and Therapy	((("Outcome Assessment (Health Care)"[Mesh]) OR "Prognosis"[Mesh]) OR "diagnosis" [Subheading]) OR "therapy" [Subheading]
NOT	
Not Editorials, etc.	((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
Limit to last 5 years ; human ; English ; male ; adult	Filters activated: published in the last 5 years, Humans, English, Adult: 19+ years
N=721	
Systematic Review N=7	PubMed subsection “Systematic [sb]”
Randomized Controlled Trials N=259	Cochrane Sensitive Search Strategy for RCT’s “(((((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])”
Other N=255	

Clinicaltrials.gov
33 studies found for: **Recruiting** | male infertility | Studies with Male Participants | Adult | Studies received from 12/19/2011 to 12/19/2016
https://clinicaltrials.gov/ct2/results?term=&type=&rslt=&recr=Recruiting&age_v=&age=1&gndr=Male&cond=male+infertility&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F19%2F2011&rcv_e=12%2F19%2F2016&lup_s=&lup_e=

15 studies found for: **Active, not recruiting** | male infertility | Studies with Male Participants | Adult | Studies received from 12/19/2011 to 12/19/2016
https://clinicaltrials.gov/ct2/results?term=&type=&rslt=&recr=Active%2C+not+recruiting&age_v=&age=1&gndr=Male&cond=male+infertility&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F19%2F2011&rcv_e=12%2F19%2F2016&lup_s=&lup_e=

43 studies found for: **Completed** | male infertility | Studies with Male Participants | Adult | Studies received from 12/19/2011 to 12/19/2016
https://clinicaltrials.gov/ct2/results?term=&type=&rslt=&recr=Completed&age_v=&age=1&gndr=Male&cond=male+infertility&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F19%2F2011&rcv_e=12%2F19%2F2016&lup_s=&lup_e=