American Urological Association (AUA)
Guideline

Evaluation and treatment of cryptorchidism: AUA Guideline

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This document was written by the Cryptorchidism Panel of the American Urological Association Education and Research, Inc., which was created in 2013. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the committee included urologists and other clinicians with specific expertise on this disorder. The mission of the committee was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment cryptorchidism.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all govern-

ment regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

Purpose: Cryptorchidism or undescended testis (UDT) is one of the most common pediatric disorders of the male endocrine glands and the most common genital disorder identified at birth. The main reasons for treatment of cryptorchidism include increased risks of impairment of fertility potential, testicular malignancy, torsion and/or associated inguinal hernia. Cryptorchidism has evolved significantly over the past half century, with respect to both diagnosis and treatment. The current standard of therapy in the United States is orchidopexy (also referred to as orchiopexy in the literature), or surgical repositioning of the testis within the scrotal sac, while hormonal therapy has fewer advocates. Successful scrotal relocation of the testis, however, may reduce but does not prevent these potential long-term sequelae in susceptible individuals. The purpose of this guideline is to provide physicians and non-physician providers (primary care and specialists) with a consensus of principles and treatment plans for the management of cryptorchidism. The panel members are representative of various medical specialties (pediatric urology, pediatric endocrinology, general pediatrics).

Methods: The primary source of evidence for this guideline was the systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review titled *Evaluation and Treatment of Cryptorchidism (*2012). That report included rigorous searches of MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and EMBASE for English-language studies published from January 1980 through February 2012 relevant to cryptorchidism. To capture more recently published manuscripts and expand the body of evidence provided in the original AHRQ report, the American Urological Association (AUA) conducted additional supplementary searches of PubMed and EMBASE for relevant articles published between January 1980 and March 2013 that were systematically reviewed using a methodology developed *a priori*. In total, these sources yielded 704 studies, after exclusions, that were used to inform the statements presented in the guideline as Standards, Recommendations or Options. When sufficient evidence existed, the body of evidence for a particular clinical action was assigned a strength rating of A (high), B (moderate) or C (low). In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

List of abbreviations

AAP	American Academy of Pediatrics
Ad	Adult dark spermatogonia
AHRQ	Agency for Healthcare Research and Quality
AR	Androgen receptor
AUA	American Urological Association
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
CT	Computed tomography
DES	Diethylstilbestrol
DSD	Disorder of sex development
ESR1	Estrogen receptor alpha
FS	Fowler Stephens
INSL3	Insulin-like 3
LGR8	Leucine-rich repeat-containing G protein- coupled receptor 8
MRA	Magnetic resonance angiogram

MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
PCB	Polychlorinated biphenyl
RCT	Randomized controlled trial
RRR	Recurrence risk ratio
RXFP2	Relaxin/insulin-like family peptide receptor 2
TDS	Testicular dysgenesis syndrome
UDT	Undescended testis
US	Ultrasound

Guideline statements

Diagnosis

1.Providers should obtain gestational history at initial evaluation of boys withsuspected cryptorchidism. (Standard; Evidence Strength: Grade B)

2.Primary care providers should palpate testes for quality and position at eachrecommended well-child visit. (Standard; Evidence Strength: Grade B)

3. Providers should refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by six months (corrected for gestational age) to an appropriate surgical specialist for timely evaluation. (Standard; Evidence Strength: Grade B)

4. Providers should refer boys with the possibility of newly diagnosed (acquired) cryptorchidism after six months (corrected for gestational age) to an appropriate surgical specialist. (Standard; Evidence Strength: Grade B)

5. Providers must immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development (DSD). (Standard; Evidence Strength: Grade A)

6. Providers should not perform ultrasound (US) or other imaging modalities in the evaluation of boys with cryptorchidism prior to referral as these studies rarely assist in decision making. (Standard; Evidence Strength: Grade B)

7. Providers should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism. (Recommendation; Evidence Strength: Grade C)

8. In boys with bilateral, nonpalpable testes who do not have congenital adrenal hyperplasia (CAH), providers should measure Müllerian Inhibiting Substance (MIS or Anti- Müllerian Hormone [AMH]) level), and consider additional hormone testing, to evaluate for anorchia. (Option; Evidence Strength: Grade C)

9. In boys with retractile testes, providers should monitor the position of the testes at least annually to monitor for secondary ascent. (Standard; Evidence Strength: Grade B)

Treatment

10. Providers should not use hormonal therapy to induce testicular descent as evidence shows low response rates and lack of evidence for long-term efficacy. (Standard; Evidence Strength: Grade B)

11. In the absence of spontaneous testicular descent by six months (corrected for gestational age), specialists should perform surgery within the next year. (Standard; Evidence Strength: Grade B)

12. In prepubertal boys with palpable, cryptorchid testes, surgical specialists should perform scrotal or inguinal orchidopexy. (Standard; Evidence Strength: Grade B)

13. In prepubertal boys with nonpalpable testes, surgical specialists should perform examination under anesthesia to reassess for palpability of testes. If nonpalpable, surgical exploration and, if indicated, abdominal orchidopexy should be performed. (Standard; Evidence Strength: Grade B)

14. At the time of exploration for a nonpalpable testis in boys, surgical specialists should identify the status of the testicular vessels to help determine the next course of action. (Clinical Principle)

15. In boys with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a boy has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age. (Clinical Principle)

16. Providers should counsel boys with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk. (Clinical Principle)

Introduction

Purpose

Cryptorchidism or undescended testis (UDT) is one of the most common pediatric disorders of the male endocrine glands and the most common genital disorder identified at birth. The main reasons for treatment of cryptorchidism include reducing the risks of impairment of fertility potential, testicular malignancy, torsion and/or associated inguinal hernia. Cryptorchidism has evolved significantly over the past half century, with respect to both diagnosis and treatment. The current standard of therapy in the United States is orchidopexy (also referred to as orchiopexy in the literature), or surgical repositioning of the testis within the scrotal sac, while hormonal therapy has fewer advocates. Successful scrotal relocation of the testis, however, may reduce but does not prevent all of these potential long-term sequelae in susceptible individuals. The purpose of this guideline is to provide physicians and non-physician providers (primary care and specialists) with a consensus of principles and treatment plans for the management of cryptorchidism. The panel members are representative of various medical specialties (pediatric urology, pediatric endocrinology, general pediatrics).

Methodology

Quality of Studies and Determination of Evidence Strength. The primary source of evidence for this guideline was the systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review titled Evaluation and Treatment of Cryptorchidism (2012). That report included rigorous searches of MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and EMBASE for English-language studies published from January 1980 through February 2012 relevant to cryptorchidism. To capture more recently published manuscripts and expand the body of evidence provided in the original AHRQ report, the American Urological Association (AUA) conducted additional supplementary searches of PubMed and EMBASE for relevant articles published between January 1980 and March 2013 that were systematically reviewed using a methodology developed a priori. In total, these sources yielded 704 studies, after exclusions, that were used to inform the statements presented in the guideline as Standards, ***Recommendations or Options.*** Quality of individual studies was rated as high, moderate, or low based on instruments tailored to specific study designs. Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias tool [1]. Conventional diagnostic cohort studies, diagnostic case-control studies, or diagnostic case series that presented data on diagnostic test characteristics were evaluated using the QUADAS-2 tool [2] that evaluates the quality of diagnostic accuracy studies. Cohort studies with a comparison of interest were evaluated with the Drug Effectiveness Review Project instrument [3]. The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes consideration of study design, individual study quality, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings and treatments for the purposes of the guideline. The AUA categorizes body of evidence strength as Grade A (well-conducted RCTs or exceptionally strong observational studies), Grade B (RCTs with some weaknesses of procedure or generalizability or generally strong observational studies) or Grade C (observational studies that are inconsistent, have small sample sizes or have other problems that potentially confound interpretation of data). The quality of the evidence was variable depending on the issue examined. For many epidemiological issues there was a combination of moderate to large sized population-based studies, some of them prospective, being the key issue, as well as the consistency of findings. When evidence was consistent it was graded B, otherwise C. For issues related to management, studies tend to be non-randomized cohorts of moderate size or randomized trials of small to moderate size. Again the key issue was consistency of findings and the same criterion indicated above was applied. Seventy percent of the graded statements were considered level B (many under the AUA's premise of moderate quality, moderate certainty).

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens [4]. ***Standards*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence. ***Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C evidence. ***Options*** are non-directive

statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; the decision is based on full consideration of the patient's prior clinical history, current quality of life, preferences and values. ***Options*** may be supported by Grade A, B or C evidence.

In some instances, the review revealed insufficient publications to address certain questions from an evidence basis; therefore, some statements are provided as *Clinical Principles* or as *Expert Opinions* with consensus achieved using a modified Delphi technique if differences of opinion emerged [5]. A ***Clinical Principle*** is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. ***Expert Opinion*** refers to a statement, achieved by consensus of the Panel that is based on members' clinical training, experience, knowledge and judgment for which there is no evidence.

Limitations of the Literature. Limitations of the literature identified by both the AHRQ and the AUA reviews include, (1) lack of studies assessing the value of hormonal stimulation testing, long-term fertility outcomes, as well as inconsistent reporting of age at diagnosis and/or at treatment; (2) scant information about imaging effectiveness for modalities other than ultrasound (US) and magnetic resonance imaging (MRI); (3) low level evidence for the effectiveness of surgical treatment other than primary orchidopexy, accompanied by a lack of a standardized definition of success, follow-up length, reporting of complications, and control of confounding variables by indication; (4) inconsistent control of confounding variables among studies evaluating the epidemiology of cryptorchidism. This could be the result of the remaining uncertainty with respect to the etiological factors strongly and consistently associated with cryptorchidism.

Peer review. The AUA conducted an extensive peer review process. The initial draft of this Guideline was distributed to 84 peer reviewers of varying backgrounds, including those who applied through open comment; 43 responded with comments. The panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the Guideline was submitted for approval to the Practice Guidelines Committee (PGC). It was then submitted to the AUA Board of Directors for final approval.

Background

Definitions

Cryptorchidism, or undescended testis (UDT), is defined as failure of a testis to descend into a scrotal position. This situation most commonly refers to a testis that is present but in an extrascrotal position, but may also lead to identification of an absent testis. In the latter situation, the testis is most commonly referred to as *vanishing (or vanished);* consistent with evidence suggesting that it was present initially but disappeared during development most likely due to spermatic cord torsion or vascular accident.

Congenital cryptorchidism refers to testes that are extrascrotal from the time of birth. *Acquired* cryptorchid testes are intrascrotal at birth but subsequently identified in an extrascrotal position. Cryptorchid testes may be *prescrotal* (above or at the scrotal inlet), in the *superficial inguinal pouch* (distal and lateral to the external inguinal ring, anterior to the rectus muscle), at the *external ring* (or prepubic), *canalicular* (within the inguinal canal), *ectopic* (most commonly perineal) or *abdominal(*«peeping» through or proximal to the internal inguinal ring, or near the bladder, iliac vessels or kidney).

Acquired cryptorchid testes are considered *ascending,* when apparent change from an intrascrotal to an extrascrotal position occurs spontaneously at some point after birth, or *entrapped,* when such change occurs after prior inguinal surgery. A *retractile* testis is one that is initially extrascrotal on examination or moves easily out of scrotal position, (often associated with a vigorous cremasteric reflex), but that can be manually replaced in stable, dependent scrotal position and remain there without tension at least temporarily. An *atrophic* testis is one that suffers significant volume loss after prior inguinal or testicular surgery, or due to prolonged location in an extrascrotal position or primary developmental failure.

Epidemiology

Prevalence/incidence of congenital v. acquired cryptorchidism. Although delayed diagnosis or treatment of cryptorchidism beyond the neonatal period is well-documented, the relative proportion of cases of true testicular ascent v. congenital cases that were not identified and/or referred early for care remains unclear [6–9]. However, the

Table 1:
Prevalence of cryptorchidism

	Study characteristics	**Estimates**
Newborn	23 studies	
All		0.1-9.0%
<2.5 kg		1.1-45.3%
>2.5 kg		1.0-4.6%
One month		
All		1.0-1.2%
Three months	7 studies	
All		0.7-1.9%
<2.5 kg		1.7-5.2%
>2.5 kg		0.9-1.6%
One year	6 studies	
All		1.1%-2.1%
<2.5 kg		1.9-7.3%
>2.5 kg		1.0-1.5%
Three years		0.8-2.5%
Six years		0.0-2.6%
Eight years		0.0-6.3%
Ten years		0.0-3.6%
Eleven years		0.0-6.6%
Thirteen years		0.0-4.0%

*Adapted from Sijstermans K, Hack WW, Meijer RW et al: The frequency of undescended testis from birth to adulthood: a review. Int J Androl 2008; 31: 1.

preponderance of data strongly supports the existence of acquired cryptorchidism as a real phenomenon whose prevalence may be similar to that of congenital cryptorchidism. In a population-based health registry study, cryptorchidism was frequently diagnosed beyond the newborn period, and there were no age-specific differences in time between diagnosis and surgical correction [10]. Similarly, in birth cohort studies [9,11], suprascrotal testes were newly diagnosed in about 2% of boys examined longitudinally at intervals up to 10 years of age. Spontaneous descent of congenitally cryptorchid testes occurred in 35-43% of newborn boys followed longitudinally, usually prior to 3 months of age [9,11,12], but re-ascent (recurrent cryptorchidism) may occur, and was reported in 22% of boys in a recent prospective study [13]. In a referral population, Wenzler et al. [14] documented spontaneous descent in 24% of boys presenting prior to age 4 months and none presenting at or after 6 months, or a total of 6.9% of boys presenting in the first year of life. The overall rate of spontaneous descent in this latter study may be low because the referral population likely excluded cases of early postnatal spontaneous descent.

Sijstermans et al. [15] compiled a systematic review estimating the prevalence of cryptorchidism by different ages and birth weights (Table 1). They identified 97 articles, but only 49 remained eligible. These studies were conducted between 1934 and 2006. Thirty-eight studies (83%) were prospective, and the other eleven were retrospective, totaling over 704,000 males. Fifty percent of the studies used a formal definition to identify and diagnose cryptorchidism, although these definitions varied widely. Ten percent of articles used the definition by Scorer [16] that considers all testes at least 4 cm below the pubic crest in full term males (2.5 cm in preterm males) as descended; 41% included location in the definition, and 13% excluded high scrotal testes.

It can be seen that for boys up to one year of age and of normal weight, the estimates are rather stable, while for the same age range but low birth weight they vary widely. This age group constitutes 57% of the studies with over 591,000 infants. It is important to highlight, as indicated by the authors of the compendium, that low birth weight and prematurity were often used synonymously. The prevalence for boys three years and older is again rather stable between null and 6.6%. In addition to birth weight and prematurity, the authors indicate that the lack of distinction between congenital (never descended from birth) and acquired (previously scrotal) cryptorchidism may explain the differences in rates. The distinction between congenital and acquired cryptorchidism could not be made for the majority of these studies as only 5 (11%) of the studies reviewed included data documenting prior testicular position.

In a large population-based study of 819,111 non-syndromic boys in Denmark, Jensen and colleagues analyzed associations between birth weight, prematurity and cryptorchidism, which occurred in 14.1 cases out of 1000 boys [17]. When correcting birth weight for gestational age, only boys in the lowest quintile (<20th percentile) were at increased risk for cryptorchidism (OR 1.4, 95% CI 1.3-1.5).

Barthold and González (2003)18 performed a review of epidemiological issues relevant to acquired cryptorchidism. One of the issues they addressed was the incidence of testicular ascent among boys with completely descended testes at birth. Eleven studies have reported these cases (see evidence table in Appendix A). The studies reviewed by these authors performed a lengthy follow-up in which a normal position was recorded prior to discovery of testicular ascent. The mean age at surgery in most series was seven years. They found that the ascended testis is generally unilateral and most likely located distal to the inguinal ring (prescrotal, superficial inguinal pouch or high scrotal).

Genetic susceptibility. In a large population-based twin study, Jensen et al. observed increasing concordance rates of treated cryptorchidism based on family relationships: 1.8% in unrelated males, 2.4-4.3% in half-brothers, 7.5% in full brothers, and 16.7% in dizygotic and 26.7% in monozygotic twins [19]. These data suggest both unknown genetic and environmental factors contribute to cryptorchidism risk.

Animal models of cryptorchidism, mostly knockout mice, have identified insulin-like 3 I*NSL3*) and its receptor relaxin/insulin-like family peptide receptor 2 R*XFP2*), also known as leucine-rich repeat-containing G protein-coupled receptor 8 L*GR8*), as molecules involved in the genesis of cryptorchidism. However, despite a large number of studies comprising over 1,000 patients screened for mutations in the *INSL3* and *RXFP2* genes, few clear exonic variants have been identified that are likely functional mutations (see Table 2), and there is poor correlation between these variants and clinical phenotype [20]. While the T222P mutation of *RXFP2* significantly reduces *INSL3* signaling experimentally [21], it is also found in normal controls [22,23].

Two other potential candidate genes, androgen receptor (*AR*), and estrogen receptor alpha (*ESR1*) are involved in sex hormone function. Exon 1 of the *AR* gene encodes highly polymorphic polyglutamine (CAG) and polyglycine (GGN) repeat sequences. *In vitro* assays have demonstrated that CAG repeat expansion or GGN deletion is associated with diminished transcriptional activity of the receptor [24]. Five different cohorts [24-28] have examined the potential association between AR exonic repeats and cryptorchidism by testing the difference in the mean number of repeats between cases and controls (see evidence table in Appendix B). Three of these studies identified no differences in repeat length between cases and controls, one reported increased CAG repeat length in two small subgroups of Portuguese males (six bilateral cryptorchidism and seven unilateral with contralateral patent processus vaginalis) [28], and the largest study reported reduced CAG repeats in Hispanic cryptorchid males from California [25]. GGN repeat length was higher in cryptorchid cases than controls in one study [24].

For the *ESR1* gene, efforts have focused on the potential difference in the frequency distribution of alleles A and G between cases and controls for SNP12 rs6932902). This SNP12 has been labeled as the tag SNP of the 5-SNP haplotype AGATA. Such allele frequency distributions have been assessed in three independent groups of cases and controls from three different ethnic backgrounds with disparate results (see evidence table in Appendix C). The A allele has been found to confer susceptibility to Japanese men [29] (OR1.99, 95% CI 1.07, 3.67), seems protective among Caucasian men from Italy (OR 0.5, 95%CI 0.28, 0.90),30 and showed lack of association among a multi-ethnic US cohort [31]. For the latter, the allele frequency for G was significantly different between moderate and severe cases (OR 10.0, 95% CI 1.2, 78.2).

In summary, although there is some suggestion that the examined genomic loci may contribute to cryptorchidism susceptibility, the evidence is weak at this point and likely due to the multifactorial nature of the trait, the heterogeneous phenotypic manifestation of cryptorchidism as well as the lack of simultaneous assessment of potential gene-environment interactions.

Table 2:
Summary of exonic variants in INSL3 and RXFP2 in cryptorchidism

Gene	Number of studies	Cases	Controls	Exonic variants
INSL3 [20]	15 (2000-08)	30/1650 (1.8%)	0/>1000	V18M, P49S, W69R, R73X, T86M, P93L, R102C, R102H,
LGR8 [1,7,20,23]	7 (2002-11)	43/1474 (2.9%)	16/2026 (0.8%)	T222P

Familial Aggregation

Two studies have explored the risk of UDT in an individual with a family history. Elert et al [32] assessed the familial risk in a group of 374 cases and 374 controls in Germany. Cases were identified in boys and men who underwent surgery for UDT between 1989 and 2001. The mean age of these males at surgery was 6 years (range 1-39 years). They found that 85 cases (23%) v. 28 controls (7.5%) had one or more family members with UDT for an overall risk of 3.6 (95% CI 2.3, 5.7). The highest risk was present if the family member was a brother (95% CI 6.9 [2.7, 17.9]), followed by an uncle (95% CI 5.2 [1.8, 15.4]) and then by the father (95% CI 4.6 [2.0, 10.6]).

The second study was a large population-based study conducted in Denmark between 1977 and 2005 [33]. Danish boys were identified from the Civil Registration Systems and their relatives from the Danish Family Relations Database. The cryptorchidism status was gathered from the Danish Hospital Discharge Register. Using these data sources, of 42,105 cases, 20,398 (48.5%) were confirmed surgically. The measure of risk the authors used is the recurrence risk ratio (RRR), the ratio between cryptorchidism prevalence for individuals with a proband (older affected relative) and the prevalence of cryptorchidism for individuals with known relatives of the same kind where none of them is a proband. For twin pairs, a weighted average contribution from dizygotic and monozygotic twins was applied. Given their almost equal distribution in this cohort, a weight of 0.5 was assigned for each. The RRR was 10.1 (95% CI: 7.78, 13.1) in twins, 3.52 (95% CI: 3.26, 3.79) in brothers, 2.31 (95% CI: 2.09, 2.54) in sons, 2.12 (95% CI: 1.74, 2.60) in maternal half-brothers and 1.28 (95% CI: 1.01, 1.61) in paternal half-brothers. This led the authors to conclude that the maternal contribution is greater than the paternal one, suggesting either an X-linked mode of inheritance or a combination of genetic factors and maternal environment. Elert et al. [32] noted similar findings in a much smaller cohort study, but did not observe a difference in rates for maternal and paternal inheritance.

Environmental Exposure. The possibility that environmental chemicals alter normal reproductive tract development has been debated in the recent literature. There is significant potential concern that endocrine-disrupting chemicals may be linked to male reproductive tract anomalies that may have a common etiology, including cryptorchidism (sometimes termed 'testicular dysgenesis syndrome') [34,35]. Concerns for a connection between endocrine-disrupting chemicals and cryptorchidism developed because of a reported higher risk related to early maternal exposure to diethylstilbestrol (DES).

Environmental Chemicals

A quantitative summary of the potential effect of exposure to pesticides and the risk of cryptorchidism is not possible because of the large variability on study designs, exposure and outcome assessment and measurement. Virtanen and Adamsson (2012) [36] qualitatively summarized 18 studies in 2012. Two large ecological studies with adequate power found different results based on the pesticide use in the area; one a significant positive association and the other a non-significant positive association. Ten studies assessing exposure in terms of parental occupation, primarily in agriculture and gardening also had sufficient power. Outcomes differed with four studies indicating a positive significant association, three a non-significant association, and three studies reporting a decreased risk. Six studies assessed the exposure in terms of pesticide levels in biological specimens, assessing the exposure in a more direct fashion, but were inconclusive because of small sample size.

There have been a number of case control studies assessing other chemicals such as polychlorinated biphenyls (PCBs), dioxins, flame retardants and phthalates. These studies have been of small sample size and have not demonstrated statistical significance [36-41].

Incidence seasonality

Mamoulakis et al.42 examined the significance of seasonal trends in cryptorchidism incidence among over 209,000 live-born boys in Greece between 1995 and 1999. The incidence of cases at birth was cyclic with a peak in March (61.0) and a trough in September (36.1). After exclusions, 583 isolated true cryptorchid cases were identified. The authors reported that maternal hCG levels at 26 weeks gestation were lower in winter months and suggest that low environmental temperature may influence maternal hCG profiles and hence the inguinoscrotal phase of testicular descent. However, this finding is of questionable relevance as the authors did not compare hCG in pregnancies with and without cryptorchid fetuses, and hCG levels are normally very low after the first trimester.

Three other studies were cited with a large number of cryptorchid cases conducted in European countries in which March is the month with peak incidence for cryptorchidism births. A fourth study in the United States of America

found two peaks: one during September-November when a trough was observed in the other studies and a second smaller peak during March-May.

Maternal environment

Maternal Body Mass Index (BMI)

Adams et al. [43] conducted a population-based case-control study using birth record data from the state of Washington during the period 1992-2008. The authors discuss three potential mechanisms relating maternal obesity to the risk of cryptorchidism and hypospadias. These are, (1) levels of circulating hormones, (2) lower overall diet quality and blood concentrations of micronutrients, (3) impaired fasting glucose and glucose tolerance before and during pregnancy. Five randomly selected controls from the same birth year were assigned to each of the 3,946 cases of cryptorchidism. Maternal BMI was missing in 30% of cases and 28% of controls. Cryptorchidism and hypospadias may be more common in first pregnancies. Maternal weight was collected from the birth certificates, while height was collected from the driver's licenses prior to 2003, and from the birth certificates from 2003 onwards. BMI was categorized using the World Health Organization (WHO) thresholds. No association between BMI and the incidence of cryptorchidism was found based on odds ratios adjusted for year of birth, maternal age, education, parity, race, and cigarette smoking during pregnancy. Based on a reference group of mothers with normal weight, the adjusted odds ratio for underweight mothers was 1.14 (95% CI 0.93, 1.39); for overweight 1.03 (95% CI 0.93, 1.14) and for obese mothers 0.99 (95% CI 0.89, 1.11). Similarly, no effect was observed when weight was analyzed as a continuous variable with changes measured per each 5 kg/m2, OR=1.01 (95% CI 0.97, 1.05).

Maternal smoking

Hackshaw et al. [44] performed a systematic review of articles published in English between 1959 and February 2010 regarding the association between maternal smoking in pregnancy and birth defects, including cryptorchidism. Study designs included cohort, case-control, and surveys. Eighteen studies provided data for cryptorchidism (8,753 cases and 98,627 controls). Overall, mothers who reported smoking during pregnancy were 13% more likely to have a child with cryptorchidism (OR1.13, 95% CI 1.02, 1.25); although this estimate includes moderate heterogeneity I2=39%; individual study estimates ranged between OR=0.41 and OR=1.69. A second estimate was calculated based on 15 studies that adjusted for potential confounders. These 15 studies assessed 8,258 boys with cryptorchidism and 72,224 controls. The overall estimate was not different to the unadjusted estimate (OR 1.16, 95% CI 1.08, 1.25).

Maternal alcohol consumption

Three studies conducted in Denmark [10,45-47] and one in the United States [48] examined the potential association between maternal alcohol consumption during pregnancy and the risk of cryptorchidism in a prospective fashion (see Appendix D). The disparity in outcome measure used (two used odds ratio, one risk ratio and the other hazard ratio) precludes quantitative aggregation but allows qualitative summarization. Alcohol consumption was found to be associated with transient cryptorchidism if the mother consumed five or more drinks per week, adjusted OR 3.10, 95% CI 1.05, 9.10) [45]. This finding was not present among boys with persistent cryptorchidism, adjusted risk ratio 0.70 (95% CI 0.40, 1.30) [46]. The third Danish study [46] aimed at assessing in more detail the association of binge drinking with persistent cryptorchidism rather than regular alcohol consumption did not find a statistical effect. The American study also failed to find an association [48].

Maternal analgesic consumption

Four cohort studies [49-52] reported the incidence/prevalence of cryptorchidism in infants and young boys born from mothers who reported on the use of mild analgesics (COX inhibitors) during pregnancy. The underlying hypothesis is that COX inhibitors may impede prostaglandin production by a mechanism not completely elucidated yet. Prostaglandins are necessary for male sexual differentiation. Three of the studies [49,50,52] show that the use of mild analgesic, mainly paracetamol, during the second trimester (end of the defined «programmatic window») increases the risk for cryptorchidism.

The way exposure information was collected does not allow us to determine whether consumption in both first and second trimester is necessary, and more precisely, when within these two periods the exposure increases the risk. This was the case in the study by Jensen et al. [49] where the risk of cryptorchidism did not increase if exposure to

analgesic was in the first or second trimester alone, but when both combined the risk increased. The rate of exposure ranged between 47% and 81% and was by far most common for paracetamol.

The association between maternal analgesic consumption and cryptorchidism estimated from multivariable models ranged between a hazard ratio of 1.33 for paracetamol consumed in the first and second trimester [49], to an odds ratio of 1.89 for paracetamol consumed in the second trimester (unknown whether also consumed during the first) [52], to an odds ratio of 2.30 for any mild analgesic consumed during the second trimester (again unknown whether consumed during the first) [50]. Two of the studies (conducted in Denmark)49,50 also showed that use of any mild analgesic for over two weeks increased the odds of cryptorchidism [50]. In another study [49], the odds of cryptorchidism increased when the prolonged analgesic use was for more than four weeks during weeks 8-14 of gestation.

Maternal estrogen exposure

Vidaeff and Sever [53] performed a systematic review of articles published in English, French, Italian and Spanish between 1990 and 2003 dealing with prenatal exposure to endocrine disruptors, xenoestrogens and/or environmental estrogens. Articles were included if they reported the adverse effect of these exposures on cryptorchidism, hypospadias, or impaired sperm quality. Nine studies were identified, but heterogeneity of retrieved information precluded aggregation into meta-analysis. Three large studies report a positive association between pesticide exposure and cryptorchidism. The authors caution about the complex nature of both the components of the exposure and the pathogenic mechanisms involving multifactorial origin and potential trans-generation effects. Available data do not support with certainty the potential contribution of environmental estrogens to an increase in male reproductive disorders, but also do not provide sufficient information to totally reject such hypotheses.

Martin et al. [54] performed a meta-analysis aimed at assessing the role of estrogen in components of the testicular dysgenesis syndrome (TDS), namely hypospadias, cryptorchidism, and testicular cancer. It excluded exposure to suspected endocrine disruptors for which the mode of action was unspecified (e.g., pesticides), exposures to phytoestrogens, and maternal endogenous hormones. Only three studies examining DES exposure show an association with cryptorchidism based on a fixed effect model (OR 2.09, 95% CI 1.13, 3.86) but not if based on a random effects model (OR 1.80, 95% CI 0.83, 3.93).

Guideline statements

Diagnosis

Guideline Statement 1

Providers should obtain gestational history at initial evaluation of boys with suspected cryptorchidism. (Standard; Evidence Strength: Grade B)

Testicular descent occurs in two phases: transabdominal descent and inguinoscrotal migration. Initial transabdominal descent occurs in the first trimester of gestation. At approximately 22-25 weeks of gestational age, the testes are located at the internal ring. The inguinoscrotal phase of testicular descent, which is androgen dependent, occurs between 25-30 weeks [55,56]. Given the relatively late migration of testes through the inguinal canal into the scrotum, the prevalence of cryptorchidism is higher in premature boys in the first months of life (1-3% in full-term and 15-30% in premature male infants) [15]. Descent of the testes into the scrotum is probable in premature boys during the first months of life, but is unlikely after six months of corrected age [16, 57]. Obtaining the gestational age is thus critical to the proper and timely referral of a child with persistent undescended testes to a surgical specialist (see Appendix E for terminology defined).

In addition to gestational age, low birth weight for gestational age has also been closely associated with cryptorchidism: the prevalence of cryptorchidism in infants <900g is approximately 100%. The prevalence of cryptorchidism decreases as the birth weight of the infant increases, and is approximately 3% in infants weighing 2,700-3,600g [15,58-63].

Spontaneous postnatal testicular descent may be lower in boys with cryptorchidism and a history of small-for-gestational age compared to boys with cryptorchidism and normal birth weight [59,64].

Guideline Statement 2

Primary care providers should palpate testes for quality and position at each recommended well-child visit. (Standard; Evidence Strength: Grade B)

A UDT may be located in the abdomen, the inguinal canal, the superficial inguinal pouch, the upper scrotum, or, may rarely be in an ectopic location (perineum, contralateral scrotum, or femoral). Approximately 70% of UDTs are palpable [65]. For testes that are not palpable, approximately 30% will be found in the inguinal-scrotal area, 55% will be

intra-abdominal, and 15% will be absent or vanishing [66,67]. Testicular position may change as infants and children grow. An internal review of 50 cohorts [68-115] of diagnostic laparoscopy performed in males with nonpalpable testes showed a highly variable distribution of testis location. (See Appendix F)

Spontaneous descent of testes may occur in the first six months of life.16,57 Additionally, testes may «ascend» out of the scrotum (acquired cryptorchidism). Given the potential for change in testicular position throughout childhood, careful evaluation of the scrotum should be performed at every scheduled well-child check, which is in line with the recommendations of the American Academy of Pediatrics (AAP) (See Appendix G).

Physical Examination

The diagnosis of cryptorchidism is made by a careful genital physical examination. The method of testicular examination varies depending on the age and developmental status of the child. Infants should be examined in the supine position with legs gently frog-legged, or sitting on the lap of the parent. Gentle downward pressure along the inguinal canal from the anterior iliac spine to the scrotum and counter palpation with the opposite hand helps to identify the lowest position of a palpable testis. Older children may be examined in the upright cross-legged or supine position. Careful examination of the groin, femoral region, perineum, contralateral hemiscrotum (to detect the rare cases of transverse testicular ectopia), and pubic areas are needed in order to correctly classify a testis as palpable or nonpalpable. The palpability of the UDT will determine the surgical approach.

Once the testis is palpated, gently grasp it with the dominant hand and continue to sweep the testis toward the scrotum with the other hand. In palpable testes that can be manipulated into the scrotum, it is important to maintain the position of the testis in the scrotum for approximately 30 seconds in order to fatigue the cremaster muscle. This will allow differentiation of a retractile testis from a UDT. Release the testis, and if it remains in place, it is a retractile testis. If it immediately retracts to a prescrotal position, it is a UDT. Repeated examinations, patient distraction techniques, a warm environment, and use of a lubricant for the examiner's hands facilitate the physical examination. The size and location of the normally located contralateral gonad should also be noted as it may increase the ability to predict the status of the UDT. A hypoplastic hemiscrotum may imply that the testis is not present. The presence of compensatory hypertrophy (length greater than 2 cm in prepubertal young boys) is highly associated with monorchia [67,116]. However, hypertrophy of the contralateral testis, if present, is neither perfectly sensitive nor specific for the presence of vanishing testis. Therefore, because surgical exploration is indicated in all children with a nonpalpable testis, these children should be referred to a surgical specialist regardless of the size of the contralateral testis.

A genital examination should be performed at every well-child check as outlined by the Bright Futures of the AAP (see Appendix G). Documentation of testes in the dependent scrotum in the first few years of life should not preclude continued examination of the genitals at every scheduled clinic visit. Systematic genital examination will allow identification and referral of boys with acquired cryptorchidism (see Guideline Statement 4). Acquired cryptorchid testes are at risk for developing the same adverse histologic changes seen in primary cryptorchid testes and contribute significantly to the number of orchiopexies performed [117-124]. Systematic and continued genital examinations will also allow identification of boys with retractile testes. While retractile testes do not require surgical correction, the risk of testicular ascent may be higher in boys with retractile testes than in boys whose testes are always positioned in the dependent scrotum [125,126]. Therefore, children with retractile testes should be monitored for «ascent» of the affected testis.

Guideline Statement 3

Providers should refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by six months (corrected for gestational age) to an appropriate surgical specialist for timely evaluation. (Standard; Evidence Strength: Grade B)

Testes that remain undescended by six months (corrected for gestational age) are unlikely to descend spontaneously [57]. In order to facilitate timely orchidopexy, boys whose testicle(s) remain undescended by six months (corrected for gestational age) should be referred to an appropriate surgical specialist [127]. The rationale for referral by six months (corrected for gestational age) is the low probability of spontaneous descent and the probable continued damage to testes that remain in a non-scrotal location.

Cryptorchid testes of boys who underwent orchidopexy at three years demonstrated poorer growth compared to undescended testes of boys who underwent orchidopexy at nine months [13,128]. This impaired testicular growth is

consistent with histologic studies of cryptorchid testes that remained undescended. Uncorrected undescended testes, in particular those that are nonpalpable, are at an increased risk for continued germ and Leydig cell loss [120]. Fertility index (defined as the number of spermatogonia per tubule) decreases in children with cryptorchid testes after one year of age. Longer duration of testis undescent correlates with higher rates of germ cell loss and adult infertility [119,129,130]. The specific etiology for this compromised fertility remains unclear, but is likely related to germ cell depletion and/or defective germ cell maturation, loss of Leydig cells, and/or an increase in testicular fibrosis [130-132]. These histological changes are associated with abnormal semen parameters in these patients during adulthood [117,133]. These findings suggest that untreated cryptorchidism is a progressive disease, not a static congenital malformation [134].

Guideline Statement 4

Providers should refer boys with the possibility of newly diagnosed (acquired) cryptorchidism after six months (corrected for gestational age) to an appropriate surgical specialist. (Standard; Evidence Strength: Grade B)

Acquired cryptorchidism is the ascent of a previously descended testis and subsequent inability to manipulate the testis back into the scrotum. Acquired cryptorchidism is a clinical condition distinct from primary UDT and is easily differentiated from congenital cryptorchidism if scrotal testicular position has been documented since birth. The prevalence of acquired cryptorchidism is 1–7% and peaks around 8 years of age [9,135,136]. The observation that acquired cryptorchidism is more common in boys with a history of proximal hypospadias suggests that a common mechanism, such as aberrant androgen signaling, may predispose to both anomalies in otherwise normal boys [137]. Additionally, boys with a history of retractile testes may be at increased risk for testicular ascent [125,126,137]. Although spontaneous descent of acquired cryptorchid testes was reported to be associated with onset of puberty, these observations have not been replicated [138]. Preliminary reports indicate that the same adverse histologic features (e.g. loss of germ cells) found in primary UDTs are also found in acquired cryptorchid testes [118].

Given the potential for ascent of previously descended testes, a scrotal examination should be performed at every well-child check. Particular attention should be given to boys with a history of hypospadias, prior contralateral cryptorchidism or retractile testes. Children with a newly diagnosed non-scrotal testis found after six months of age should be referred to a surgical specialist.

Guideline Statement 5

Providers must immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development (DSD). (Standard; Evidence Strength: Grade A)

Approximately 20-30% of all patients with cryptorchidism have bilateral UDTs [57]. In this situation, it is critical to determine if the gonads are palpable or nonpalpable. A newborn with a male phallus and bilateral nonpalpable gonads is potentially a genetic female (46 XX) with congenital adrenal hyperplasia until proven otherwise. Failure to diagnose congenital adrenal hyperplasia can result in serious harm, as a high proportion of patients with this condition are unable to regulate their electrolyte levels and may present with shock, hyponatremia and hyperkalemia [139]. Thus, serum electrolytes should be monitored. Additionally, karyotype and a hormonal profile (including 17-hydroxyprogesterone levels, LH, FSH, testosterone and androstenedione) must be obtained with simultaneous consultation with a pediatric endocrinologist and a pediatric urologist. Although the initial electrolyte evaluation can be obtained by the first-line provider, consultation with the aforementioned specialists should be obtained due to the complexity of the condition and the need for coordinated multi-specialty care.

Guideline Statement 6

Providers should not perform ultrasound (US) or other imaging modalities in the evaluation of boys with cryptorchidism prior to referral, as these studies rarely assist in decision making. (Standard; Evidence Strength: Grade B)

In the hands of an experienced provider or specialist, more than 70% of cryptorchid testes are palpable by physical examination and need no imaging. In the remaining 30% of cases with nonpalpable testis, the challenge is to confirm absence or presence of the testis and to identify the location of the viable nonpalpable testis.

Factors that influence this recommendation against imaging (US, computed tomography [CT] scan or MRI) include imaging accuracy, cost, availability, rate of false positives and need for anesthesia in boys with retractile testes. Given the low cost and wide availability of US without need for anesthesia, it is the most commonly used test [140]. Nevertheless, US is non-contributory in routine use, with sensitivity and specificity to localize nonpalpable testis at 45% and 78%, respectively [141]. Typically, prepubertal intra-abdominal testes are not detected by US [142,143]. The cost and ionizing radiation exposure associated with CT scanning precludes its use. MRI with or without angiography has been more widely used with greater sensitivity and specificity but is deterred by cost, low availability and need for anesthesia [144-148].

At this time, there is no radiological test that can conclude with 100% accuracy that a testis is absent. Therefore, a surgical exploration, such as diagnostic laparoscopy (or open exploration), must be performed on all nonpalpable unilateral and many bilateral cryptorchid patients. Diagnostic laparoscopy is the gold standard with high sensitivity and specificity. If testicular absence is confirmed, the surgery is finished. If a testis is found, the surgery continues and laparoscopic or open orchidopexy is completed, thereby providing diagnosis and therapy simultaneously. Thus, regardless of preoperative radiological findings, these studies rarely assist in the decision making and may at times yield misleading information (such as absence when actually present or *vice versa*) [140,149].

Guideline Statement 7

Providers should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism. (Recommendation; Evidence Strength: Grade C)

A newborn boy with bilateral nonpalpable testes must be evaluated for disorder of sexual development (DSD) and should not be circumcised until after the workup is complete, even if a completely normal phenotypic penis is documented on examination. A 46 XX individual with severe congenital adrenal hyperplasia can be mistaken for a boy with bilateral cryptorchidism. The possibility of DSD, or other syndromes should also be entertained when unilateral or bilateral cryptorchidism is present with phallic anomalies, such as hypospadias or micropenis. (Further discussion of all possible scenarios is beyond the scope of this guideline.) In these cases, the presence of a nonpalpable gonad or proximal hypospadias significantly increases the risk of DSD. Radiological, genetic and endocrinological evaluations are indicated in cryptorchid males with disorder of sex development, in conjunction with hormone levels discussed in guideline statement 8 below.

Guideline Statement 8

In boys with bilateral, nonpalpable testes who do not have congenital adrenal hyperplasia (CAH), providers should measure Müllerian Inhibiting Substance (MIS or Anti- Müllerian Hormone [AMH]) and consider additional hormone testing to evaluate for anorchia. (Option; Evidence Strength: Grade C)

Masculinized infants with bilateral nonpalpable testes require prompt careful consideration and testing. Partially or completely masculinized infants with bilateral nonpalpable testes must be rapidly evaluated for 46 XX DSD due to life-threatening congenital adrenal hyperplasia (discussed above).

In contrast, if the infant with bilateral nonpalpable testes has normal penile development or micropenis and 46 XY karyotype, an evaluation to distinguish vanishing testis syndrome (bilateral congenital anorchia) versus bilateral abdominal testes is warranted. The latter is approximately 20 times more frequent than bilateral anorchia [150]. In order to avoid surgical exploration in the 46 XY male with anorchia, studies to assess for the presence of any viable testicular tissue should include serum MIS and consider additional hormone testing (inhibin B, FSH, LH, and testosterone).

Within the testis, Leydig cells respond to endogenous LH or exogenous hCG by producing testosterone while Sertoli cells respond to endogenous FSH by producing MIS and inhibin B. The failure of testosterone to increase after hCG stimulation alone is not diagnostic of anorchia; testicular dysgenesis with UDT may fail to respond to hCG stimulation. If the hCG stimulation test is used, it must be confirmed with a significant elevation in serum FSH and LH [151]. If the patient has anorchia and is less than 12 months of age, serum LH is high, FSH is high, MIS and inhibin B are undetectable, and testosterone is low [152]. In infants with anorchia, the postnatal testosterone surge will be absent. In the recent past, intramuscular injections of hCG with serum testosterone levels (hCG stimulation test) were recommended in the evaluation of bilateral nonpalpable testes to assess for Leydig cell function or absence. While the utility of hCG stimulation testing remains disputed, most recent studies suggest that a phenotypic 46 XY male with bilateral nonpalpable testes has isolated anorchia if undetectable levels of MIS and inhibin B with an elevated FSH level are present [153], making neither hCG stimulation testing nor surgical exploration necessary for the

Table 3:
Outcomes of follow-up from the referred cohorts with retractile testes

First Author	Location	Patients	Testes	Mean Age (yrs)	Mean Follow-up (yrs)	Resolution	Undescended
Agarwal [157]	USA	122	204	5	2.8	30%	32%
Bae [158]	Korea	43	64	3	4.4	45%	14%
La Scala [159]	Switzerland	150		5	3.8		<23%
Marchetti [160]	Italy	40	41	No Information	2.3	34%	25%
Stec [126]	USA	172	274	4	2.2	NI	7%

diagnosis of isolated anorchia [154]. If the endocrine markers of Sertoli and Leydig cell function are normal, then testicular tissue is present despite being not palpable and warrants surgical therapy.

Guideline Statement 9

In boys with retractile testes, providers should assess the position of the testes at least annually to monitor for secondary ascent. (Standard; Evidence Strength: Grade B)

Studies have reported an extremely broad range of incidence of testicular ascent out of the scrotum (between 2-45%) in boys with retractile testes [18,126]. It has been well documented that retractile testes are at increased risk for testicular ascent [18] which may be mechanistically related to the presence of a hyperactive cremasteric reflex, foreshortened patent processus vaginalis or entrapping adhesions. Seventy-seven percent of ascended cases are unilateral and located distal to the inguinal canal [18]. There are five series of the natural history of retractile testes (all referred) and three studies that address the prevalence of retractile testes among boys (this provides values of the prevalence in the general population). The outcomes of follow-up from the referred cohorts are summarized in Table 3. Given ascended and possibly retractile testes may also be at risk for germ cell maldevelopment and diminished fertility [118,155] and ascended testes are typically diagnosed in early or middle childhood [18], a physical examination including a testicular examination is recommended at least annually at every well-child visit in accordance with Bright Futures AAP recommendations [156].

Treatment

Guideline Statement 10

Providers should not use hormonal therapy to induce testicular descent as evidence shows low response rates and lack of evidence for long-term efficacy. (Standard; Evidence Strength: Grade B)

Overview of the Literature. Primary hormonal therapy with hCG or luteinizing hormone-releasing hormone (LHRH or gonadotropin-releasing hormone (GnRH)) has historically been used for many years, mostly in countries other than the United States. The action of hCG is virtually identical to that of pituitary LH although hCG appears to have a small degree of FSH activity as well. It stimulates production of androgens by the Leydig cells. The exact mechanism of action of increased androgens in stimulating testicular descent is not known but may involve an effect on the testicular cord or cremaster muscle. hCG is administered by intramuscular injection (IM) while GnRH can be administered intranasally. Multiple series have been published, but due to differences in patient age, treatment schedules, poor follow-up and possible inclusion of retractile testes, very divergent results have been reported. Studies show a significant risk of recurrence [161-167]. Although an individual study may show a reasonable effect in inducing testicular descent, the overall review of all available studies fails to document long-term efficacy. Many hCG dosage schedules are reported, ranging from 3-15 doses [168-170]. hCG appears to be as effective in 3 or 4 doses versus 9 or 10 doses. Studies that compared doses and dosing schedules within hormone type were of poor quality (see Appendix H for Quality Assessment of Individual Studies used in AHRQ Evidence Report) and are too heterogeneous to allow useful conclusions. Success rates for descent into the scrotum are 25-55% in uncontrolled studies, but decrease to only 6-21% in randomized, blinded studies. Distal inguinal testes in older boys are more likely to descend in response to hormonal treatment than abdominal testes. Repeated courses have offered little advantage. Side effects of hCG treatment seen in up to 75% of boys include increased scrotal rugae, pigmentation, pubic hair, and penile growth, which may regress after treatment cessation. A total dose of more than 15,000 IU of hCG must be avoided since it may induce epiphyseal plate fusion and retard future somatic growth. hCG has also been reported to cause a temporary increase in intratesticular pressure and to render the testes

hyperemic and enlarged. hCG treatment also increased the density per unit volume of the seminiferous tubules [171]. Others showed that treatment with hCG caused a temporary increase in germ cell apoptosis both in normal and cryptorchid testes. No long-term evaluation of hCG treatment was done [172].

Agonistic analogs of LHRH, such as Nafarelin or Buserelin, stimulate the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland and twice daily administration leads to decreased secretion of gonadal steroids by 4 weeks. This treatment is available as a nasal spray, but is only approved to induce testicular descent outside of the United States. Interpretation of results is again hindered by multiple treatment strategies. Success rates in uncontrolled studies range from 13-78% while better controlled investigations resulted in 6-38% [173,174]. The recognized side effects of GnRH (increased androgens, including increased penile or testicular size, scrotal erythema, or erections) seem to be less than seen with hCG. No long-term evaluation of LHRH treatment was done. For both hCG and GnRH it has been reported that hormonal treatment may harm the germ cells in one to three-year old cryptorchid boys who did not respond to the hormones used to induce testicular descent [175].

Nineteen publications from 14 distinct studies addressed the effectiveness of initial hormonal therapy for the treatment of cryptorchidism, but only three were of good quality [167,170,176-188]. Only seven studies included a placebo arm [167,176,177,181,182,185,187]. One study examined long-term fertility outcomes associated with the use of perioperative hormonal therapy [188]. Although there are numerous studies, most are only of fair or poor quality [170,189]. In the rare case in which a patient with cryptorchidism is deemed too high a risk for surgery, hormonal therapy may be considered as a primary treatment to induce testicular descent.

A few studies address the use of hCG to help distinguish a retractile testis from a true UDT. In a prospective uncontrolled study, 15 of 26 retractile testes (58%) descended with hCG ($p<0.001$) compared to 13 of 64 (20%) UDTs. Based on pretreatment physical examination, 100% of retractile testes descended if the testis was in the high scrotal position but only 40% descended if the testis was in the superficial inguinal pouch or inguinal region [189]. Another study that examined the use of hCG or GnRH to induce descent of the UDT also used hCG to treat five boys with retractile testes. The testes were noted to be dependent in the scrotum in all five boys after treatment [170].

Studies of LHRH and/or analogs to induce testis descent. Six double blind randomized controlled trials (all of fair or poor quality) examined the efficacy of LHRH in the treatment of cryptorchidism [167,176,177,181–183,185,187]. One study randomized 141 boys with cryptorchidism age 2 to 12 years to receive either LHRH 0.4mg or placebo intranasally three times a day for 4 weeks [177]. One hundred twenty-three (87%) participants included 62 (97 testes) in the LHRH group and 61 (90 testes) in the placebo group. Success rates immediately following treatment was not statistically significant (9.7% of LHRH compared to 1.6% of placebo).

One study (three papers from the original group) examined the effectiveness of LHRH in 1 to 12 year old boys [181–183]. Of 252 participants, 237 (281 UDTs) with complete follow-up were randomized to intranasal LHRH or placebo for 4 weeks. Treatment was unblinded 8 weeks after randomization 4 weeks of study drug followed by 4 weeks off treatment). Nine percent of boys randomized to LHRH achieved complete testicular descent compared to 8% in the placebo group. No testicle initially located above the external inguinal ring descended.

Other trials comparing LHRH to placebo had slightly higher rates of descent in the treatment arms relative to placebo, but were of poor quality. One assessed descent into the scrotum in 47 cryptorchid boys aged 1.5 to 10.5 years following intranasal LHRH for one month [185]. Although 18 testes (62%) had an initial «therapeutic effect» (defined as «significant move from the pretreatment location towards the bottom of the scrotum») with LHRH compared to one (3%) in the placebo arm, only six of the successfully treated testes

located at the scrotal neck remained descended at 6-12 months after treatment while two were located in the inguinal canal. Six to 12 months later, these last two testes had re-ascended out of the scrotum and required surgical repair.

Another poor-quality double-blinded RCT enrolled 50 boys aged 3 to 8 years with unilateral UDT to receive either intranasal LHRH 200ug or placebo six times a day for 28 days [187]. The primary outcome was complete descent into the scrotum assessed immediately following the completion of treatment and six months after randomization. Immediately following treatment, 20% 5 of 25) of the boys had responded to LHRH treatment. Of these, three were considered complete responses and two were «borderline.» Twelve percent 3 of 25) of patients in the placebo group experienced testicular descent immediately following treatment. Response to treatment was not durable, with only

Table 4:
Short-term testicular descent in two-arm, randomized, placebo-controlled studies

Study **N** **Length of Follow-up** **Quality**	**LHRH Dose**	**LHRH Frequency**	**LHRH Duration**	**LHRH Descent (%)**	**Placebo Descent (%)**
Olsen et al., 1992 [177] N= 123 4 Weeks Fair	400 µg	3 times daily	4 weeks	9.7	1.6a
De Muinck Keizer-Schrama and Hazebroek et al. 1986-1987 [181-183] N=237 8 Weeks Poor	200 µg	3 times daily	4 weeks	9.0	8.0
Hagberg and Westphal 1982 [185] N=50 4 Weeks Poor	100 µg	3 times daily	28 days	62.0	3.0
Karpe et al, 1983 [187] N= 50 6 Months Poor	100 µg	6 times daily	28 days	20.0	12.0
Wit el al., 1986 [167] N=49 8 Weeks Poor	400µg	3 times daily	28 days	37	18

CI= Confidence interval; LHRH= luteinizing hormone releasing hormone; N= number
[a]Statistical significance was evaluated and reported only for this comparison — p=0.12 (95% CI, 0.1 to 16.6), and not evaluated for any other study.

8% 2 of 25) in the LHRH arm and 4% 1 of 25) in the placebo arm still descended after 6 months. Neither this study nor the previous study identified factors that were associated with testicular re-ascent.

A similar RCT of poor quality randomized 49 boys (69 testes) aged 1.2 to 11.9 years to either intranasal LHRH 800ug or placebo three times a day for 28 days [167]. Thirty-seven percent in the LHRH arm had some degree of descent at 8 weeks compared to 18% of placebo-treated testes. However, complete testicular descent occurred in only 3 LHRH boys (9%) and in no placebo-treated boy.

Studies on hCG and/or its analogs to induce testis descent. Few studies [184,186,190] have examined the optimal dosing regimens of hormonal treatment to induce testicular descent (Table 5). Many have primarily focused on comparing higher vs. lower doses of hCG in order to ease administration and minimize side-effects. In one study, 183 cryptorchid boys were randomized to receive either hCG 1500 IU IM injection every other day for 14 days (88 patients) or four IM injections (100 IU/kg) every 4–5 days to a maximal dose of 3000 IU (95 patients).184 No difference in successful descent to the scrotum was noted with different doses. Boys in whom the UDT was initially in the mid-inguinal canal or lower had higher success rates than those who had testes located above the mid-inguinal canal.

Another study randomized 332 boys aged 1 to 13 years to receive either 2 lower dose hCG injections per week for 5 weeks or 1 higher dose hCG injection every 7–10 days for 3 weeks (essentially the same total dose in both arms).186 Success was assessed between 8 weeks and 6 months after full treatment. The dosing schedule with more injections had a significantly higher complete success rate than the schedule with fewer injections (39% vs. 30%, $p<0.05$).

A prospective observational study of good quality compared low-dose hCG (500 IU/week for 3 weeks) to a higher-dosing regimen (1,500 IU/m2 three times a week for 3 weeks) and failed to show a difference between the two doses [190]. Success was defined as complete descent into the scrotum and was assessed immediately following the treatment.

Studies comparing hormonal regimens to induce descent. Four studies have compared the effectiveness of hCG vs LHRH therapy to induce testicular descent (Table 6) [170,176,178,191]. One study is a double-blind randomized

Table 5:
Testicular descent in studies comparing dosages of hCG

Study N Length of Follow-up Quality	**hCG Dose**	**hCG Frequency**	**hCG Duration**	**Descent, Side Unspecified (%)**	**Descent, Unilateral (%)**	**Descent Bilateral (%)****
Aycan et al., 2006 [190] N=35 3 weeks Good	500 IU	Once a week	3 weeks	66.7	NR	NR
	1,500 IU/m2	3 times a week	3 weeks	57.1	NR	NR
Forest et al., 1988 [184] N=183 2-3 weeks Poor	1,500 IU	Every other day	14 days	NA	50.8	48.3
	100 IU/Kg to a max of 3,000 IU	4 injections every 4-5 day interval	NR	NA	50.9	50.0
Hesse and Fischer, 1988 [186] N=332 8-12 weeks Poor	300-1,000 IU*	2 injections a week	5 weeks	NA	44.2	40.8
	1,000-5,000 IU±	1 injection every 7-10 days	3 weeks	NA	35.5	30.9

hCG=human chorionic gonadotropin; IU=international unites; NA=not applicable; NR=not reported

*1-2 yrs old: 300 IU; 2-6 yrs old: 500 IU; 6-13 yrs old: 1,000 IU

±1-3 yrs old: 1,000; 3-6 yrs old: 1,500; 6-10 yrs old: 3,000; 10-13 yrs old: 5,000

**No comparisons were statistically significant

control trial comparing the effectiveness of intranasal LHRH, IM hCG, and placebo and is of good quality.170 Boys with unilateral (n=29) or bilateral (n=4) UDTs were assessed immediately following treatment and then monthly for up to three months after the conclusion of full treatment. One participant in the hCG arm (6%) had complete descent compared to three in the LHRH arm (19%) without a statistically significant difference. A parallel uncontrolled study of 13 boys examined retractile testes treated with the same hCG regimen and 38% had complete descent of the retractile testis into the scrotum supporting the possible effectiveness of hCG to help identify retractile testes [170].

Other studies focused on combinations of hormonal therapy to determine if multidrug regimens worked better than single agents. One study [178] compared the effectiveness of four different hormonal regimens in 155 boys with unilateral palpable cryptorchidism age 10 to 48 months: hCG vs hCG/hMG vs LHRH vs LHRH/hCG [178]. Short term success was about 20% for all groups. The overall long-term success rate (as qualified by authors of these studies) in the study was 15%, with 13-19% success rates within the four groups. This study also recorded side effects – 74% of boys on hCG and 5% of those on LHRH initially reported signs of androgenization, such as penis growth that receded at long-term follow-up and erections.

Two papers from a single study compared intranasal buserelin to inhaled placebo with descent checked three months after the conclusion treatment followed by IM hCG [179,180]. Thirty-six percent of boys in the Buserelin/hCG group were noted to have complete testicular descent at three months, as opposed to 11% 2 of 19) in the placebo/hCG group ($p<0.01$). However, one must note that all but one of the testes that responded to treatment were originally located in the prescrotal position.

Another study examined 324 boys with palpable unilateral or bilateral UDTs who were treated with one of five hormonal regimens: hCG, hMG, LHRH, hMG and hCG vs LHRH/hCG [191]. Every six months a new treatment was randomly assigned prospectively for newly enrolling boys aged 6 months to 13 years. hCG alone was the most effective treatment (35%), followed by LHRH/hCG (30%), LHRH alone (29%), and hCG/hMG (26%), and hMG alone (0%). There was no significant difference in effectiveness between the four effective therapies. However there was no placebo control group and follow-up was only 6 months.

A fair-quality study assessed the effectiveness of a four week treatment hCG, LHRH or placebo in boys aged 1.8-13 years [176]. Complete follow-up was available in 220 boys. For bilateral cryptorchidism, 23% treated with hCG had complete descent of both testes into the scrotum, as opposed to 9% in the LHRH group and 0% in the placebo group in short term follow-up ($p=0.001$). With unilateral UDTs, hCG was effective in inducing complete descent in 15% as opposed to 0 percent in either the LHRH or placebo groups ($p=0.02$).

Table 6:
Testicular descent in studies comparing LHRH with hCG*

Study **N** **Length of Follow-up** **Quality**	**hCG** **(%)**	**hCG+HMG** **(%)**	**LHRH** **(%)**	**LHRH+hCG** **(%)**
Rajfer et al., 1986 [170] N=33 12 weeks Good	5.9	NA	18.8	NA
Bertelloni et al., 2001 [178] N=155 6 months Poor	18.9	12.8	12.8	15.0
Esposito et al., 2003 [191] N=324 4-6 weeks Poor	34.5	25.9	29.4	29.6

hCG=human chorionic gonadotropin; HMG=human menopausal gonadotropin; LHRH=luteinizing hormone releasing hormone; NA=not applicable
*No comparisons were significant

Use of hormones to improve fertility (rather than to induce testicular descent). No reports on long-term fertility outcomes following isolated hormonal therapy (no surgery at any time) were found in our literature search. Hormonal therapy may have prophylactic value to optimize germ cell maturation and/or sperm production (in distinction from the use of hormones to induce testicular descent). LHRH or hCG administration prior to orchidopexy has been shown to improve the fertility index on biopsies obtained at the time of orchidopexy [179,193]. One small study showed that use of LHRH analogue in boys with very poor testis histology (total germ cell count less than 0.2 germ cells/tubule in UDT and less than 0.6 germ cells/tubule in CDT) has an advantageous effect on the developing germ cells. Patients who had no germ cell count on the biopsy did not show improvement after hormonal therapy but those who had some germ cells demonstrated improvement [192].

In another good-quality prospective study, 42 boys with 63 UDTs were prospectively randomized to receive either orchidopexy alone (21 patients) or with neoadjuvant GnRH therapy (21 patients). In both groups testicular biopsies for histology fertility index were performed during orchidopexy. Preoperative GnRH significantly improved the fertility index in primary cryptorchid testes. The average fertility index increased above the prognostically important threshold of 0.6, improving the individual fertility potential. The most advantageous fertility prognosis was achieved with neoadjuvant GnRH administration for bilateral orchidopexy within the first year of life [193].

One good-quality study explored long-term fertility outcomes of hormonal therapy as an adjunct to orchidopexy. They compared 15 cryptorchid boys who underwent orchidopexy followed by Buserelin every other day for 6 months to 15 age-matched controls who were treated by orchidopexy alone. The primary outcomes were semen analysis parameters measured in early adulthood (mean age=19 years). Those with surgery and Buserelin had significantly higher sperm counts (90 million sperm per ejaculate compared to 1 million in the surgery only group, $p<0.001$). In addition, 11% percent of those who received surgery and hormone therapy had normal morphology as opposed to none in the surgery alone group [188].

This improvement in germ cell count and maturation may eventually reflect a better prognosis for fertility. It is still unclear if this effect on testis histology persists into adulthood improving fertility and paternity potential or disappears once the hormonal stimulus is removed.

Guideline Statement 11

In the absence of spontaneous testicular descent by six months (corrected for gestational age), specialists should perform surgery within the next year. (Standard; Evidence Strength: Grade B)

In a 10 year, retrospective study of 1,235 consecutive boys with cryptorchidism referred to pediatric urology practice, all patients with eventual spontaneous descent initially presented by six months (corrected for gestational age). Of those boys initially presenting beyond age six months no patient had spontaneous testicular descent [57].

Orchidopexy in the first 18 months of life is recommended to preserve available fertility potential. In the majority of cases the total number of germ cells is within the normal range in cryptorchid testes during the first six months of life, but about 25% of the cryptorchid boys are born with a reduced number of germ cells [194]. After 15 to 18 months of age some cryptorchid boys lack germ cells in the testes and the number of boys without germ cells in a testicular biopsy increases to about 40% in bilateral cryptorchid boys at 8-11 years of age [130]. In total the number of germ cells in undescended testes remains low and does not increase with age. Histologic examination of cryptorchid testes has shown that testes that remain undescended are associated with progressive loss of germ and Leydig cells [119,120,130]. The UDT fails to show normal maturation at both three months and five years of age. At three months of age, the fetal gonocytes are transformed into adult dark (Ad) spermatogonia. At five years of age, the Ad spermatogonia become primary spermatocytes. Both of these steps are abnormal in the UDT, and to a lesser extent, the contralateral descended testis. Previous beliefs that the UDT was normal between birth and 1 year of age are incorrect, since they were derived from counts of all germ cells without taking into account whether maturation was occurring. After two years of age, thermal effects on the testis being left out of position are seen possibly independent of the endocrinologic effects.

A retrospective study examined the testis biopsy total germ cell counts in 226 cryptorchid boys aged 6 months-16 years [195]. Of 184 patients with unilateral UDT, 87 also underwent biopsy on the contralateral descended testis. A total of 42 patients had bilateral UDTs. Age matched comparisons were made between fertility index measurements of the UDT and those previously reported of normal testes. Additional case matched comparisons of fertility indexes were made in those children who underwent biopsy of the UDT and its contralateral descended mate. When comparing undescended to descended testes, there was no significant difference in the fertility index of patients 1 year old or younger but fertility index differences were statistically significant in all of the other age groups. Fertility index measurements were significantly decreased from normal expected values in all age groups with unilateral cryptorchidism and in all but the 13 to 18-month-old group with bilateral cryptorchidism.

Guideline Statement 12

In prepubertal boys with palpable, cryptorchid testes, surgical specialists should perform scrotal or inguinal orchidopexy. (Standard; Evidence Strength: Grade B)

While it is optimal to perform surgery for the cryptorchid testis by 18 months of age (see previous discussion in statement 11), there are clear benefits to performing orchidopexy in all prepubertal boys at the time of diagnosis of a cryptorchid testis [196]. With regard to fertility, there has not been any direct assessment or long-term follow-up of patients with early vs. late orchidopexy. Nevertheless, even though progressive and adverse histologic changes will occur in the cryptorchid testis prior to puberty, there is evidence to suggest that there are likely fertility benefits that can still be realized with surgical correction of the cryptorchid testis prior to puberty, even if not performed in the first 18 months of life [197-200]. With respect to cancer risk, it is widely recognized that the cryptorchid testis isassociated with an inherent risk of malignant degeneration. Early reports of this increased risk were likely overestimated and recent review of the literature suggests that the overall relative risk is 2.75-8 [196]. There is now ample evidence to suggest that this risk is decreased when orchidopexy is performed prior to puberty [196,201-203]. Prepubertal orchidopexy results in a two to six fold reduction in the relative risk compared with postpubertal orchidopexy. In the post pubertal child with cryptorchidism, consideration should be given to performing an orchiectomy or biopsy, although there needs to be careful consideration of other factors including associated medical conditions, anesthetic risk, and status of the contralateral testis. Further discussion of the adult with cryptorchidism is beyond the scope of this guideline.

Orchidopexy remains one of the most common urologic procedures performed in pediatric patients. The technique for the standard two- incision approach (inguinal and scrotal) has not changed in decades. The inguinal portion of the procedure is performed to mobilize the cord structures and gain adequate length for repositioning the testis in the scrotum, along with closure of a patent processus vaginalis, when present. The secondary scrotal incision is performed to create a subdartos pouch for placement and fixation of the testis. This can be done as an outpatient procedure with minimal morbidity. Given the long standing well recognized historical success of this common procedure, there is a paucity of recent literature to document its effectiveness. However, recent studies that have evaluated open surgical intervention for the cryptorchid testis, even with inclusion of testes that are intra-abdominal, the overall success has been documented to be greater than 96% (range from 89-100%) (See Table 7). Subsequent atrophy of the testis is very uncommon and reported to be less than 2%. (See Table 8).

Table 7:
Success rates after orchidopexy for nonpalpable testes (open or laparoscopic, mixed techniques-primary, 1 or 2 stage Fowler-Stephens)

Author Country	Quality	Total Participants/ techniques	Total Testicles	% Success (N Testicles Treated)
Stec et al., 2009 [208] United States	Good	136 Open or laparoscopic	156	89.1 (92)
Baker et al., 2001 [209] United States	Poor	226 Laparoscopic	263	97.2 (178)
Chang et al., 2001 [210] United States	Poor	80 Laparoscopic	92	100 (66)
Denes et al., 2008 [67] Brazil	Poor	46 Laparoscopic	54	96 (26)
Dhanani et al., 2004 [211] United States	Poor	74 Open or laparoscopic	83	100 (28)
Kim et al., 2010 [212]* South Korea	Poor	67 Laparoscopic	86	98 (49)
Moursy et al., 2011 [89] Egypt	Poor	66 Laparoscopic	76	100 (28)
Pooled %		Total: 695	Total: 810	96.4

N=number
*Controlled for location. All studies were retrospective cohorts.

For the palpable testis that is low lying, single incision orchidopexy is also a viable option. This primary scrotal approach was introduced by Bianchi and Squire [204] and has since gained widespread use and has been documented in retrospective studies to be equally effective to two incision orchidopexy in selected patients with testes located distal to the external inguinal ring that can be mobilized adequately via a scrotal incision [205,206]. The primary single incision scrotal approach has potential advantages with respect to enhanced recovery and cosmesis, as well as reduced operative time. This technique can be effective even when there is a patent processus/hernia sac present. Adequate high ligation of the sac may be achieved in the many cases even though the external oblique fascia is not opened [207]. In cases where adequate ligation cannot be achieved, the procedure can still be converted to a conventional two incision technique.

Guideline Statement 13

In prepubertal boys with nonpalpable testes, surgical specialists should perform examination under anesthesia to reassess for palpability of testes. If nonpalpable, surgical exploration and, if indicated, abdominal orchidopexy should be performed. (Standard; Evidence Strength: Grade B)

In boys that are brought to the operating room with a nonpalpable testis, a thorough examination should be performed following induction of general anesthesia to further determine if the testis is palpable. If the testis is palpable, open orchidopexy should be undertaken. However, if the testis remains nonpalpable, then a decision needs to be made to either pursue laparoscopic or open exploration. Laparoscopy in the treatment of cryptorchidism has two roles: (1) as an exploratory tool to locate a nonpalpable undescended testicle in the abdomen; and (2) as a minimally invasive method of orchidopexy. Previous studies evaluating laparoscopy for determining the location of the testicle have reported similar findings to open exploration [213,214]. Success of the ensuing surgeries was also similar, regardless of exploratory approach. However, given technical advancements and increased familiarity of younger urologic surgeons with minimally invasive techniques, laparoscopy has become the preferred method of exploration for the nonpalpable testis for most pediatric urologists. Nevertheless, depending on the training and comfort level of the individual surgeon with laparoscopic techniques, open surgical management of the intra-abdominal testis is also appropriate given the lack of evidence to demonstrate that laparoscopic techniques have distinct advantages over open techniques with respect to success of the orchidopexy itself [69,215–217].

If an intrabdominal testis is found with anatomy that is felt to be appropriate for salvage, one of three surgical options can be chosen regardless of whether one approaches the testis laparoscopically or with an open approach. The three types of surgical repair that one may consider are primary orchidopexy, one-stage Fowler Stephens (FS) orchidopexy, and two-stage FS orchidopexy. Extensive review of previous studies evaluating the effectiveness of these

Table 8:
Atrophy rates after orchidopexy for nonpalpable testes

Author Country	Quality	Total Participants	Total Testicles	% Atrophy (N Testicles Treated)
Baker et al., 2001 [209] United States	Poor	226	263	2.2 (178)
Denes et al., 2008 [67] Brazil	Poor	46	54	4 (26
Humphrey et al., 1998 [83] United Kingdom	Poor	48	20	0 (8)
Moursy et al., 2011 [89] Egypt	Poor	66	76	0 (33)
Radmayr et al., 2003 [92] Austria	Poor	84	57	0 (28)
Pooled %		Total: 470	Total: 470	1.83

procedures reveals that the weighted success rate for all three approaches exceeds 75%, with an overall reported rate of 96.4% for primary orchidopexy, 78.7% for one-stage FS, and 86% for two-stage FS. (See Tables 9 and 10). While initial review of these success rates may suggest that primary orchidopexy is superior to the two other FS approaches, one must take into account that all of these studies are observational cohort designs and are limited in their conclusions due to numerous factors including surgeon bias as to what procedure was performed and lack of randomization of the surgical techniques in many of the studies. This limits one's ability to make any definitive conclusions regarding the superiority of primary orchidopexy to either the one- or two-stage FS approach. Nonetheless, these studies do provide some insight into regarding the surgical success of these different procedures. There is clear consensus that if the testicular vessels are long enough to reach into the scrotum, then the vascular supply should be spared and a primary orchidopexy is performed in preference to FS orchidopexy. One should make every effort to preserve the primary blood supply to the testis. The FS methods are reserved for cases in which the vessels are too short to allow adequate repositioning of the testis into the scrotum. In the FS approach, the testicular vessels are divided and the blood supply to the testis is maintained through collaterals, including the artery of the vas deferens. When the FS orchidopexy is done in one stage, the testicular vessels are ligated and the testicle is immediately moved down into the scrotum; in the two-stage approach, only ligation is done at the time of the first stage, without mobilization of the testis. The patient is then followed for three to six months, to presumably allow for improved collateral circulation to develop. A second stage repair is then undertaken with repositioning of the testis in to the scrotum [67,83,89,92,208-212]. While results from previous studies may suggest that the two-stage approach is superior to the one-stage approach, it is difficult to make this determination since the groups of patients and their associated testicular vessel anatomy in these studies were not necessarily the same. Thus, specific treatment choices were most likely made on the basis of where the affected testicle was located and in part, surgeon preference. Because these studies did not control for these variables, the results can only be interpreted as providing noncomparative data on outcomes in groups with differing clinical presentations. Therefore, when a primary orchidopexy cannot be performed in cases where the testicular vessels are too short, the decision to perform a one-stage or two-stage FS orchidopexy is left to the discretion for the surgeon based on the location of the testis, associated vascular supply to the testis, and the anatomy of the peritesticular structures.

Guideline Statement 14

At the time of exploration for a nonpalpable testis in boys, surgical specialists should identify the status of the testicular vessels to help determine the next course of action. (Clinical Principle)

The identification of the testicular vessels should be the end point of any exploration for a nonpalpable testis. As previously mentioned in the guideline, radiologic imaging is typically not helpful in this situation because of its lack of both sensitivity and specificity for the identification of an abdominal testis. Several surgical approaches exist for the surgeon caring for the patient with nonpalpable testis, which include laparoscopic exploration, inguinal exploration or scrotal exploration. Each approach offers benefits as well as limitations. Regardless of approach, the objective of the procedure is the same, which is to either identify the previously nonpalpable testis or identify the termination of the testicular vessels. The testicular vessels may end blindly anywhere along the course of descent

Table 9:
Success rates after one-stage Fowler-Stephens for nonpalpable testes

Author Country	Quality	Total Participants	Total Testicles	% Success (N Testicles Treated)
Stec et al., 2009 [208] United States	Good	136	156	63 (27)
Baker et al., 2001 [209] United States	Poor	226	263	74.1 (27)
Chang et al., 2001 [210] United States	Poor	80	92	84 (19)
Chang et al., 2008 [218] United States	Poor	48	48	94.3 (35)
Comploj et al., 2011 [219] Austria	Poor	41	50	79 (33)
Denes et al., 2008 [67] Brazil	Poor	46	54	33 (3)
Kim et al., 2010 [212]* South Korea	Poor	67	86	82 (11)
Pooled %		Total: 644	Total: 749	78.7

N=number
*Controlled for location. All studies were retrospective cohorts.

of the testis. The exact location may range from the retroperitoneum along the psoas, the inguinal canal or commonly the scrotum itself.

On physical examination, a vanishing testis may manifest as a testicular «nubbin,» which can be palpated in the scrotum, and is representative of a completely atrophic testis. The identification of a vanishing testis at the time of exploration is the end point of surgical exploration [220]. Typically a hemosiderin deposit will be visible on the pathologic specimen. A potential complication resulting from this approach can be inadvertent injury to a long-looping vas that could occur during surgical exploration or there may be an erroneous diagnosis, although the risk of these unfavorable outcomes is unknown.

The advent and miniaturization of laparoscopic instrumentation has afforded the surgeon the ability to inspect the retroperitoneum within the abdominal cavity with minimal morbidity. This allows the surgeon to perform an exhaustive search from the level of the kidney to the internal ring. In situations where the testis is identified, a decision is made to proceed with either orchidopexy or orchiectomy. When the testis is not identified, the surgeon must identify the vessels. The vessels may end blindly within the abdomen or exit the internal ring. The identification of the vas deferens should not guide management as it is of distinct embryologic origin and may not be fused to the testis. Of note, in cases of vanishing testes that have descended distal to the internal ring, the testicular vessels typically are less robust as they enter the internal ring as compared to the normal descended side. When the vessels end blindly in the retroperitoneum, the surgeon may terminate the procedure or explore distal to the internal ring to confirm the absence of testicular tissue or remove a vanishing testis. In situations where the vessels clearly enter the internal ring, the surgeon must explore either the inguinal canal or the scrotum, depending on the surgeon's preference. If a palpable nubbin is present, in the scrotum, potentially representing a vanishing testis, then scrotal exploration can safely be performed [220]. Advocates of the inguinal approach feel that this gives the surgeon the best approach to confirm the vessels are indeed traversing the internal ring. Regardless of the approach, the specimen should be sent for pathologic confirmation, to confirm a vanishing testis and no presence of malignancy. Special mention should be made regarding a «peeping testis.» This phenomenon may occur when a patent processus vaginalis prevents palpation of the testis. When the abdomen is insufflated with laparoscopy, the testis travels through the internal ring and can be palpated. This patient can be managed safely with either laparoscopic orchidopexy or inguinal orchidopexy.

Guideline Statement 15

In boys with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a boy has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age. (Clinical Principle)

Table 10:
Success rates after two-stage Fowler-Stephens for nonpalpable testes

Author Country	Quality	Total Participants	Total Testicles	% Success (N Tes-ticles Treat-ed)
Stec et al., 2009 [208] United States	Good	136	156	67.6 (37)
Baker et al., 2001 [209] United States	Poor	226	263	87.9 (58)
Chang et al., 2001 [210] United States	Poor	80	92	86 (7)
Chang et al., 2008 [218] United States	Poor	48	48	80 (10)
Comploj et al., 2011 [219] Austria	Poor	41	50	82 (17)
Denes et al., 2008 [67] Brazil	Poor	46	54	88 (25)
Dhanani et al., 2004 [211] United States	Poor	74	83	98 (49)
Kim et al., 2010 [212]* South Korea	Poor	67	86	67 (3)
Moursy et al., 2011 [89] Egypt	Poor	66	76	88.8 (36)
Pooled %		Total: 784	Total: 908	86.0

N=number
*Controlled for location. All studies were retrospective cohorts.

When operating on an abdominal testis, the surgeon may encounter situations that preclude an orchidopexy. These situations may arise when the patient has an atretic and/or short vas deferens, very short testicular vessels that place the testis high within the retroperitoneum, a dysmorphic testis or a testis in a postpubertal male. In these situations, an orchiectomy may be prudent in the presence of a normal contra-lateral descended testis. To help determine whether orchiectomy is advisable, it may be appropriate to perform an intra-operative biopsy of the affected testis, but the utility of this is not proven. If an orchiectomy is performed, then the patient and family should be counseled about the importance of wearing protective gear during sporting activity. Another option for treatment is autotransplant of the undescended testis, however this has been done sparingly [221-224].

Guideline Statement 16.

Providers should counsel boys with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk. (Clinical Principle)

There are two major long-term concerns for patients with a history of cryptorchidism: an increased incidence of developing testicular cancer and a heightened risk of subfertility [225-227].

Testicular malignancy. Men with a history of cryptorchidism have an increased risk of testicular cancer. The increased incidence of malignancy in cryptorchid testes varies from 49/100,000 (0.05%) to 12/1,075 (1%) [227,228]. Early reports stated a significantly higher risk of carcinoma in an abdominal testis; however, inclusion of boys with abnormal karyotype and/or genitalia may have confounded the results [229,230]. One hypothesis for the etiology of the testicular cancer is that it is related to the abnormal position of the testis. However, the mild increase in cancer in the contralateral descended testis argues for an intrinsic testicular abnormality as the cause [231. Although earlier findings have suggested that orchidopexy does not decrease the risk of testicular cancer, more recent studies have demonstrated that orchidopexy performed before puberty decreases the risk of testis cancer compared to those boys with cryptorchidism who undergo orchidopexy after puberty [231]. However, the risk of testis cancer does not decrease to that of normal controls even when orchidopexy is performed at an early age [231,232]. The increase in the incidence of malignancy in the cryptorchid testis warrants close follow-up, especially after puberty. Every previously cryptorchid boy should be taught how to perform a monthly testicular self-examination after puberty to potentially facilitate early cancer detection.

Fertility. Formerly bilateral cryptorchid men have greatly reduced fertility compared with men with a history of unilateral cryptorchidism and the general male population [233-237]. One retrospective study showed a paternity rate of 62% (38% infertile) in formerly bilaterally cryptorchid men compared with a matched control group of 94% (6% infertile), indicating a six fold increased risk [238]. In contrast, unilaterally cryptorchid men had a paternity rate of 89.5%, which is similar to the level of fertility found in other studies of the general population (94%). Examination of subfertility, or time to pregnancy, shows that bilaterally cryptorchid men have greatly increased waiting times to pregnancy (33.9 months compared with 11.1 months for unilateral UDTs and controls). An assessment of paternity among men with monorchidism, whether as a result of an absent testis or orchiectomy, found no difference compared with those with unilateral cryptorchidism or control men [239]. Another study examined the association of pretreatment UDT location with fertility rates and various hormone levels (inhibin B, LH, FSH, testosterone) in adulthood [240]. The authors concluded that pre-operative location in men with previous unilateral UDT is not a major determinant of fertility as measured by paternity reporting, sperm count, or hormone levels. A long-term study followed 91 young adults with previous surgical correction of unilateral UDT and 19 with bilateral UDT.241 Evaluation compared initial testis bilateral testis biopsy histopathology with adult hormonal studies (LH, FSH, testosterone, inhibin B) and semen analysis. No significant differences in semen analysis parameters were seen among the normal v. abnormal germ cell groups. In unilateral UDT, sperm density and sperm count in the abnormal adult dark (Ad) spermatogonia per tubule group remained within normal range but were significantly decreased ($p=0.005$ and $p=0.028$). FSH levels were significantly higher in patients with unilateral UDT with abnormal Ad spermatogonia counts but remained within normal range ($p=0.009$). In bilateral UDTs, sperm density was below normal range and significantly decreased in the abnormal Ad spermatogonia group ($p=0.05$). Further, FSH level, sperm count, and sperm motility for the abnormal Ad spermatogonia per tubule group were outside normal clinical range, but these results were not statistically significant. Total germ cell count via biopsy at orchidopexy was not associated with significant changes in hormone levels or semen analysis results in adulthood, but Ad spermatogonia counts were more significant. Testis biopsy at orchidopexy may have limited use in predicting future fertility in unilateral UDT but may be more clinically useful in predicting fertility potential for those with bilateral UDTs.

Recently, a long-term study followed 91 young adults with previous surgical correction of 963 bilateral UDT and 87 with unilateral UDT. Evaluation compared initial testis biopsy histopathology with adult hormonal studies (FSH) and semen analysis. In bilateral cryptorchidism the mean age corrected number of germ cells per transverse tubule positively correlated to sperm density and to volume of pair of testes and negatively correlated to serum FSH. In cases of no germ cells there was approximately a 75 to 100% risk of infertility, based on a lack of germ cells in one or both testes [242]. In unilateral cryptorchidism, a lack of germ cells in testicular biopsies taken at surgery was associated with approximately 33% risk of later infertility. Between ages 2 and 12 years the timing of unilateral orchidopexy may vary without an effect on subsequent fertility potential. When biopsy at surgery lacks germ cells in unilateral cryptorchidism, there is an approximate 33% age independent risk of subsequent infertility. Otherwise patients may be fertile after unilateral orchidopexy between ages 2 and 12 years [243,244].

Future research

More research is needed to address long-term follow-up of surgically treated ascending UDTs. These studies should compare fertility and testis cancer rates with UDTs identified and treated in infancy.

Additionally, a randomized control trial is needed to compare long-term testicular function after one-stage versus two-stage laparoscopic Fowler-Stephens abdominal orchidopexy. While a one-stage approach has a slightly lower success rate, the two-stage approach has added risks. A similar comparison of open versus laparoscopic abdominal orchidopexy could be employed.

Continued research should also investigate the effects of genetic susceptibility and environmental toxins on the risk of cryptorchidism and/or testicular maldevelopment.

Studies of paternity in patients surgically treated for cryptorchidism, and its correlation with semen analysis, androgen function, and testis histology data as available, are needed.

Long-term outcome data are needed in boys with monorchidism due to a vanishing testis and monorchidism; additional research should whether excision of the vanishing testis is indicated and the necessity for scrotal fixation of the contralateral testis.

Finally, further studies are needed to determine whether orchiopexy between six and eighteen months of age is superior to later surgical treatment in improving fertility potential in adulthood.

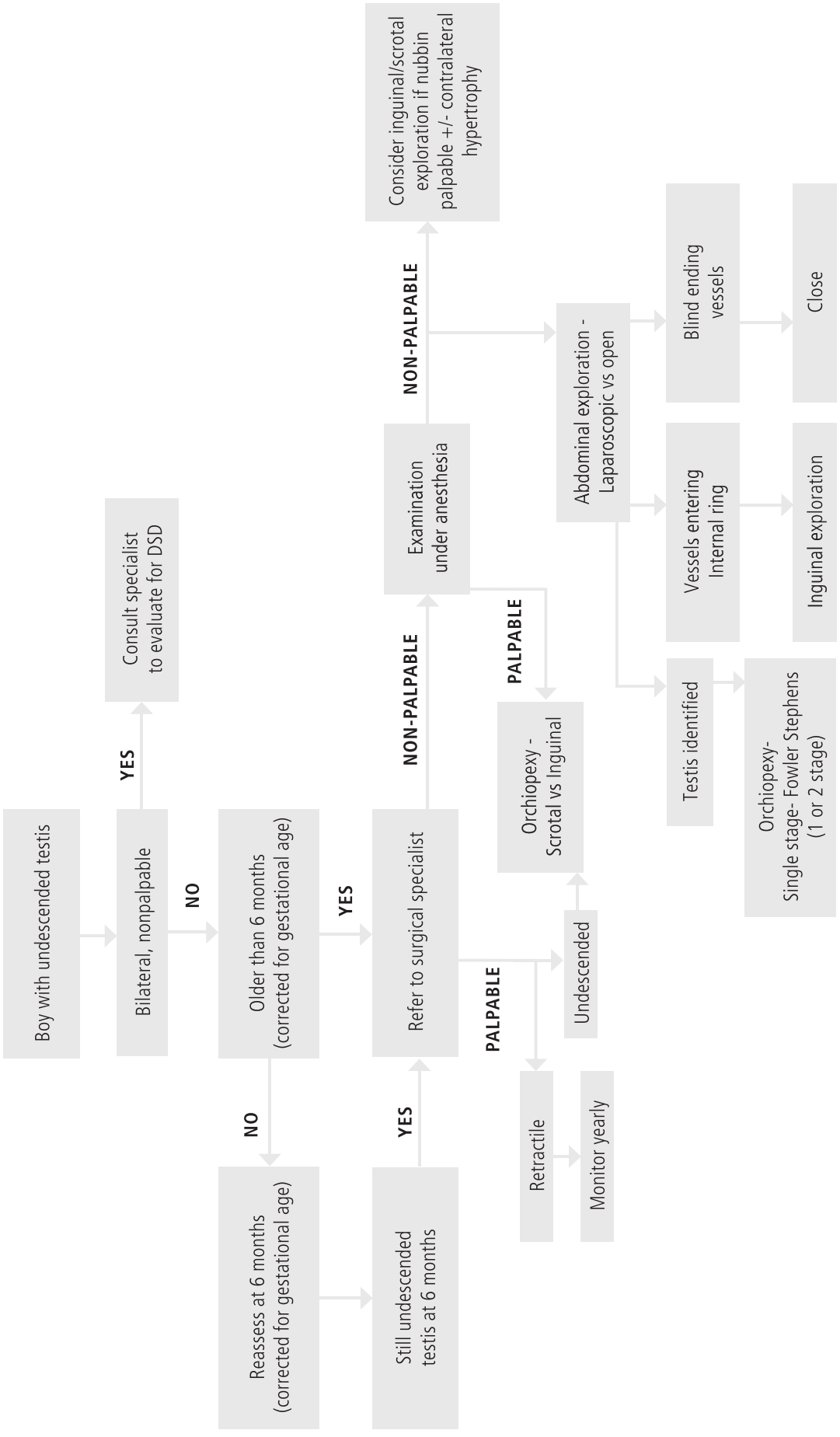

Fig. 1. Evaluation and Treatment of Cryptorchidism

Appendix A

Clinical data on cases of testicular ascent

References	No. Cases		Position (at surgery)				No. Hernias/ Testes	No. Side (unilat/ bilat)
		Mean Age (yrs)	Prescrotal/ High Scrotal	Superficial Inguinal Pouch	Inguinal	Abdominal		
Myers and Officer [10]	7	6.6	—	—	—	—	—	3/4
Atwell [28]	10	9.4	7	1	2	—	10/11	9/1
Schiffer et al [29]	3	6.7	—	2	—	—	—	3/0
Belman [30]	6	—	1	4	1	—	3/6	—
Robertson et al [31]	13	8.1	—	—	—	—	10/13	13/0
Eardley et al [32]	34	7.5	15	19	3	—	24/39	29/5
Mayr et al [33]	19	7.0	5	9	13	—	14/27	19/2
Rabinowitz and Hulbert [34]	21	7.2	2	19	2	—	12/23	19/2
Gracia et al [35]	36	7.0	8	5	32	1	18/46	11/8
Clarnette et al [36]	25	7.6	—	—	—	—	10/33	17/8
Rusnack et al [37]	91	7.4	79	11	—	1	39/91	91/0
Total No. (%)	265		117 (48)	70 (29)	53 (22)	2	140/289 (48)	77 (23)

*As published in Journal of Urology

Barthold JS and Gonzalez R: The epidemiology of congenital cryptorchidism, testicular ascent and orchiopexy. J Urol 2003; 170: 2396.

Appendix B

Evidence table of studies examining the association of CAG repeats in the AR gene and cryptorchidism

Sasagawa 2000	**Ferlin 2005**	**Silva-Ramos 2006**	**Radpour2007**
Study characteristics			
Tokyo, Japan Case-control	Padova, Italy Case-control, prospectively recruited.	Porto, Portugal Case-control, prospectively recruited from two hospitals.	Tehran, Iran Case-control
Sample characteristics			
48 Japanese Pts w/crypto (age 1-32, mean 13 yrs); 17 BL, 29 UL UDT and 2 w monorchia). Controls: 100 males w/ proven fertility	105 ex-cryptorchid men (55 UL; 50 BL) who presented no other obvious causes of testicular damage. Age 23–42 yrs, age at orchidopexy 1-12 years. Precise location of testes at surgery could not be determined in all cases. 115 fertile non-cryptorchid controls whose wives were pregnant.	42 cryptorchid boys (age 3 - 77; mean 20.9 yrs); 7 BL, 35 UL (6 w/ clinically patent processsus vaginalis (PPV) in the contralateral; 3 UL ectopic; 2 UL intraabdominal). Six w/ family hx of crypto. (Cases should not present any other genital malformation). 31 controls (hospital staff) w/o personal or family hx of genital abnormalities; age 22-69 yrs, mean 42 yrs.	76 unrelated Iranian males w/ crypto (27 UL; 49 BL) w/o spontaneous descent. 190 healthy fertile controls. All studied patients were 46,XY males. Patients with visible cytogenetic aberrations were excluded.
Measurement of CAG repeats			
Genomic DNA from peripheral leukocytes amplified by PCR (30 cycles). Repeat length analysis by GeneScan.	Genomic DNA extracted from peripheral blood leucocytes. AR exon 1 amplified in two different PCR reactions under the same standard conditions with 8% dimethylsulphoxide and same cycle.	Genomic DNA extracted from blood samples stored at -20°C & amplified by PCR.	Genomic DNA from peripheral blood lymphocytes was amplified by PCR in 2 different reactions. Genotyping done blinded to case-control status.
Cryptorchidism ascertainment			
Not indicated.	Cohort of men previously orchidopexied.	Sole inclusion criterion was the presence of crypto.	Ultrasound examination of the testes.
CAG repeats among cryptorchidism cases (mean ± SD; second line range and median)			
23.4 ± 0.48 (overall) Range: 16 – 32; median: 23 23.7 ± 0.64 (31 UL) Range: 18 – 32; median: 24 23.8 ± 0.69 (17 BL) Range: 16 – 28; median: 23; (SE rather than SD provided)	21.8 ± 2.9 (overall 105 crypto) Range: 12 – 29; median: 22 21.8 ± 3.0 (55 UL) Range: 12 – 29; median: 21 21.8 ± 2.7 (50 BL) Range: 13 – 27; median: 22	22.4 ± 3.2 (overall) (p-v=0.206) Range: 15 – 29; median: 22.5 22.1 ± 3.3 (35 UL) (p-v=0.474) Range: 15 – 29; median: 21 24.7 ± 1.8 (7 BL) (p-v=0.019) Range: 21 – 26; median: 25.5 25.2 ± 2.9 (6 UL w/ PPV) Range: 20 – 29; median: 25	21.9 ± 2.5 (overall) Range: 17 – 30; median: 21 21.5 ± 0.8 (27 UL) Range: 17 – 29; median: 21 22.4 ± 1.6 (49 BL) Range: 19 – 30; median: 22
CAG repeats among controls			
23.5 ± 0.29 Range: 15 – 32; median: 23	21.6 ± 3.3 Range: 9 – 31; median: 22	21.5 ± 2.7 Range: 16 – 26; median: 22	21.8 ± 2.8 Range: 16 – 28; median: 21

Appendix C

Evidence table of studies examining the association of ESR1 SNPs and cryptorchidism

Yoshida 2005	**Galan 2007**	**Wang 2008**
Study characteristics		
Tokyo, Japan, 1995-2003 Case-control	Florence, Italy Case-control	USA (Wilmington, DE) Case-control
Sample characteristics		
63 Japanese cryptorchid males, aged 1–13 yr, (median, 5.0 yrs) and 47 control males, aged 4–12 yr (median, 7.5 yrs) 47 UL: inguinal region in 39; abdominal cavity in 7; 1 vanishing testis. 16 BL: both testes inguinal region in 15; abdominal cavity in 1 Individuals recruited from the urban or suburban area of Tokyo or Yamagata City. They were free of particular residential environments, specific dietary habits, and intake of drugs with hormonal effects.	118 cryptorchid males of Italian origin (Central Italy); 71 UL, 47 BL The Italian control group includes 168 men from Central Italy with normal sperm parameters and no hx of cryptorchidism.	152 cryptorchid males who had non-syndromic UL (120) or BL (32) UDT, and had no other discernible congenital abnormalities UDT located in the prescrotal region, external ring, or superficial inguinal pouch, inguinal canal or abdominal area 160 unrelated control subjects All Pts & controls recruited from A.I. duPont Hospital for Children [Wilmington] Exclusion criteria: boys with a hx of prematurity, and those with retractile testes, or that spontaneously descended within the first 6 months of life.
Sample and genetic analysis methods		
30 SNPs were measured along the ESR1 gene. Leukocyte genomic DNA was amplified by PCR with primers designed to amplify a 300-bp region around e/SNP. Genotyping performed by 5′ nuclease assay (TaqMan method). Haplotype analysis performed to identify one associated with cryptorchidism phenotype.	Germline DNA extracted from peripheral blood. For controls, DNA from frozen semen was used too. Five polymorphisms for the AGATA haplotype were genotyped by PCR protocols. Genotyping quality controls were performed.	Genomic DNA was obtained from peripheral blood leukocytes, buccal swab, or tissues from orchidopexy or circumcision. Puregene DNA purification kits were used for DNA extraction. TaqMan SNP Genotyping Assays was used to genotype the 5 SNPs (SNP10-SNP14). Haplotype association analysis performed using PLINK v1.01.
Cryptorchidism ascertainment		
Not specified	Not specified	Not specified
Control selection		
Controls (came from the urban or suburban area of Tokyo or Yamagata City) were found to have no discernible abnormality by cytogenetic, skeletal, and endocrine studies	Of the 168 men, 109 fathered at least one child spontaneously or had normal fertilization after IVF for pure female (tubal) factor infertility, whereas 59 men were students from the local university.	The 160 controls were healthy male infants and children presenting for circumcisions or voiding problems. Each boy had full descent of the testes, no significant testicular retractility, and no additional urogenital anomalies or known syndromes.
Haplotype frequency distribution and association		
15 of 30 SNPs presented certain degree of heterozygosity. These were in HWE. Within block covering SNPs 10-14, four major haplotypes accounted for 95% (patients) and 93% (controls) of all haplotypes. AGATA haplotype frequency was greater in patients than in controls. SNP 12: A vs G OR=1.99 (95% CI 1.07, 3.67)	SNP10-13 did not deviate from HWE but SNP14 deviated in both cases and controls. SNP12 frequencies: GG GA AA Crypto 101 (85.6) 17 (14.4) 0 (0.0) Control 124 (73.8) 43 (25.6) 1 (0.6) OR=0.50 (95% CI 0.28, 0.90)	No difference in distribution of race was found between cases and controls. SNPs in Caucasian group were in HWE. No difference for SNP12 in Caucasians. Severe cases were more likely to have a GG genotype than moderate cases, OR=8.8 (1.1, 69.7). G allele OR=9.3 (1.2, 73.4). Mild cases were also less likely to have GG genotype and G allele compared to severe case but not significantly.

Appendix D

Evidence table of studies assessing the association between maternal alcohol consumption and cryptorchidism

Damgaard2007	Jensen2007	Strandberg-Larsen2009	Mongraw-Chaffin2008
Study characteristics			
Copenhagen, Denmark 1997-00, Turku, Finland 1997-99. Prospective birth cohort study. Eligible women (2,229 Danish and 2,728 Finnish) residing in hospital referral areas were consecutively recruited during early pregnancy. Inclusion criteria: both parents and grandparents of the unborn child had to be born and raised in Denmark or Finland.	Aarhus, Denmark 1984-87. Prospective collection of prenatal exposures and obstetric information from a 16–19 years of follow-up in a nationwide patient register. Population-based random sample (n = 15,434) of boys born January 1984 and December 1987 drawn in the Danish Civil Registration system to assess comparability of the cohort.	Copenhagen, Denmark 1996–2002 (The Danish National Birth Cohort). Partial overlap (22%) with Damgaard's Danish cohort. Pregnant women invited to participate by their GP at first antenatal visit. Fifty percent of GP participated and 60% of invited women consented. Analysis limited to women who gave birth to a singleton boy and completed first interview.	Berkeley, CA, USA 1959-1967 Prospective study ≥40-yr f-up of 20,754 pregnancies occurring b/w 1959-67 in CA. Cases were matched to three controls from the same cohort on birth year and race. If more than three controls were available, these were selected at random from the pool of matches.
Sample characteristics			
Denmark, 1,042 boys (1,029 mothers), Finland 1,454 boys (1,446 mothers). 128 cryptorchid boys at birth [matched w/ 2,368 healthy controls] (94 Danish, 34 Finnish) Only 33 (19 Danish, 14 Finnish) [matched w/ 2,215 healthy controls] remained cryptorchid at 3 mos.	5,716 boys, 270 cases of crypto diagnosed, 185 of these underwent orchiopexy. Mothers: average gestational alcohol intake of five or more drinks per week. Age, parity, alcohol consumption smoking habits, infertility treatment.	41,268 live-born singleton, 1,598 cases. Of these, 355 boys were diagnosed with crypto but had no maternal report. Of the 810 boys diagnosed with crypto, ["diagnosis of crypto"] 398 had orchiopexy ["orchipexy"]	84 cases at birth persisting to at least age 2 yrs among 7,574 live-born sons whose mothers were interviewed in early pregnancy.
Alcohol consumption ascertainment			
Quantitative data on alcohol consumption, smoking, and caffeine intake obtained by questionnaire and/or interview once during the third trimester of pregnancy, before pregnancy outcome known. For a sub-group (n = 465) [no specification on who they were – cohort and/or controls], information on alcohol consumption was obtained twice during pregnancy by interviews.	Pregnant women attending their last scheduled regular antenatal care visit (~36th gestational wk), filled in a comprehensive self completed questionnaire, and returned it by mail. Alcohol/wk [units = 12g. of alcohol]. Binge episodes [intake of 8+ units of alcohol on one occasion]	Maternal alcohol consumption assessed in two computer-assisted telephone interviews around gestational weeks 17 and 32. One drink = one bottle of beer (0.33 l), one glass of wine, or one glass of spirits, each approx. 12 g of alcohol. Total = sum of weekly intake. Binge drinking: 5+ drinks on a single occasion since the onset of pregnancy.	In structured interview, mother's alcohol consumption ascertained by asking how many glasses of beer, wine, or whiskey she drank in a week. Total drinks of alcohol consumed per wk were obtained by adding the number of glasses drunk per week for the 3 beverages.
Cryptorchidism ascertainment			
Examination at birth and 3 months. Preterm boys examined at expected delivery date. Gestational age based on routine US at 18–20 wks. When not available (2.1%), last menstrual period used. Data on birth weight and parity obtained from birth records. Testis considered cryptorchid if found in a high scrotal, supra-scrotal or inguinal position or if non-palpable. Retractile testes considered a normal variant. Majority were transient cryptorchid cases but still presented slightly elevated gonadotropin levels at 3 months.	Cases ascertained by clinical examination at birth and at 3 mos. Most cases were transient (spontaneous descent within 3 months). Among persistent cases no excess risk was observed (only 33 observations). All diagnosis or surgical procedures during hospital admissions of these boys in the yrs. 1984–2003 were extracted from the Danish National Patient Register. Two endpoints: boys having a crypto diagnosis without orchiopexy ('no orchiopexy') and boys with a diagnosis who also underwent orchiopexy ('orchiopexy').	Maternal report at 6 or 18 months and/or crypto dx in National Hospital Discharge Registry (NHDR), 398 of 1,598 were verified by orchiopexy (identified in the NHDR).	Condition should be present at 2 yrs of age to examine risk factors for persistent

Damgaard2007	**Jensen2007**	**Strandberg-Larsen2009**	**Mongraw-Chaffin2008**
Univariate estimate			
Drinks/week continuous (*): (n= 2,477) 1.26 (1.13–1.40) Binge [five or more alcoholic drinks at one occasion/ day] episodes: Yes 1.25 (0.85, 1.87) (*) Additionally, several OR from 0 drink to ≥ 9 drinks per week Drinks/wk OR (95% CI) 0 Ref 0.1-4.9 1.69 (1.16, 2.45) ≥ 5 4.97 (2.00, 12.40)	Risk ratios, ref (<1 drink/wk) a) All cases (n=270) 1-4 0.9 (0.7, 1.1) 5-9 0.7 (0.4, 1.3) ≥10 0.8 (0.2, 2.5) b) Surgery (n=185) 1-4 0.8 (0.6, 1.1) 5-9 0.6 (0.3, 1.2) ≥10 0.7 (0.2, 3.0) c) No surgery (n=85) 1-4 1.0 (0.6, 1.5) 5-9 1.1 (0.5, 2.4) ≥10 0.9 (0.1, 6.7) Binge episodes (Ref=No) RR for binge drinking a) All cases 1.2 (0.9, 1.7) b) Surgery 1.3 (0.9, 1.9) c) No surgery 1.0 (0.6, 1.8)	Hazard ratio, ref (0 drinks/wk) a) Maternal report of crypto dx 0.5-1.5 0.87 2-3.5 0.82 4+ 0.63 b) Crypto dx c) Surgery 0.5-1.5 0.92 0.89 2-3.5 0.87 0.77 4+ 0.61 0.77 Binge drinking episodes a) Maternal report of crypto dx 1 0.90 2 0.89 3+ 0.99 b)Crypto dx c) Surgery 1 0.86 0.74 2 0.79 0.56 3+ 0.94 0.93	Odds ratio 3.3 drinks/wk 1.05 (0.86, 1.29)
Multivariate estimate			
MV odds ratio (OR) adjusted for country, smoking, caffeine intake, maternal age, social class, parity, birth weight. Ref: 0 drinks/wk. Drinks/week continuous: (n=2,477) 1.17 (1.03, 1.34) Binge episodes: Yes 1.18 (0.77, 1.83) Drinks/wk OR (95% CI) 0.1-4.9 0.95 (0.61, 1.49) ≥ 5 3.10 (1.05, 9.10)	MV risk ratios (RR) adjusted for maternal and paternal age at delivery, time to index pregnancy, infertility txt, parity, SES group, mother's daily smoking, birth weight, gestational age, placental weight. Ref: < 1 drink/wk a) All cases (n=270) 1-4 0.9 (0.7, 1.2) 5-9 0.7 (0.4, 1.3) ≥10 0.7 (0.2, 2.2) b) Surgery (n=185) 1-4 0.8 (0.6, 1.2) 5-9 0.5 (0.2, 1.2) ≥10 0.6 (0.1, 2.7) c) No surgery (n=85) 1-4 1.0 (0.6, 1.6) 5-9 1.1 (0.5, 2.6) ≥10 0.8 (0.1, 6.0) Binge episodes No (Ref) a) All cases (n=270) Yes 1.3 (0.9, 1.8) b) Surgery (n=185) Yes 1.4 (0.9, 2.1) c) No surgery (n=85) Yes 1.0 (0.5, 1.8)	MV hazard ratio (HR) adjusted for maternal age, parity, time to pregnancy, infertility txt, self-reported diabetes, smoking, occupational status. Ref: 0 drinks/wk a) Maternal report of crypto dx 0.5-1.5 0.89 (0.79, 0.99) 2-3.5 0.82 (0.69, 0.99) 4+ 0.63 (0.41, 0.94) b) Crypto dx 0.5-1.5 0.93 (0.80, 1.08) 2-3.5 0.87 (0.68, 1.12) 4+ 0.58 (0.32, 1.06) c) Surgery 0.5-1.5 0.91 (0.73, 1.13) 2-3.5 0.79 (0.54, 1.15) 4+ 0.77 (0.36, 1.63) Binge drinking a) Maternal report of crypto dx 1 0.88 (0.77, 1.02) 2 0.85 (0.70, 1.06) 3+ 0.94 (0.73, 1.21) b) Crypto dx 1 0.83 (0.68, 1.01) 2 0.73 (0.53, 1.01) 3+ 0.85 (0.60, 1.21) c) Surgery 1 0.70 (0.52, 0.94) 2 0.50 (0.29, 0.85) 3+ 0.81 (0.49, 1.34)	MV odds ratio (OR) adjusted for smoking, caffeine consumption, body mass index, son's birth weight. 3.3 drinks/wk 0.99 (0.83, 1.20)

Appendix E

Definitions

Pediatricians are physicians who are board certified in pediatrics.

Primary Care Providers, in the context of these guidelines, are any licensed healthcare professionals who provide primary care services to patients.

Providers include, in the context of these guidelines, any licensed health care professional involved in the care of patients with suspected cryptorchidism such as: allied health professionals (Nurse Practitioners, Registered Nurses, Physicians' Assistants), physicians: pediatricians (including subspecialists), urologists and general surgeons (including subspecialists), or other licensed health professionals with specialized training and/or medical expertise in this area.

Specialists refer to a physician or allied health professional or other licensed health professional with specialized training/ expertise, who are trained in a particular specialty of medicine including urology, endocrinology, or pediatric subspecialty.

Surgical Specialists refer to any physician who is trained or who has expertise in a specific branch of surgery, including (in the context of this guideline) urologic surgery, pediatric general surgery, or pediatric urology.

Appendix F

Distribution of nonpalpable testes location as identified by diagnostic laparoscopy

Group	Absent/Unknown Vanishing/Atrophic	Inguinal	Internalring/ Peeping	Intra-abdominally/ Above internal ring
#1: ≤16 year-old [68-100]	Meta-analytic mean*=33.2%, I2=92% Minimum=3.4%	Skewed distribution with 44% null	Skewed distribution with 44% null	Meta-analytic mean*=40.3%, I2=91% Minimum =8.8%
#2: Prepubertal + older males or unknown [101-115]	Skewed distribution with meta-analytic mean*=32.5%, I2=92% Minimum=13.5%	Skewed distribution with 33% null	Zeroinflated distribution with 47% null. Non-null values centered at 35%.	Meta-analytic mean*=36.9%, I2=78% Minimum =21.6%

*Meta-analytic mean indicates that estimate of the mean was obtained using meta-analysis. I2 indicates the degree of heterogeneity.

These cohorts were divided into two groups (see Table 3). Group #1 includes boys 16 years-old and younger (34 cohorts) [69-100]. Group #2 includes cohorts with a large proportion of prepubertal boys (mean or median age is small), as well as some cases where the male is older than 16 [101-115]. Two cohorts in Group #2 do not report the age distribution [110,113]. Therefore, the distribution of the location of testes was estimated separately for these two sets of cohorts.

In Group #1, a total of 3,166 testes were assessed for an average of 93 testes per study; for Group #2, 1,525 testes were assessed and yielded an average of 102 testes per study. For the purpose of determining the distribution, absent/ unknown testes and vanishing or atrophic were all combined because it is suspected that these are not well differentiated in some studies. Eight studies [101-103,106,112,114,115] showed differentiation between absent and vanishing testes; the average rate of absent/unknown testes in these cohorts was 3%.

Distributions were similar between the two groups, excluding older cohorts. In these cases, the minimum percent of intra-abdominally located testes was higher in Group #2 than in Group #1 (21.6% vs. 8.8%). Similarly, the minimum percent of absent or vanishing testes was also higher in Group #2 than in Group #1 (13.5% vs 3.4%). These data suggests more intra-abdominally testes will be present in older boys.

This meta-analysis shows that in any cohort of diagnostic laparoscopy for nonpalpable testes, at least 8% of testes will be located intra-abdominally and a small percent of testes will be absent/vanishing/atrophic (3.4%).

References for Appendix F

Full citations available in Evaluation and Treatment of Cryptorchidism: AUA Guideline.

Appendix G

Academy of Pediatrics 2014 Recommendations for Preventative Pediatric Health Care

* As published in *PEDIATRICS*

Committee on Practice and Ambulatory Medicine, Bright Futures Periodically Schedule Workgroup. From the American Academy of Pediatrics Policy Statement: 2014 Recommendations for Pediatric Preventive Health Care. Pediatrics 2014; 133; 568.

Appendix H

Quality Assessment of Individual Studies

Quality was assessed using three published tools, depending on the study design. Two reviewers independently assessed the quality of each study, and then results were adjudicated. For randomized controlled trials (RCTs), we used the Cochrane Risk of Bias tool[1] for cohort studies, the Newcastle-Ottawa Quality Assessment Scale[2]; and for prognostic studies of imaging, the Quality Assessment of Diagnostic Accuracy Studies-Revised (QUADAS-2) tool[3]. The results of these tools were then translated to the Agency for Healthcare Research and Quality standard of "good," "fair," and "poor" quality designations using conversion thresholds developed by the team, as no explicit guidance exists.

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

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