

Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Evaluation and Treatment of Cryptorchidism*

Draft review available for public comment from April 24, 2012 to May 22, 2012.

Research Review Citation: Penson DF, Krishnaswami S, Jules A, Seroogy JC, McPheeters ML. Evaluation and Treatment of Cryptorchidism. Comparative Effectiveness Review No. 88. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 13-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2012.
www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Executive Summary	Page 22, Line 50: yes, to all of these questions. I would note that in this review that authors have elected to largely omit the topics of long-term fertility and malignancy outcomes. In the "research gaps" section, the authors have commented that "studies of long-term outcomes of treatment, both fertility and cancer, are notably missing from this literature." I would argue that there is some literature regarding both of these topics (examples with respect to the cancer outcome include Pettersson et al N Engl J Med 2007;356:1835-41, and the nice review by Wood and Elder, J Urol 181:452-461, February 2009). Since the topic of cryptorchidism is a very broad one, I think it reasonable that the authors have focused in this review on the short-term goals of getting the cryptorchid testis into the scrotum. In this context, the longer term outcomes associated with cryptorchidism are reasonably omitted from the review. However, some information on these outcomes is available, and I would suggest that authors indicate that such topics would be amenable to further systematic review.	We sought studies that reported on fertility and cancer outcomes, but found few that met inclusion criteria for this review. In part this is because the review is a comparative effectiveness review, examining specifically the effectiveness of interventions. Many of the longer term studies are epidemiologic in nature and do not present data in such a way that it can be used to assess effectiveness. Epidemiologic studies and review articles were not included in our analysis per our a priori inclusion criteria. It certainly may be possible for a systematic review to be conducted on the epidemiologic literature by another group in the future, but such a review would be outside the scope of a comparative effectiveness review.
Peer Reviewer #5	Executive Summary	Page 11, Line 11: Background: 1. Regarding surgical options, the authors mention orchiopexy, Fowler – Stevens one and two stage approaches, yet fail to mention the possibility of orchiectomy when an atrophic testicle (nubbin) is noted. In essence 4 surgical options exist.	The reviewer is correct in that orchiectomy is a fourth option, but the focus of this review was on procedures to maintain testicular tissue, assuming there is viable tissue.
Peer Reviewer #5	Executive Summary	Key Question 1a: utility of imaging 1. I am disappointed that the authors did not include at least one to two statements regarding cost for examination, especially regarding MRA or MRV with little alterations to the need for surgery despite noting the location of the testicle. Extremely expensive test for a short slide, no cost benefit.	Without collecting specific data on costs systematically, we do not feel that it is appropriate to include this information.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Executive Summary	<p>Key Question 2: Effectiveness of Hormonal Therapy</p> <p>1. Disappointed to note the authors did not review long term observations for testicular descent following hormonal studies, most papers looking at long term response will find approximately 25% of testes ascend with follow-up. I believe failure to mention or discuss this fact is detrimental for the ability to assess the effectiveness of hormonal therapy. <i>Pediatric Surg Internationa</i> 21:240-254, 2005</p>	<p>The reference the reviewer is referring is a review article. It refers to a meta-analysis published in the <i>Journal of Clinical Endocrinology and Metabolism</i> in 1995 by Pyorala, et al, which noted that 24% relapse rate with longer-term follow-up. Because this study was a meta-analysis it would not have been included in our literature review. Furthermore, the authors of the 2005 review article note that the meta-analysis was limited by the "inclusion of studies with heterogenous drug treatment protocols and suboptimal methodologies". Because our literature review did not confirm these outcomes, we have not changed the text.</p>
Peer Reviewer #5	Executive Summary	<p>Key Question 5: Harm of work-up or treatment</p> <p>1. There is no mention regarding controversy of acute and long term complications following hormonal therapy,. Specifically regarding acute inflammatory changes, i.e., increased germ cell apoptosis, the reduction in the number of germ cells and long term testicular atrophy in adult hood with the most apparent harm occurring in children treated with hormones between 1-3 years of age. Failure to at least address this controversy is a deterrent to the synopsis. <i>J Ped Surg</i> 28: 254-8, 1993, <i>J Clinical Invest</i> 100: 2341-2346, <i>J of Urol</i> 163: 1290-92,2000</p>	<p>The reviewer raises reasonable comments about pathologic findings in testicles previously treated with hormonal therapy. The report is focused on patient-centered outcomes, however.</p>
Peer Reviewer #6	Executive Summary	<p>Page 6, Line 33-38: Does imaging provide important information to guide surgical approach? This statement may be overreaching based on the data that are provided. It's accurate for inguinal testes, but these are usually testes that we can palpate so we know what surgical approach we are going to use anyway. For nonpalpable testes the gold standard is abdominal exploration. Ultrasound is not accurate for intra-abdominal testes that we can't palpate therefore surgical exploration is still necessary. Therefore, I don't think the data support that imaging is an important guide to surgical approach.</p>	<p>We agree with the reviewer. In fact, we conclude that "No specific imaging technique is able to completely identify anorchia or descent of the testicles and thus eliminate the need for further surgical evaluation. Accuracy varies by location of the testicles, with less invasive methods demonstrating poor accuracy for abdominally located testicles and those that are atrophied. " We have changed the text in the abstract accordingly</p>

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Peer Reviewer #6	Executive Summary	Page 10, Line 30: In the third paragraph, it is stated that 70% descend in the first year of life—it is actually in the first 3-4 months.	While there are some studies that support the reviewer's comment, there are also a number of studies suggesting indicate that the proportion that descend in the first 3 months of life is lower. Similarly, a number only report outcomes at one year. Of note, we did not systematically review the literature on spontaneous descent as it was not the focus of the review. Therefore, we feel it is most accurate to conservatively report one year spontaneous descent rates; we do, however, modify our statement to indicate that most descend in the first 3 months.
Peer Reviewer #6	Executive Summary	Page 10, Line 39: With regard to hormonal therapy, this treatment is not being used clinically at present. There are no approved hormonal treatments for UDT, either to stimulate testicular descent or to improve testicular histology in an UDT.	We understand that this treatment may not be widely in use, but believe that it is being used in some circumstances. The amount of literature on the subject suggests that it should be addressed for providers who may be considering its use.
Peer Reviewer #6	Executive Summary	Page 10, Line 21-22 : The manner in which this paragraph is set up is misleading b/c caregivers of children should be intentionally examining boys for this condition at each well-child check. It should not be something that is incidentally found. The way it is phrased as "tend to present" sends the wrong message.	We have changed the sentence to read: "Cryptorchidism is often apparent to parents and examination for the conditions is part of general pediatric care. Therefore, boys with cryptorchidism are usually identified early in life, often within the first year. "
Peer Reviewer #6	Executive Summary	Page 10, Line 29-30: This also is subtly conveying a message that we don't want to give primary care providers. If we are trying to follow AAP recommendations that orchidopexy should occur around 1 year of age these patients need to get into the pediatric urologist/surgeon's office prior to 1 year of age. We know that the data show it is very rare for spontaneous testicular decent after 9 months.	We have deleted the sentence that began "In this case"
Peer Reviewer #6	Executive Summary	Page 10, Line 35-36 : a more specific statement surrounding watchful waiting should be placed here. Watchful waiting is only appropriate during a certain time interval-during the first 9 months of life, certainly not after a 1 year of age.	We have changed the sentence to read "watchful waiting in the short term"
Peer Reviewer #6	Executive Summary	Page 10, Line 40-41: With regard to the hCG stimulation test in boys with bilateral nonpalpable testes, it is also important that the serum FSH and LH be significantly elevated; there are reports dating back to the 1980s showing that dysgenetic testes may not respond to hCG stimulation with an increase in testosterone, yet the serum FSH or LH may be in the normal range. In fact, a high FSH has been shown to be highly accurate in the diagnosis of anorchia.	We appreciate this comment and have changed the text accordingly.
Peer Reviewer #6	Executive Summary	Page 10, Line 40-41: Finally, the use of serum mullerian inhibiting factor should be mentioned.	Serum mullerian inhibiting factor was not included in this review.

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Peer Reviewer #6	Executive Summary	Page 10, Line 50-51: Given that studies have shown variable reliability with imaging this statement would be better if it was phrased with less certitude. For example, "Imaging also is used in attempt to determine..."	We agree and have changed the sentence as suggested.
Peer Reviewer #6	Executive Summary	Page 11, Line 28: In the last paragraph of Background, there is not much uncertainty regarding the clinical pathway—a surgical procedure is necessary if the child has an UDT. Pediatric urologists do not think that imaging (US) is indicated, because in most circumstances the result will not change the need for a surgical procedure. In many of the studies mentioned in the report, when the testis was identified by US in the inguinal canal, the urologist was able to palpate the testis, even though it was nonpalpable by the primary care physician. If it is nonpalpable by the urologist, there is a 33% chance that the testis is in the abdomen or high in the inguinal canal, in which case US is unlikely to accurately identify the testis and a 67% chance that the testis is atrophic and in the scrotum or distal inguinal canal, in which case US would not show any testis. The primary exception to the recommendation against US is in the obese patient, in whom an inguinal UDT is difficult to palpate. There is no general agreement regarding the optimal approach for an abdominal UDT, as acknowledged by this report.	We appreciate your perspective on current clinical practice and remind the reviewer that the key questions were developed with the assistance of content experts and public review.
Peer Reviewer #6	Executive Summary	Page 11, Line 53-57: Under Key Questions, Question 1a is reasonable, assuming that surgical exploration (with or without laparoscopy) is recognized as being necessary in virtually all cases. Irrespective of the result of the US, surgical exploration is necessary. MRA has been shown in a handful of patients to be highly accurate, but this study requires anesthesia also, and if it demonstrates a testis to be present, then another general anesthesia is necessary to perform the operation. Recent studies have suggested that having two general anesthetics in the first two years of life may adversely affect cognitive function later on in childhood. KQ1b is reasonable.	Thank you
Peer Reviewer #6	Executive Summary	Page 12, Line 3-11: KQ2 is reasonable, but should be used to demonstrate that it is not indicated at the present time.	The EPC does not make recommendations; rather we report the state of the evidence.
Peer Reviewer #6	Executive Summary	Page 12, Line 12-19: KQ3 The inguinal orchiopexy (which the AHRQ calls primary orchiopexy) is pretty standard. It would be appropriate to evaluate the prescrotal orchiopexy (through a scrotal incision) also. In addition, the success rate of various surgical approaches to the abdominal testis also are important to assess.	We did not exclude prescrotal orchiopexy but found no comparative studies on this.
Peer Reviewer #6	Executive Summary	Page 12, Line 20-23: KQ4 Appropriate—It is important to determine when undescended testes become abnormal histologically (based on biopsy data).	Thank you
Peer Reviewer #6	Executive Summary	Page 12, Line 24-25: KQ5 Good question to analyze.	Thank you

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Peer Reviewer #6	Executive Summary	Page 16, Line 28-29: Under Results, Key Question 3 (page ES-7), Fowler-Stevens should be Fowler-Stephens.	This has been corrected.
Peer Reviewer #6	Executive Summary	Page 18, Line 56-57: Key Question 4 (page ES-10)—the effect of hormonal therapy should not be included; it is not part of clinical practice.	See response above.
Peer Reviewer #6	Executive Summary	Page 22, Line 14-57: Page ES-13: Under Research Gaps, a major one is the lack of appropriate screening of boys for an undescended testis by primary care physicians, as well as their indications for surgical referral. In addition, the appropriate timing or orchiopexy is not addressed. There is an ongoing prospective clinical trial regarding timing of orchiopexy: Kollin C, Karpe B, Hesser U, Granholm T, Ritzén EM. Surgical treatment of unilaterally undescended testes: testicular growth after randomization to orchiopexy at age 9 months or 3 years. J Urol. 2007 178:1589- 1593; 2007.	This is a good point, but somewhat outside the scope of our review. Research gaps are intended to capture gaps within the context of our key questions. We note the study on timing of treatment and hope that further data from this study will provide useful information to extend our work.
Peer Reviewer #6	Executive Summary	Page 22, Line 14-57: Also, the likelihood of spontaneous testicular descent in boys born with an undescended testis should be addressed. Furthermore, the difference between congenital and ascending testes should be acknowledged, and analyzed.	While we can mention these differences in the introduction, it is outside of the scope of the review to analyze data on rates of spontaneous descent.
Peer Reviewer #6	Executive Summary	Page 22, Line 14-57: Finally, the long-term fertility following orchiopexy is an important point that should be addressed, with outcomes based on age at orchiopexy and unilateral vs. bilateral orchiopexy.	We agree and note this in the future research section
Peer Reviewer #6	Executive Summary	This document is comprehensive, but misses some of the basic concepts regarding undescended testes (UDT). First, the Executive Summary seems misdirected. The Summary should state the significance of cryptorchidism, namely, that the maturation from a germ cell to a mature sperm in an undescended testis does not occur. In addition, although cryptorchidism is considered a congenital condition, many boys are diagnosed later in childhood; many of them had a retractile testis that became an “ascending” undescended testis. The summary simply focuses on imaging, hormonal therapy, and comparison of surgical therapy for abdominal testes.	We have revised the introduction somewhat, but are cognizant that this comparative effectiveness review is a review of intervention studies and is not intended to provide a complete overview of cryptorchidism itself.
Peer Reviewer #1	Introduction	The introduction is reasonably clear and straightforward.	No response
Peer Reviewer #2	Introduction	acceptable	No response
Peer Reviewer #3	Introduction	Page 29, Line 20: I do have a few comments: (Page 1, 1st paragraph 'severe' is misspelled.)	We have made this correction

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Peer Reviewer #3	Introduction	Page 29, Line 24-25: 1. Paragraph 2 states that 'cryptorchidism is often apparent to parents and is easy to detect on routine physical examination'. Also, under 'treatment strategies' it is referred to as "usually fairly obvious to parents and providers when the testicle is not found in the normal position.' I would disagree with this statement. While the condition can be apparent in many cases, simple visual inspection of the scrotum can be misleading. Furthermore the examination of young boys can be challenging and the distinction between retractile and truly undescended testes can be difficult. Perhaps simply tempering the comment would be sufficient.	We have changed the sentence to read: Cryptorchidism may be apparent to parents, and examination for the condition is commonly a part of general pediatric care.
Peer Reviewer #3	Introduction	Page 29, Line 34-35: Paragraph 3 states that '70% of testicles spontaneously descend within the first year of life.' I think it is important to note that the vast majority of those testes that will be descended at one year, do so within the first three months.	We have added the phrase, "most occurring in the first three months."
Peer Reviewer #3	Introduction	Page 29, Line 37-38: Paragraph 3 states that there were >600,000 office visits for cryptorchidism. This is from a single sample not an actual annual total estimate. The sample rate per 100,000 is accurate and the 600,000 figure should be listed as the sample size from which the rate estimate is derived.	Corrected.
Peer Reviewer #3	Introduction	Page 29, Line 43-44: Paragraph 3 also states 'costs of infant ...orchiopexy'. This should be referred to as 'charges' rather than costs since the actual resource use as well as the actual reimbursement can be considerably different.	Corrected.
Peer Reviewer #3	Introduction	Page 29, Line 54: Paragraph 4 states that the risk of malignancy is '40 times greater that the general population.' While this number is commonly quoted in text books it appears to have been the result of one biased sample. Please see: Journal of Urology, Vol. 181, 452-461, February 2009 for more details (reference #11).	We have changed the text to reflect the reviewer's comment and more recent estimates of the risk of malignancy.
Peer Reviewer #3	Introduction	The introduction is well written and concise.	Thank you.
Peer Reviewer #3	Introduction	This report does not deal with ascending testes (secondary or acquired undescended testes). While it is difficult to separate such cases in most literature reports on cryptorchidism/orchiopexy, recent data suggests that acquired undescended testes account for many orchiopexies being performed today. See Hack et al. International Journal of Andrology, 2012, 35, 41–45 for details.	The reviewer is correct that the report does not address treatment of ascending testes.
Peer Reviewer #4	Introduction	Excellent - easy to read	No response
Peer Reviewer #5	Introduction	Page 31, Line 55-56: Key Question 1a: utility of imaging 1. I am disappointed that the authors did not include at least one to two statements regarding cost for examination, especially regarding MRA or MRV with little alterations to the need for surgery despite noting the location of the testicle. Extremely expensive test for a short slide, no cost benefit.	Because we did not collect this information systematically and it was not part of our research questions, we did not feel that it was appropriate to include it.

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Peer Reviewer #5	Introduction	Page 32, Line 3-11: Key Question 2: Effectiveness of Hormonal Therapy 1. Disappointed to note the authors did not review long term observations for testicular descent following hormonal studies, most papers looking at long term response will find approximately 25% of testes ascend with follow-up. I believe failure to mention or discuss this fact is detrimental for the ability to assess the effectiveness of hormonal therapy. <i>Pediatric Surg Internationa</i> 21:240-254, 2005	The reference the reviewer is referring to is a review article. It refers to a meta-analysis published in the <i>Journal of Clinical Endocrinology and Metabolism</i> in 1995 by Pyorala, et al, which noted that 24% relapse rate with longer-term follow-up. We have confirmed that all of the studies included in that review were identified in our search, but not all of them met our inclusion criteria. Furthermore, the authors of the 2005 review article note that the meta-analysis was limited by the "inclusion of studies with heterogenous drug treatment protocols and suboptimal methodologies".
Peer Reviewer #5	Introduction	Page 32, Line 24-5: Key Question 5: Harm of work-up or treatment 1. There is no mention regarding controversy of acute and long term complications following hormonal therapy,. Specifically regarding acute inflammatory changes, i.e., increased germ cell apoptosis, the reduction in the number of germ cells and long term testicular atrophy in adult hood with the most apparent harm occurring in children treated with hormones between 1-3 years of age. Failure to at least address this controversy is a deterrent to the synopsis. <i>J Ped Surg</i> 28: 254-8, 1993, <i>J Clinical Invest</i> 100: 2341-2346, <i>J of Urol</i> 163: 1290-92,2000	The reviewer raises reasonable comments about pathologic findings in testicles previously treated with hormonal therapy. The report is focused on patient-centered outcomes, however.
Peer Reviewer #5	Introduction	Page 30-31: Background: 1. Regarding surgical options, the authors mention orchiopexy, fowler – Stevens one and two stage approaches, yet fail to mention the possibility of orchiectomy when an atrophic testicle (nubbin) is note. In essence 4 surgical options exist.	The reviewer is correct in that orchiectomy is a fourth option, but the focus of this review was on procedures to maintain testicular tissue, assuming there is viable tissue. Therefore, studies of orchiectomy are not reviewed.
Peer Reviewer #6	Introduction	Page 29, Line 54: Page 1--next to last line, the reference that the relative risk of testicular cancer being 40x higher is old--see reference 11 in the report (Wood and Elder)	We have revised this statement per the Wood reference and appreciate the reviewer's correction. Indeed, this estimate is likely to be inflated.

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Peer Reviewer #6	Introduction	The AHRQ report is a comprehensive review of the available literature regarding cryptorchidism that aims to address five key questions. In terms of the ability to perform this aim, it seems fairly sufficient in this regard. However, several areas of concern exist from both a literature review perspective as well as relevance to contemporary clinical practice. One area the report fails to address is retractile testis. There is literature in regards to this condition and it should be included. It does not represent cryptorchidism but often is misdiagnosed for this condition. If you look at large population data, the rate of orchidopexy is 3X the incidence. This likely means that children with retractile testis are undergoing surgical intervention. A Key question should address: diagnosis, evaluation and surgical intervention for this condition.	We appreciate this comment but note that diagnosis of cryptorchidism was outside the scope of this particular review.
Peer Reviewer #7	Introduction	Page 19, Line 19: "Dye" should be changed to contrast.	Corrected.
Peer Reviewer #7	Introduction	Page 29, Line 21: "Intersex" should be replaced with DSD	Replaced the term "intersex" with the term "disorders of sexual development" anywhere it appears in the text.
Peer Reviewer #7	Introduction	Page 29, Line 34: pg 1- "about 70% of cryptorchid testes descend in first year of life"- incorrect statement- old data	We have corrected this statement to be more accurate and reflect that most descents occur in the first 3 months of life.
Peer Reviewer #7	Introduction	Page 29, Line 54: "relative risk of testis CA after UDT is 40X gen population"- incorrect statement	We have corrected this statement and have added the Wood reference, which identifies the degree to which that estimate is likely to exaggerate the risk.
Peer Reviewer #1	Methods	These are well described.	Thank you
Peer Reviewer #2	Methods	search appears to be have been performed appropriately and is well-described.	Thank you
Peer Reviewer #3	Methods	Page 38, Line 37: It appears that focusing the scope of the review on pre-pubertal diagnosis and management may have had something to do with the relative lack of information/discussion regarding malignancy with cryptorchidism. There appears to be data to support the notion that early treatment (pre-pubertal) affects the risk of malignancy. (see excluded reference#580: pettersson et al. N Engl J Med: 2007, 356(18):1835-41). I think a more complete discussion of malignancy risks should be included and would fit under KQ 4, even if the pre-pubertal risk is simply related to cryptorchidism diagnosis and is not modified by prepubertal treatment. For completeness sake a discussion of the higher risk in cryptorchid males who reach puberty should be added to the report.	This report is based on a comparative effectiveness review, which, by design, focuses on the effectiveness of treatment in pre-pubertal males. It is beyond the scope of the review to include a synthesis of epidemiologic data beyond what is in the introduction, including the effectiveness of orchiopexy in post-pubertal males. We appreciate the reviewer's comment but have not altered the text for the reason above.

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Peer Reviewer #4	Methods	My main concerns are KQ 1 is that it encourages imaging for cryptorchidism, when current practice by pediatric urologists generally avoids imaging in this setting. In following the usual guidelines of ordering a diagnostic study only if it assists in clinical decision-making, the ability to localize the testicle pre-operatively by imaging does not meet this criteria, since it does not change the need for management, since this patient will still need to undergo surgical intervention. Furthermore, a MRA / MRV in the infant population most likely will require sedation or anesthesia, which has the potential for significant risks as well.	We do not agree that asking the question encourages use. Indeed, our conclusion is as follows: "No specific imaging technique is able to completely identify anorchia or descent of the testicles and thus eliminate the need for further surgical evaluation. Imaging provides important does not appear to reliably add additional information to guide surgical approach, but results are mixed, with studies not pointing to a specific approach with adequate accuracy at identifying atrophied testicles . Accuracy of imaging is strongly related to location of the testicles, with less invasive methods demonstrating poor accuracy for abdominally located testicles and those that are atrophied."
Peer Reviewer #6	Methods	well presented and clear	Thank you
Peer Reviewer #7	Methods	Inclusion/exclusion criteria are justified, though it seems some important studies may have been removed in KQ2- hormones. Appears that descent was mainly studied and fertility addressed only if evaluated in that study. Many hormonal histology/fertility studies did not address descent success. Search is logical. Statistics appropriate.	Thank you
Peer Reviewer #1	Results	The results section is well described, although as mentioned in the introductory comment, the results need to be considered, taking the limitations of this retrospective review into account.	Thank you.
Peer Reviewer #2	Results	Page 70, Line 26-27: results section is quite detailed and well done with the following exception: In Table 21, results of two stage fowler stephens orchidopexy, the final reference listed is Stec 2009 with a success rate listed of 89.1%. This is incorrect. Review of the Stec paper shows that they reported a success rate of 67.6% for two stage FSO. The 89.1% figure is the success rate for single-stage primary orchidopexy (NOT FSO), and the authors of the AHRQ review have correctly listed this figure in Table 19. This figure is incorrect in Table 21, however. It is unclear if the 89.1% figure listed in table 21 is just a typo, or if this incorrect value was actually incorporated into the summary statistics for success rate after two stage FSO – the authors may wish to check this. Since the Stec study was one of only 6 included studies that provided success rates after two stage FSO, the difference between 89.1% and 67.6% is substantial and, if incorporated mistakenly into the summary statistics, could clearly impact the final result.	We appreciate the reviewer's sharp eye for detail. We inadvertently transposed the wrong data to this table (and another). We have corrected this error and included the correct data in the tables.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Page 57, Line 18: The only major omissions seem to be related to fertility and malignancy. There is a wealth of information regarding seemingly progressive histologic degradation and differences in semen parameters the longer the testes remain undescended. While these surrogate outcomes may not correlate well with the most important (and patient centered) outcome of paternity rates for those desiring offspring, they should still be discussed more completely. This would strengthen the suggestions for further research to better understand associations.	We agree with the reviewer that there data have been published on histologic outcomes and differences in semen analysis in cryptorchidism. However, as the reviewer also points out, these proxy outcomes do not always correlate well with the important and patient-centered outcome of fertility. To this end, we limited our search criteria at the onset to these important patient-centered outcome. As such, our presentation of results must be limited to those results presented in the studies that meet criteria for inclusion.
Peer Reviewer #4	Results	The results are all-inclusive of the current literature. The key messages are explicit and applicable.	Thank you.
Peer Reviewer #4	Results	My comment about KQ3 and potential fertility issues is that this area of research is limited by 1) the long lag time between surgery (orchiopexy) as an infant and actual time of fertility when one is procreating, and 2) difficulty with obtaining semen specimens in the adolescent age group if one is attempting to analyze these to measure future fertility potential. The same challenges are faced in the area of adolescent varicocele research	We agree that the necessity for long term follow up makes this research challenging and have incorporated this note into the future research section.
Peer Reviewer #6	Results	Page 46, Line 3-6: KQ1a. For determining a course of treatment, is imaging equivalent to laparoscopy in determining the presence and location of a non-palpable testicle? Doesn't matter because you will go on to have surgery nonetheless. In the off chance you cannot find the testis, then it may help after the fact.	The key questions were developed with the help of technical experts and with Peer Reviewer #6 input; they cannot be changed at this time.
Peer Reviewer #6	Results	Page 56, Line 11-13: KQ1b. In male children with bilateral, non-palpable testicles, does the use of hormonal stimulation testing reduce the need for surgery as part of a treatment plan? No but it does supplement the surgery and validates the findings....Again no mention of the need to rule out CAH.	Thank you for sharing your perspective.
Peer Reviewer #6	Results	Page 64, Line 27-31: 11. KQ3. What is the comparative effectiveness of surgical therapies (one-stage vs. twostage, laparoscopic vs. open approach, (orchietomy vs. orchiopexy) for the treatment of cryptorchidism for outcomes including but not limited to: a. Left out Prentiss maneuver patients	We report the results as they are available in the studies that meet criteria for inclusion. We did not identify any studies comparing outcomes following the Prentiss technique to other forms of orchiopexy.
Peer Reviewer #6	Results	12. Some pathologists label nubbin and vanishing testis syndrome the same thing.	Thank you
Peer Reviewer #6	Results	13. Fertility- No mention to the age of orchidopexy which is not controlled in respect to semen parameters and paternity rates following the procedure.	We report the results as they are available in the studies that meet criteria for inclusion; unfortunately, studies do not provide adequate data to discuss modifiers, including age.

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Peer Reviewer #6	Results	14. No mention to need for confirmation of anorchia bc of risk of cancer in abdominal is higher	It is standard practice to confirm anorchia in all patients with nonpalpable testes, regardless of the suspected location.
Peer Reviewer #6	Results	15. No mention to timing of orchidopexy should also be done to maximize fertility/paternity potential only that it may facilitate the ability to bring testis to scrotal position.	We report the results as they are available in the studies that meet criteria for inclusion; unfortunately, studies do not provide adequate data to discuss modifiers, including timing.
Peer Reviewer #6	Results	well presented and clear	Thank you
Peer Reviewer #7	Results	Page 64, Line 14: Results: Key Question #2 focuses on success of testis descent from hormones but seems to gloss over fertility effect- "no fertility outcomes" for comparison studies but other studies have explored this.	We report the results of those studies that met our inclusion criteria; unfortunately, comparative effectiveness studies currently lack data on these outcomes.
Peer Reviewer #7	Results	<p>Page 79:Key Question #5 should also comment on wound infection, bleeding, reoperation rate, readmission rate after orchiopexy.</p> <p>Overlooked manuscripts (significant that might address many of the reviews questions on timing of treatment and long-term implications): McAleer and Kaplan- JUrol- biopsy/histology of UDTs and timing recommendation for orchiopexy</p> <p>J. Park et al- spontaneous descent of testis/ timing of orchiopexy.</p> <p>C. Schwentner et al- neoadjuvant hormonal therapy pre-orchiopexy and effect on testis histology</p> <p>A. Pettersson et al- NEJM- risk of testis ca with UDT</p> <p>P. Lee- Fertility/paternity after cryptorchidism</p> <p>multiple studies on testis histology by F. Hadziselimovic</p>	We appreciate the references to the epidemiologic studies available on outcome in cryptorchidism. We have ensured that these references are included in our background and discussion, but note that they do not meet criteria for inclusion in the analysis itself. We recognize that our review, as a narrowly scoped CER, does not provide the full picture that guidelines developers and clinicians will use to make clinical decisions and have ensured that good reviews are noted in our analysis. Specifically, the Park and Petterson papers are noncomparative, the Schwentner paper reports on histological, not patient-centered, outcomes.
Peer Reviewer #1	Discussion-Conclusion	The discussion and conclusions are reasonable, although the effect of the changing age or orchidopexy, and the discovery of acquired undescended testes need to be put more clearly into the conclusions, so that a reader who just reads the executive summary or the conclusions does not miss the key points.	We appreciate the reviewer's comment. Unfortunately, we did not encounter any reports that met our inclusion criteria comparing treatments for acquired undescended testes. Our review of the literature concerning the modifying effect of age at the time of treatment and outcomes revealed conflicting reports, which is mentioned in the results section.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Discussion-Conclusion	Page 90, Line 14-15: yes, to all of these questions. I would note that in this review that authors have elected to largely omit the topics of long-term fertility and malignancy outcomes. In the "research gaps" section, the authors have commented that "studies of long-term outcomes of treatment, both fertility and cancer, are notably missing from this literature." I would argue that there is some literature regarding both of these topics (examples with respect to the cancer outcome include Pettersson et al N Engl J Med 2007;356:1835-41, and the nice review by Wood and Elder, J Urol 181:452-461, February 2009). Since the topic of cryptorchidism is a very broad one, I think it reasonable that the authors have focused in this review on the short-term goals of getting the cryptorchid testis into the scrotum. In this context, the longer term outcomes associated with cryptorchidism are reasonably omitted from the review. However, some information on these outcomes is available, and I would suggest that authors indicate that such topics would be amenable to further systematic review.	We agree that a review outside of the scope of a comparative effectiveness review could potentially synthesize the epidemiologic data on longer term outcomes among individuals with cryptorchidism. Because our review was specifically a comparative effectiveness review of a specified set of interventions, we sought studies that were clearly effectiveness studies, and in this set of studies, longer term outcomes are notably missing. It is certainly true that designing such studies and collecting data over such a long period of time poses substantial challenges, and the reviewer's point that a separate analysis of epidemiologic data might shed light on this question is well taken. We have, nonetheless, added a brief summary of existing epidemiologic studies to the discussion to ensure that readers are aware of this body of literature.
Peer Reviewer #3	Discussion-Conclusion	The included discussion topics are well covered and clear. More detail regarding fertility and malignancy as described above would be useful.	Thank you. See response below.
Peer Reviewer #4	Discussion-Conclusion	The authors have appropriately stated the implications and limitations.	Thank you. See response below.
Peer Reviewer #5	Discussion-Conclusion	As noted above failure to address the cost of diagnostic studies, with little to no benefit regarding alterations of surgical approaches in the days of cost effective patient management is a deterrent to the article and needs to be addressed.	Because we did not systematically collect data on costs, we cannot have confidence in any estimates we would provide. Furthermore, the EPC program does not conduct cost effectiveness analyses. Our focus is on effectiveness.
Peer Reviewer #5	Discussion-Conclusion	As noted above failure of the authors to address ascent of the testis following hormonal therapy is a concern giving the physician the concept that once the testis is in the scrotum following hormonal treatment no additional follow-up is necessary, this should be rectified.	We appreciate the reviewer's concern and agree that follow-up is required in these patients. We have added text in the discussion and conclusions to reflect this.
Peer Reviewer #5	Discussion-Conclusion	Failure to note the controversy regarding possible harm following hormonal treatment is also of concern. This synopsis should present a well rounded picture to the physician regarding all aspects, financial concerns for cost effective management and long term sequelae of treatment both lacking in the section regarding hormonal therapy. Especially since the authors allude that hormonal therapy maybe appealing to some parents to prevent the need for surgery they should be aware of the risk of possible failure on long term follow-up and possible long term injury.	Harms of hormonal treatment are not well documented in the comparative effectiveness literature. We note the theoretical harms of treatment, and have discussed harms when they are reported. We agree that harms should be better documented and have noted this in future research.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Discussion-Conclusion	Regarding long term paternity, a synopsis of the excellent work of Dr Peter Lee may be found in Urology 66, 427-431,2007, this paper is probably the best of those who have looked a paternity post orchiopexy finding no difference from normal paternity rates in individuals with a unilateral UDT, with reduced fertility in bilateral UDT.	We have referenced this paper in the introduction and discussion sections of the review because, although it does not meet requirements for inclusion as a treatment effectiveness study, it provides good data for decision makers.
Peer Reviewer #5	Discussion-Conclusion	Overall this review is somewhat disappointing failing to discuss some of the major key controversies of the field.	We are sorry the reviewer feels this way. The key questions were developed in collaboration with clinical experts on our TEP and were based on the suggestions of the review nominator.
Peer Reviewer #6	Discussion-Conclusion	Page 81, Line 12-13: This initial part of the discussion is framed in a manner that leads the reader to believe that the discussion is going to go on to say that this systematic review provides evidence that these modalities (hormonal stimulation and imaging) are efficacious. It should be rephrased to reflect that the goal of these modalities would be to perform as mentioned. Perhaps by saying instead: "While surgical approaches can provide definite answers, the goals of the use of either or both imaging and hormonal stimulation would be to provide clinicians and families w/ information in a non-invasive way to guide treatment."	We have revised as suggested.
Peer Reviewer #6	Discussion-Conclusion	Page 88, Line 44-46: This statement needs to be more specific because as the data show it is not accurate for abdominal testes and this is the main situation where it would actually be helpful in surgical planning.	We have revised our commentary on the utility of imaging.
Peer Reviewer #6	Discussion-Conclusion	Background--In regards to the clinical situation involving non-palpable bilateral testis. There appears to be no review of the literature in regards to Mullerian Inhibiting Substance. Contemporary practice of this clinical scenario is somewhat mixed with a segment of practitioners currently opting to send a MIS as opposed to performing an HCG stimulation test in order to identify functional tissue. In addition: 1. Peter Lee's paternity data in adult men gives on children undergoing orchiopexy, not mentioned. This is probably one of the most glaring omissions in the report. (Lee PA: Horm Res. 2001;55(5):249-53). His entire career is dedicated to this topic. Most clinician's practice patterns are based on his population data reports. 2. There is no mention of testis biopsy data and timing of orchidopexy. Again, this is extremely critical and needs to be addressed. Urol Int. 2005;75(3):227-30. (Testicular biopsy during orchidopexy procedure: does it have an adverse effect on fertility?Iskit SH, Tu?tepe H, Tugay M, Kiyan G, Kotilo?lu E, Da?li TE.) This entire subject should be reviewed because it is vital to the timing of orchidopexy and more importantly should we biopsy as well.	The key questions and scope of this review were developed with the support of technical experts and were available for Peer Reviewer #6 review and comment. Neither MIS nor biopsy during orchiopexy were included in the scope. While these certainly may be worthy topics, they are not a part of this project.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion-Conclusion	With respect to the formulation of key questions, it is curious is to why KQ1a and b exist. For KQ1a, imaging utility may not be clinically relevant. If the testis is palpable, then an inguinal incision is made and in some cases a scrotal incision. Imaging for this scenario should not be performed. It will only increase health care cost. I believe there is data for this. If the testis is non-palpable, then imaging has little role as well. The main reason here is that regardless as to what the imaging test demonstrates, a diagnostic laparoscopy must be performed because of the high risk of testis cancer associated with an abdominal testis that may be missed with a FN on an imaging study that fails to identify the testicle. The only scenario in which imaging may be applicable is with a positive MIS and a negative diagnostic laparoscopy. In this scenario, a through evaluation of the retroperitoneum should be undertaken with MRA.	The key questions and scope of this review were developed with the support of technical experts and were available for Peer Reviewer #6 review and comment.
Peer Reviewer #6	Discussion-Conclusion	With regards to mainly question 1b, much of this review comprises literature that ranges from the most part from 1980-1995. With one exception, hormonal stimulation as a treatment has been abandoned. a. This does not represent clinical practice. b. Most feel that some of the patients that benefited from this treatment were perhaps retractile and not undescended. c. There is a large review that I did not see in the references that mentions that the rate of orchidopexy is three fold higher than the prevalence of the disease. (Peter Lee I believe has this data)	We believe that clinical practice varies and that it is important to objectively review the published evidence to provide adequate and clear data to clinicians and families facing medical decisions.
Peer Reviewer #6	Discussion-Conclusion	4. Key 5 Key Question 5: "Harms of Workup or Treatment" Need to look for TCH study for bladder injury: Bladder injuries during laparoscopic orchiopexy: incidence and lessons learned. Hsieh MH, Bayne A, Cisek LJ, Jones EA, Roth DR. J Urol. 2009 Jul;182(1):280-4; discussion 284-5. Epub 2009 May 17.	The referenced paper is a single arm study the notes three cases of bladder injury during laparoscopic orchiopexy in 100+ patients. The injuries are associated with laparoscopic surgery in general, and not specific to orchiopexy.
Peer Reviewer #6	Discussion-Conclusion	6. No mention as to approach may suffer selection bias in regards to # of atrophy.	We do not understand this comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion-Conclusion	7. No testis biopsy data. Ad Spermatagonia or PLAP results in regards to patients undergoing orchidopexy. Research Gaps a. First paragraph does not alter clinical treatment. It will only increase cost of identification. The use of imaging really has no role because the risk of being wrong, false negative, is too high because it is the risk of cancer in the testis in essence. b. No mention to the role of imaging in patients with positive hCG and negative exploration. Here MR probably has a role. c. Not appropriate to recommend hCG as treatment option because many of those patients may have been retractile and this treatment has been abandoned. d. No mention as to recommended age of treatment and data on germ cell aplasia. This is different than the ability to place testis in scrotum. Cannot jump to conclusion that there is no RCT concerning laparoscopic orchidopexy first and second stage therefore we need one. The report articulates well as to why a primary or staged procedure is performed. (mainly based on length of vessels).	We have presented the data that were available to address the key questions for this review. Of particular note, it is not the role of the EPC program to make clinical recommendations; therefore, this report focuses on a report of the science as it exists.
Peer Reviewer #7	Discussion-Conclusion	Implications/lack of data with implications are clearly stated. See above for omitted literature.	Thank you.
Peer Reviewer #7	Discussion-Conclusion	Future research covered in Research Gaps section. Disagree that fertility measures are inadequate- these are the standard across all infertility research. While a study concerning the "ability to achieve paternity" is the ultimate goal, it requires a 20-30 yr follow-up across multiple institutions- likely never to be achieved. Testosterone studies would also require about a 15 yr follow-up.	While these may be the standard across all infertility research, they are still proxy outcomes. Campbell-Walsh Urology reports that 55% of men presenting for infertility work-up present with a normal semen analysis. Conversely, many patients with abnormal semen parameters achieve paternity. Finally, there is debate about how to define a normal semen analysis. In a best case scenario, this is an adequate proxy outcome. While long-term studies like the ones proposed in the future research section are difficult, they are not impossible.
Peer Reviewer #7	Discussion-Conclusion	Disagree with the conclusion on long-term outcomes- some data are available but appear to not be included in this analysis.	Studies were included in the analysis based upon whether they met inclusion criteria, which were defined <i>a priori</i> . Studies with long-term outcomes tended not be comparative in nature or to include patients who were treated for cryptorchidism after puberty and were appropriately excluded.
Peer Reviewer #6	References	Page 205, Line 45: Kollin et al, J Urol 2008, should be stressed in analysis of timing of orchiopexy.	Thank you.
Peer Reviewer #1	General	The document is clear enough and would be useable for health bureaucrats as long as the limitations described in my introductory remarks were clearly articulated so that someone unfamiliar with the field is not put in a position where they would easily misinterpret the results.	Thank you.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	The report has reasonable clinical meaningfulness, but there are some limitations of the report which are not articulated very well in the report.	Thank you - we have revised the report
Peer Reviewer #1	General	These limitations need to be taken into account when trying to access the evidence for various approaches in the management of undescended testes. These limitations will be discussed further below.	We have addressed specific comments as noted.
Peer Reviewer #1	General	The target population and audience are reasonably well defined, and the key questions are appropriate and explicitly stated.	Thank you
Peer Reviewer #1	General	The problem with the limitations of the study are that it describes the literature review from 1980-2001. The authors of the review do not make sure that the reader is aware that papers published in the 1980's were from patients that might have been treated in the 1960's or 70's, when the standard age for orchidopexy was somewhere between 5 and 15 years of age. At that time it was not known that germ cell development in early infancy might be important for subsequent reduction of cancer risk and improved fertility. Over the last 30 years evidence has gradually emerged that testes that are operated on later in childhood have progressively more severe secondary atrophy and damage which will predispose to both infertility and increasing risk of malignancy. The study reads as if there has been no change in the literature, and that all of the studies that have been reviewed are actually providing evidence about our current management, when in fact they are describing management in a previous generation in most cases. As progressive knowledge about the damage to undescended testes as childhood progresses has accumulated, the generally recommended age for orchidopexy has been falling progressively over time. Experimental evidence that is not addressed at all in the review suggests that the correct age for orchidopexy may in fact be early in the first year of life in babies. Clearly the papers that are reviewed in this review, do not address this issue, as not enough time has passed to allow assessment of children at this age.	In fact, our review is from 1990 to February 2012. We appreciate these comments, but we have included the most recent literature possible.
Peer Reviewer #1	General	The second issue which needs to be more clearly articulated in the conclusions is that the reason for lack of long term follow up evidence is merely a function of the time interval between intervention and outcome. With orchidopexies currently being done in infancy, a fertility outcome is 20-30 years into the future, while a malignancy risk outcome is 20-40 years into the future. The authors would be wise to insure that the readers of this report are aware of these limitations, because these limitations have a significant impact on interpretation of the results that are currently in the literature.	We have added text related to this issue.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	Another issue which is completely absent from the review is the fact that over the 30 years of the review interval, it has become apparent to researchers in the field that undescended testes is actually of two separate varieties, a congenital failure of migration to the scrotum occurring prenatally, but also an acquired postnatal version where the testis fails to remain in the scrotum as the child enlarges with age. This second version of acquired undescended testes looks like it has different fertility outcome and malignancy implications for children. It is very likely therefore, that one of the reasons for many of the studies reported in this review having mixed results is the fact they were probably describing patients that were a mixed bag of both congenital and acquired undescended testes. This is not the fault of the experimenters of the time, because when the studies were done the differences between these two groups were not fully appreciated. However, the fact that the studies include what is likely to be a heterogeneous population of congenital and acquired undescended testes patients means that the results are not nearly as easy to interpret as might have been assumed at the time. For example, there is now a reasonable suggestion in the literature that hormone treatment might only be effective in children with what in retrospect we would now call acquired undescended testes rather than congenital failure of migration.	This is important information, but beyond the scope of the comparative effectiveness review.
Peer Reviewer #2	General	yes, well structured, organized, and clear. conclusions are helpful.	Thank you.
Peer Reviewer #2	General	A nicely done, comprehensive review of the literature on a common problem. key questions well stated	Thank you
Peer Reviewer #3	General	The report is well structured and clear. Addressing comments above would be helpful for directing investigators and agencies interested in funding further research.	Thank you. We have done so.
Peer Reviewer #3	General	This is a generally useful review of the current diagnostic and therapeutic modalities for cryptorchidism. The methods are well described and results well summarized. The target audience is well defined.	Thank you
Peer Reviewer #4	General	The report is well-structured and organized, and allows the reader to easily follow their main points. The conclusions should be able to be understood by both medical professionals as well as lay individuals	Thank you
Peer Reviewer #4	General	The authors have performed an extensive review of the literature regarding cryptorchidism in boys. The older literature is difficult to compare with the more recent literature, as surgical standard of practice has changed over the past few decades (median age at time of surgery has dropped from approximately 5 - 9 years old down to 6 months - 1 year).	We agree.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	General	The report is clinically meaningful and the target population is clearly defined. The audience (urologists and PCPs) is assumed, not clearly stated. The key questions are appropriate though questions #4 and 5 are less useful. Question #3 should also include an evaluation of the scrotal (Bianchi) orchiopexy. Two key questions are missing: 1. Is a testis biopsy helpful in predicting abnormal histology and long-term fertility? 2. Does the use of adjuvant hormonal therapy improve long-term fertility?	The single comparative effectiveness study on Bianchi orchiopexy is included in KQ3