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PEYRONIE'S DISEASE: AUA GUIDELINE

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Purpose: The purpose of this guideline is to provide a clinical framework for the diagnosis and treatment of Peyronie's disease (PD).

Methods: A systematic review of the literature using the Pubmed, Embase, and Cochrane databases (search dates 1/1/1965 to 1/26/15) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of PD. The review yielded an evidence base of 303 articles after application of inclusion/ exclusion criteria. These publications were used to create the guideline statements. If sufficient evidence existed, then the body of evidence for a particular treatment was assigned a strength rating of A (high quality evidence; high certainty), B (moderate quality evidence; moderate certainty), or C (low quality evidence; low certainty); evidence-based statements of Strong, Moderate, or Conditional Recommendation, which can be supported by any body of evidence strength, were developed based on benefits and risks/burdens to patients. Additional information is provided as Clinical Principles and Expert Opinion when insufficient evidence existed.

Guideline Statements:

Diagnosis:

1. Clinicians should engage in a diagnostic process to document the signs and symptoms that characterize Peyronie's disease. The minimum requirements for this examination are a careful history (to assess penile deformity, interference with intercourse, penile pain, and/or distress) and a physical exam of the genitalia (to assess for palpable abnormalities of the penis). *(Clinical Principle)*

2. Clinicians should perform an in-office intracavernosal injection (ICI) test with or without duplex Doppler ultrasound prior to invasive intervention. *(Expert Opinion)*

3. Clinicians should evaluate and treat a man with Peyronie's disease only when he/she has the experience and diagnostic tools to appropriately evaluate, counsel, and treat the condition. *(Expert Opinion)*

Treatment:

4. Clinicians should discuss with patients the available treatment options and the known benefits and risks/burdens associated with each treatment. *(Clinical Principle)*

5. Clinicians may offer oral non-steroidal anti-inflammatory medications to the patient suffering from active Peyronie's disease who is in need of pain management. *(Expert Opinion)*

6. Clinicians should not offer oral therapy with vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, or a combination of vitamin E with L-carnitine. *[Moderate Recommendation; Evidence Strength Grade B(vitamin E/omega-3 fatty acids/ Vitamin E + propionyl-L-carnitine)/ C(tamoxifen/procarbazine)]*

7. Clinicians should not offer electromotive therapy with verapamil. *(Moderate Recommendation; Evidence Strength Grade C)*

8. Clinicians may administer intralesional collagenase clostridium histolyticum in combination with modeling by the clinician and by the patient for the reduction of penile curvature in patients with stable Peyronie's disease, penile curvature >30° and <90°, and intact erectile function (with or without the use of medications). *(Moderate Recommendation; Evidence Strength Grade B)*

9. Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional collagenase regarding potential occurrence of adverse events, including penile ecchymosis, swelling, pain, and corporal rupture. *(Clinical Principle)*

10. Clinicians may administer intralesional interferon α-2b in patients with Peyronie's disease. *(Moderate Recommendation; Evidence Strength Grade C)*

11. Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional interferon α-2b about potential adverse events, including sinusitis, flu-like symptoms, and minor penile swelling. *(Clinical Principle)*

12. Clinicians may offer intralesional verapamil for the treatment of patients with Peyronie's disease. *(Conditional Recommendation; Evidence Strength Grade C)*

13. Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional verapamil about potential adverse events, including penile bruising, dizziness, nausea, and pain at the injection site. *(Clinical Principle)*

14. Clinicians should not use extracorporeal shock wave therapy (ESWT) for the reduction of penile curvature or plaque size. *(Moderate Recommendation; Evidence Strength Grade B)*

15. Clinicians may offer extracorporeal shock wave therapy (ESWT) to improve penile pain. *(Conditional Recommendation; Evidence Strength Grade B)*

16. Clinicians should not use radiotherapy (RT) to treat Peyronie's disease. *(Moderate Recommendation; Evidence Strength Grade C)*

17. Clinicians should assess patients as candidates for surgical reconstruction based on the presence of stable disease. *(Clinical Principle)*

18. Clinicians may offer tunical plication surgery to patients whose rigidity is adequate for coitus (with or without pharmacotherapy and/or vacuum device therapy) to improve penile curvature. *(Moderate Recommendation; Evidence Strength Grade C)*

19. Clinicians may offer plaque incision or excision and/or grafting to patients with deformities whose rigidity is adequate for coitus (with or without pharmacotherapy and/or vacuum device therapy) to improve penile curvature. *(Moderate Recommendation; Evidence Strength Grade C)*

20. Clinicians may offer penile prosthesis surgery to patients with Peyronie's disease with erectile dysfunction (ED) and/or penile deformity sufficient to prevent coitus despite pharmacotherapy and/or vacuum device therapy. *(Moderate Recommendation; Evidence Strength Grade C)*

21. Clinicians may perform adjunctive intra-operative procedures, such as modeling, plication or incision/grafting, when significant penile deformity persists after insertion of the penile prosthesis. *(Moderate Recommendation; Evidence Strength Grade C)*

22. Clinicians should use inflatable penile prosthesis for patients undergoing penile prosthetic surgery for the treatment of Peyronie's disease. (*Expert Opinion*)

SECTION 1: PURPOSE

This guideline's purpose is to provide direction to clinicians and patients regarding how to recognize Peyronie's disease (PD), conduct a valid diagnostic process, and approach treatment with the goals of maximizing symptom control, sexual function, and patient and partner quality of life (QoL) while minimizing adverse events and patient and partner burden. The strategies and approaches recommended in this document were derived from evidence-based and consensus-based processes. There is a continually expanding literature on PD; the Panel notes that this document constitutes a clinical strategy and is not intended to be interpreted rigidly. The most effective approach for a particular patient is best determined by the individual clinician and patient in the context of that patient's history, values, and goals for treatment. As the science relevant to PD evolves and improves, the strategies presented here will be amended to remain consistent with the highest standards of clinical care.

SECTION 2: METHODOLOGY

Systematic review. A systematic review was conducted to identify published articles relevant to the diagnosis and treatment of PD. Literature searches were performed on English-language publications using the Pubmed, Embase, and Cochrane databases from 1/1/1965 to 1/26/2015. Data from studies published after the literature search cut-off will be incorporated into the next version of this guideline. Preclinical studies (e.g., animal models), commentary, and editorials were excluded. Additional exclusion criteria were as follows: patients constituted a mixed group among which most patients had congenital curvature rather than PD, and outcomes were collapsed across groups; article focused primarily on surgical technique with minimal or no patient information or outcomes reported; no outcomes reported or outcomes data not extractable; or duplicate report of data presented elsewhere. Review article references were checked to ensure inclusion of all possibly relevant studies. Multiple reports on the same patient group were carefully examined to ensure inclusion of only non-redundant information. The systematic review yielded a total of 303 publications relevant to preparation of the guideline.

PD Diagnosis and Treatment. The systematic review revealed insufficient publications to address PD diagnosis from an evidence basis. With regard to treatment, a total of 281 articles met the inclusion criteria; the Panel judged that these were a sufficient evidence base from which to construct the majority of the treatment portion of the algorithm (see Appendix A). Data on study type [(e.g., randomized controlled trial (RCT), controlled clinical trial (CCT), observational study], treatment parameters (e.g., type of treatment, dosing, follow-up), patient characteristics [e.g., age, symptom duration, penile deformity, plaque, pain, erectile dysfunction(ED)], outcomes (e.g., effects on deformity, plaque, pain, ED, QoL), and adverse events were extracted.

Quality of Individual Studies and Determination of Evidence Strength. The quality of individual studies that were either RCTs or CCTs was assessed using the Cochrane Risk of Bias tool.[1] The quality of case-control studies and comparative observational studies was rated using the Newcastle-Ottawa Quality (NOQ) Assessment Scale.[2] Because there is no widely-agreed upon quality assessment tool for single cohort observational studies, the quality of these studies was not assessed.

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 not only individual study quality but consideration of study design, 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 and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.[3]

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (see Table 1). ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength			
	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/ Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/ Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/ Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/ Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/ Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/ Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	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	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		

or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *is likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations also can be supported by any body of evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/

burdens appear balanced, the best action also depends on individual patient circumstances and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

For some clinical issues, particularly diagnosis, there was little or no evidence from which to construct evidence-based statements. Where gaps in the evidence existed, the Panel provides guidance in the form of *Clinical Principles* or *Expert Opinion* with consensus achieved using a modified Delphi technique if differences of opinion emerged.[4] 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. The Panel proceeded with full awareness of the limitations of the PD literature. Some of these limitations derive from the fact that PD is characterized by symptoms that change over time and by some symptoms that may resolve in the absence of treatment (i.e.,Berookhim 2014; Grasso 2007; Mulhall 2006).[5-7] The changing nature of PD symptoms and the possibility that improvement in some patients may be a consequence of the passage of time makes the study of treatment effects challenging. Some symptoms, such as pain, are highly susceptible to placebo effects. These characteristics of PD make it difficult to interpret studies that do not control for the natural history of symptoms or for placebo effects (e.g., observational studies). In addition, because patients may have highly variable courses with or without treatment, findings from studies that have small sample sizes – even well-designed studies – potentially lack generalizability because of the inherent instability of findings derived from small numbers of patients. Further, the quality of any empirical literature depends on its capacity for accurate measurement. An additional complexity of the PD literature is that many studies rely on patient perceptions of changes in deformity and penile dimensions as primary outcomes. This approach is problematic because studies that have compared objective and subjective measures of deformity and penile dimensions report limited or no correspondence between these two methods (e.g., Bacal 2009; Hudak 2013; Matsushita 2014; Taylor & Levine 2008).[8-11] Additional limitations include highly variable inclusion criteria across studies in terms of symptom severity and symptom duration.

Process. The Male Sexual Dysfunction Panel was created in 2013 by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Co-Chairs who in turn appointed the additional panel members with specific expertise in this area. The AUA conducted a thorough peer review process. The draft guidelines document was distributed to 78 peer reviewers. The panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the PGC. Then it was submitted to the AUA Board of Directors for final approval. Funding of the panel was provided by the AUA; panel members received no remuneration for their work.

SECTION 3: BACKGROUND

Definition. The Panel defines PD as an acquired penile abnormality characterized by fibrosis of the tunica albuginea, which may be accompanied by pain, deformity, ED, and/or distress.

Epidemiology. Findings regarding prevalence rates depend on the methodology employed, the sample under study, how PD is defined, and how men are queried with ranges from 0.5% to 20.3% within specific populations. Using a population-based methodology in a U.S. sample aged 18 years and older, Dibenedetti (2011) reported a prevalence rate of 0.5% for men who had been formally diagnosed with PD, a rate of 0.8% for men who had been diagnosed or treated for PD, and a rate of 13.1% for men who had been diagnosed or treated or had any symptom of PD.[12] Schwarzer (2001) conducted a community-based study among men in Cologne, Germany and reported a prevalence rate of 3.2% in men aged 31-78 years.[13] Another population-based study in Italian men reported a prevalence rate of 7.1% among men aged 50-69 years.[14] Among men older than age 40 years screened for prostate cancer in the U.S., a prevalence of 8.9% was reported.[15] Men older than 50 years screened for prostate cancer in Southern Brazil had a prevalence rate of 3.7%.[16] Rates may be higher among men who present with comorbidities. El-Sakka (2006) reported a prevalence rate of 7.9% among men who presented with ED.[17] Arafa (2007) reported a rate of 20.3% among men who were diabetic with ED.[18] Together, this group of studies suggests that prevalence rates historically have been under-estimated. The higher rates detected in more recent studies suggest a greater awareness of the disease and its symptoms.

Pathophysiology. PD is an acquired inflammatory disorder of the tunica albuginea. Microvascular trauma to the penile shaft associated with penile buckling in the erect or semi-erect state secondary to sexual activity is thought to be the most common inciting event; however, many patients do not recall an incident that

preceded symptom onset. It is hypothesized, however, that repetitive minor trauma to the penis initiates a cascade involving significant extravascular protein deposition, fibrin trapping, macrophage recruitment, cytokine overexpression, and release of elastase leading to changes in the tunical collagen from type 1 to a predominant type 3.[19-22] Additionally, trauma is associated with changes in elastin content of the tunica with subsequent inelasticity of the tunica leading to scarring.[20,22] The natural degradation of fibrin may be altered secondary to proteins, such as transforming growth factor B1 and plasminogen activator inhibitor type 1, resulting in aberrant tunical healing.[19,23,24]

Natural History. PD is characterized by symptoms with a variable course, some of which may improve or resolve without treatment in some patients. Mulhall (2006) reported on 246 men newly-diagnosed with PD who had no medical treatment and were followed for at least 12 months.[7] At follow-up, all patients who had reported pain at baseline indicated improvement in pain and most (89%) reported complete resolution of pain. Among men with curvature, 12% had improvement, 40% remained stable, and 48% had worsened curvature. Berookhim (2014) reported on 176 men with uniplanar curvature who opted for no treatment and were followed for at least 12 months.[5] Sixty-seven percent experienced no change in curvature, 12% improved (mean 27 degree change), and 21% worsened (mean 22 degree change). Men who experienced no change were more likely to be older and to have had symptoms for greater than six months. Men who experienced improvement were more likely to be younger and to have had symptoms for less than six months. Paulis & Cavallini (2013) followed 82 patients who refused PD treatment for approximately 18 months.[25] Among patients with pain, 26% had pain disappearance, 37% had pain improvement, 13% had worsened pain, and 26% had unchanged pain. Among patients with curvature, 7% had reduction (mean 5.8 degrees), 11% had no change, and 82% had curvature that worsened (men 12.3 degrees). Plaque volume increased in nearly all patients (96%) but increases were greater among patients <45 years of age. Grasso (2007) followed 110 men annually for five years (mean follow-up 6.4 years).[6] Approximately 68% of patients < age 50 years and 31.5% of patients > age 50 years experienced worsened curvature during follow-up. Significant predictors of worsened curvature were the presence of diabetes and, in contrast to Berookhim (2014), younger age. However, the two studies differ greatly in follow-up duration (>6 years in Grasso, 2007, compared to 12 months in Berookhim, 2014). Pain resolved in more patients > 50 years of age (69%) than in patients < 50 years old (20%). These data suggest that for many or most patients pain will resolve over time without intervention; curvature (or other types of deformity), however, is much less likely to improve and may require treatment if it compromises sexual function and/or is the source of patient or partner distress (see **Impact on Psychosocial Functioning and QoL**). These data also highlight the challenge to interpret studies that are not designed to control for the passage of time.

Impact on Psychosocial Functioning and QoL. The panel fully recognizes that PD can have a profound negative impact on men's QoL. Many men with PD experience emotional distress, depressive symptoms, and relationship difficulties.[26] As many as 81% of men with PD indicate "emotional distress."[27] More serious psychological sequelae can occur; one study reported 48% of men had clinically meaningful depressive symptoms (26% moderate, 21% severe) as assessed by the Center for Epidemiological Studies Depression (CESD) scale. It is important to note that these depressive symptoms remained consistently high over time, suggesting PD has a lasting psychological impact on these men.[28] Additionally, the stress of PD often extends to men's relationships, and more than half (54%) of men report relationship difficulties as a result of PD.[29] Men express concerns about the physical appearance of their penis and report PD negatively impacts their masculine self-image.[30] Men with PD also indicate a reduction in sexual satisfaction. They report increased anxiety in a sexual situation, a decrease in sexual confidence, and a concern that they are not satisfying their partner.[30] Lastly, men with PD report a sense of isolation as they find it difficult to communicate with their healthcare professionals or partners about PD.[30] With these issues in mind, the Panel stresses the importance of assessing for distress in the PD patient before treatment begins and during treatment course.

SECTION 4: PATIENT PRESENTATION

Symptoms. PD is a symptomatic disorder characterized by a disorganized, excessive deposition of collagen that results in formation of a plaque within the penile tunica albuginea. The plaque may restrict tunica lengthening on the effected side during erection, which can lead to penile curvature, penile deformity, penile discomfort, penile pain, and/or ED. Changes in the appearance and function of the penis can be associated with emotional and psychosocial consequences, such as bother, depression, and relationship difficulties.

There are several potential patient presentation scenarios that are seen in clinical practice; some scenarios are more common than others. A most common presentation is the male in his mid-50s who presents with recent onset of penile curvature accompanied by mild to moderate penile pain. The patient usually does not recall a specific sexual or non-sexual event (e.g., an injury) that preceded onset of

symptoms. Most often his penile erection is still firm enough for sexual intercourse. The penile curvature or pain, however, may either preclude intercourse or may make intercourse difficult for the patient and/or his partner. The patient and clinician usually cannot palpate any abnormalities on the penile shaft in the non -erect state. The recent onset of penile curvature and varying degrees of penile pain, without a palpable penile abnormality, in the non-erect state, may be considered diagnostic.

Less common presentations include younger men (i.e., in their 20s or 30s) who present with Peyronie's symptoms. This patient may recall a specific sexual event that preceded onset of penile curvature. This patient will have varying degrees of penile pain and may have a palpable penile plaque in the non-erect state. Another less common presentation will be of a middle-aged male patient with a more advanced degree of penile curvature, for example a dorsal and lateral curve with erection, or an indentation in the mid penile shaft with erection. A penile plaque may or may not be palpable in the non-erect state. Again, these conditions will be accompanied by varying degrees of penile pain. A PD patient also may present with ED as his primary complaint and may have undiagnosed PD. Potentially, the PD plaque and/or curvature may only become apparent during pharmacologic testing or at the time of surgery as a penile prosthesis is being inserted.

Active vs. Stable Disease. It is useful clinically to distinguish between the patient with active disease and the patient with stable disease because treatment type depends on whether the patient's symptoms are dynamic or stable.

Active disease. Active disease is characterized by dynamic and changing symptoms. Penile and/or glanular pain or discomfort with or without erection is the defining symptom of the active stage. Symptom onset may be associated with a history of penile buckling during intercourse. The patient may or may not manifest the presence of penile induration – a palpable plaque associated with painful penile deformity and possible curvature. Plaque(s) and penile deformities, including curvature (dorsal, lateral, ventral), shortening, indentation, hinge effect, narrowing, or hourglass deformity, may not be fully developed at this stage. Distress may be present in response to pain and to progressive deformity. Erectile function may be intact or may be compromised by pain and/or developing deformity.

Stable disease. In the patient with stable disease, symptoms have been clinically quiescent or unchanged for at least three months based on either patient report or clinician documentation. Pain with or without erection may be present but is less common. Stable disease means that the deformity is no longer progressive. Curvature may be uniplanar or biplanar and may not be dependent on the size and magnitude of the plaque. Plaque(s) can be palpated or documented on ultrasound. The most common plaque location is on the mid-shaft dorsal aspect of the penis toward the penile hilum or distally retrocoronal. The typical patient presents with a dorsal, dorso-lateral, or ventral penile deformity. Rarely rotational deformities may occur. There may be additional manifestations in the stable phase, including difficulty in maintaining erectile function and inability to sustain intercourse. Erectile function may be compromised by pain and/or deformity or may be reduced because of symptoms of ED not related to deformity or pain. It is reported that ED may be present in up to 33% of PD patients with greater than 50% of patients reporting that ED predated the onset of PD symptoms. Distress is generally present, and the degree of distress will depend on the patient's perception of his symptom severity.

Differentiation. The differential diagnosis is limited. In the young patient, the presence of lifelong ventral penile curvature, no penile pain, no penile plaque, and varying degrees of ability to have intercourse suggest a diagnosis of congenital penile curvature; this presentation should not be mistaken for PD. A thrombosed or torn dorsal penile vein may cause acute onset penile ecchymosis, penile pain, and swelling. A penile fracture is an acute event characterized by a popping sound of the tunica during intercourse, accompanied by penile swelling and ecchymosis. Of note, these two conditions are very acute. Usually the patients present within hours or days, while the PD patient presents in a subacute time frame of weeks to months. Rarely, a primary penile cancer or a metastatic lesion to the penis can be mistaken for PD. Even rarer is a primary penile sarcoma, such as a penile epithelioid sarcoma, or a leiomyosarcoma, which are mistaken for PD.

SECTION 5: DIAGNOSIS

The Diagnostic Approach. Insufficient literature was identified to constitute an evidence base for diagnosis of PD in clinical practice. For this reason, the section titled *Diagnosis* is based on Clinical Principle or Expert Opinion with consensus achieved using a modified Delphi technique when differences of opinion emerged. This section is intended to provide clinicians and patients with a framework for determining whether a diagnosis of PD is appropriate; it is not intended to replace the judgment and experience of the individual clinician faced with a particular patient.

Guideline Statement 1.

The clinician should engage in a diagnostic process to document the signs and symptoms that characterize Peyronie's disease. The minimum requirements for this examination are a careful history (to assess penile deformity, interference with intercourse, penile pain, and/or distress) and a physical exam of the genitalia (to assess for palpable abnormalities of the penis). *(Clinical Principle)*

Discussion. *History.* The clinician should meticulously elicit the patient's history of penile symptoms, including onset, precipitating factors, duration, changes over time, prior treatments used, and other conditions (e.g., ED) that may affect treatment options. It is critical to elicit precise details on the nature of any deformities, such as curvature, palpable plaque(s), hourglass deformity, hinge deformity, contracture, shortening or other changes. The location of palpable plaque(s) (if present) should also be noted. In addition, the patient should be asked about past and current penile pain. It should be clarified whether the pain is always present or occurs only with erection. Prior therapies for the condition and the results should be elicited. The clinician also may inquire regarding a family history of PD as well as a history of related conditions, such Dupuytren's disease.

Assessment of sexual function is of particular importance. Penile sensation, ejaculatory function, erectile function (including relevant comorbidities), difficulty/pain with penile penetration, and concerns regarding penile length and girth should be assessed. In patients who report inability or difficulty with penetration, it should be clarified if the problem stems from penile deformity, from lack of penile rigidity, or from both issues. Patient and partner comfort and satisfaction with intercourse should be assessed. Finally, the level of patient/partner distress related to the condition should be assessed as this will determine the extent of therapy indicated. For patients and/or partners with significant distress, consideration should be given for referral to a mental health professional with expertise in sexuality.

Physical examination of the genitalia. A careful examination of the genitalia should be performed that includes stretching and palpation of the flaccid penis (for discussion of the erect penis, see discussion under Guideline Statement 2) and documentation of circumcision status and any anomalies (e.g. hypospadias). The goal of the examination is to provide baseline values that document the presence of deformity, the point of maximum curvature, presence/ location/size of penile plaque(s), penile length, and areas of tenderness. Measurement of stretched penile length (SPL) from the penopubic skin junction to the coronal sulcus or the tip is recommended to establish baseline penile length prior to any intervention.

Guideline Statement 2.

Clinicians should perform an in-office intracavernosal injection (ICI) test with or without duplex Doppler ultrasound prior to invasive intervention. *(Expert Opinion)*

Discussion. A careful history, physical examination of the genitalia, and documentation of the presence or absence of deformity, plaque, pain, and/or distress may be sufficient for a diagnosis of PD. However, prior to the initiation of any invasive treatment (e.g., intralesional treatments, penile prosthesis placement, or surgery), an ICI test is recommended. The ICI test enables assessment of penile deformity, plaque(s), and pain in the erect state. The point of maximum curvature can be determined, measurements of erect penile length and girth can be obtained, and erectile function can be assessed. When the ICI test is combined with duplex ultrasound, additional measurements of plaque size and/or density can be made, calcified and non-calcified plaques can be differentiated, and information on the vascular integrity of the penis can be obtained.

Home photography of the erect penis with the use of a protractor or the use of goniometry during an erection in the office may be sufficient to document penile deformity from PD in some cases. In the patient with complex deformity (e.g., hourglass deformity or bidirectional curvature) and/or who reports ED, confirmation of these conditions with ICI is central to developing an effective treatment plan. ICI is also essential prior to any invasive intervention. In patients who report changes in penile sensation, biothesiometry may be useful to establish baseline values of sensation prior to any invasive intervention.

Guideline Statement 3.

Clinicians should evaluate and treat a man with Peyronie's disease only when he/she has the experience and diagnostic tools to appropriately evaluate, counsel, and treat the condition. *(Expert Opinion)*

Discussion. It is the expert opinion of the panel that the PD patient is best managed by a clinician who has the training, experience, and resources to conduct a full diagnostic evaluation, to interpret the evaluation appropriately, and to adequately counsel the patient on the various treatment options.

SECTION 6: TREATMENT

Issues to Consider. It is important to recognize that PD is a symptom complex that may compromise sexual function and QoL but does not appear to affect survival. Given this context in pursuing a treatment plan, the clinician should carefully weigh the potential benefit to the patient of a particular treatment against that treatment's risk for adverse events, the severity of adverse events, and the reversibility of adverse events. For some patients, thoughtful counseling regarding the nature of PD and the typical disease course may be sufficient to alleviate concerns, and a patient may choose not to pursue further treatment. After patient education on normal penile function, the risks and benefits of the various treatment alternatives, and agreement on realistic treatment goals (if the patient desires treatment and is willing to engage in treatment), then a shared decision regarding the treatment plan can be conducted. The guideline statements in this section are intended to provide a framework to assist the clinician in counseling patients and in developing an individualized treatment plan that optimizes sexual function and QoL.

To the Panel's knowledge, there is no agreed-upon minimum curvature necessary prior to intervention. In published studies across intervention types (e.g., oral, topical, intralesional, surgical) that reported average baseline curvature, the range is 10 to 90 degrees, and the median is approximately 48 degrees. Approximately half of studies, therefore, evaluated patients with mean curvature <48 degrees, and many evaluated patients with mean curvature <30 degrees. Distress over symptoms, penile appearance, and penile function is an important component of the patient experience of PD. The patient's level of concern regarding his symptoms and his willingness to undergo various types of treatment should be fully considered in the treatment decision-making process in addition to objective measures of curvature and erectile function.

The Panel reviewed the evidence on all therapies for PD, including oral, topical, intralesional, mechanical, combination, and surgical therapies. The Panel had three major purposes in evaluating PD treatments. The first purpose was to ensure that patients are not offered treatments that clearly lack efficacy, particularly as the use of those treatments may preclude the use of other treatments that could improve symptoms and alleviate distress. The threshold for categorizing treatments as lacking efficacy was relatively low and was considered met when any single study or group of studies produced generally negative findings. The second purpose was to identify treatments that may have efficacy with regard to one or more PD symptoms. The threshold for efficacious treatments was high because of the need for studies that controlled for PD natural history and placebo effects, engaged in rigorous measurement procedures, were adequately statistically powered, and were replicated. Replication in a high-quality design or convergent findings from a group of sufficiently powered observational studies was considered essential for sufficient certainty that findings would generalize. The third purpose was to identify treatments that may be promising but for which insufficient evidence currently exists to support even a Conditional Recommendation. In the Panel's view, the treatments in this category, even if promising, are unproven until a larger and/or more rigorous evidence base is available. The treatments that fell into this category are discussed in a section that follows the guideline statements called **Other Treatments**.

Guideline Statement 4.

Clinicians should discuss with patients the available treatment options and the known benefits and risks/burdens associated with each treatment. *(Clinical Principle)*

Discussion. As part of initial counseling, clinicians should explain what is known and not known about PD, its causation, and its natural history. To optimize effectiveness of and patient satisfaction with any treatment for PD, it is critical for patients to have realistic expectations regarding the likely magnitude of treatment effects and the probability and type of adverse events. With this context in mind, clinicians should carefully review the potential benefits and risks/ burdens of each treatment option. Baseline symptom levels of deformity, pain, plaque, and/or distress, patient history and comorbidities, and patient and partner priorities for treatment goals also will determine the best treatment choices for a particular patient. Clinicians should support patients in integrating the available treatment choices with the patient's symptom status, current physical health, and treatment goals.

Guideline Statement 5.

The clinician may offer oral non-steroidal anti-inflammatory medications to the patient suffering from active Peyronie's disease who is in need of pain management. *(Expert Opinion)*

Discussion. One of the hallmark symptoms of active PD is the presence of pain with or without erection. Pain may result in significant distress and may compromise sexual function. Patient pain level can be assessed using a visual analog scale (VAS). Clinicians may offer oral non-steroidal anti-inflammatory agents to help manage pain in the active phase. Pain level should be periodically re-assessed to measure treatment efficacy.

Guideline Statement 6.

Clinicians should not offer oral therapy with vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, or a combination of vitamin E with L-carnitine. *[Moderate Recommendation; Evidence Strength Grade B(vitamin E)/ B(omega-3 fatty acids)/ B (Vitamin E + propionyl-L-carnitine)/ C (tamoxifen)/ C(procarbazine)]*

Discussion. The Recommendation is Moderate for each of the therapies discussed below. In the Panel's judgment the use of therapies without efficacy, even in the absence of significant adverse events, constitutes a moderate risk/burden in terms of postponing or pre-empting the use of other efficacious treatments, the inability to alleviate patient distress, the time expended on treatments that do not work, and the costs associated with these medications or substances. Further, the Panel notes that oral therapies are not appropriate for patients with stable disease.

Vitamin E. Seven studies reported on the effects of Vitamin E, either alone or in combination with another treatment.[31-37] Three studies were randomized designs – one RCT (Safarinejad 2007), one randomized design with interferon comparison groups (Inal 2006), and one crossover study (Pryor & Farrell 1983). The RCT reported that the vitamin E and placebo groups had similar curvature and plaque increases.[37] One observational study (Claro 2004) reported minimal curvature and plaque decreases from baseline to post-treatment, but Inal (2006) reported that curvature and plaque, on average, increased. Of the treatment arms that combined vitamin E with some other treatment, only ESWT + vitamin E (Claro 2004) reported a significant decrease in curvature. Other combined treatments or comparison groups reported a small decrease or an increase. In the RCT, similar percentages of patients reported improvement or worsening in the vitamin E and placebo groups with nearly two-thirds of patients with worsened curvature in both groups.[37] With regard to pain, the vitamin E and placebo groups improved similarly. Pryor & Farrell (1983) indicated that a larger percentage of the vitamin E group improved compared to the placebo group; however, there is an inherent confound in this design because a crossover design cannot control for passage of time. The comparison and combined treatment groups in Inal (2006) had more pain-free patients at treatment end than did the vitamin E only group.

These studies provide no compelling evidence that vitamin E reduces curvature, plaque, or pain. Body of evidence strength is Grade B based on one high-quality RCT (Safarinejad 2007), one moderate quality crossover study that does not control for passage of time (Pryor & Farrell 1983), and one moderate quality randomized design without a placebo group (Inal 2006).

Tamoxifen. Three studies examined the effects of tamoxifen.[38-40] One study was an RCT (Teloken 1999) and one study was a randomized design with a comparison group administered acetyl-L-carnitine (Biagiotti & Cavallini 2001). In Teloken (1999), the tamoxifen and placebo groups exhibited similar small decreases in curvature and similar percentages of patients reported curvature improvement. In Biagiotti & Cavallini (2001) the comparison group was administered acetyl-l-carnitine; the carnitine group exhibited a significantly greater curvature decrease (7.5 degrees) compared to the tamoxifen group (decrease of half a degree, on average). In Biagiotti & Cavallini (2001), both groups exhibited decreased plaque volume, but the decrease was greater in the acetyl-l-carnitine group. In Teloken (1999), the tamoxifen group exhibited increased plaque volume while the placebo group remained relatively stable. In Teloken (1999) pain relief rates were statistically similar between tamoxifen and placebo treated patients. In Biagiotti & Cavallini (2001), the acetyl-l-carnitine group had a higher rate of pain improvement (92%) compared to the tamoxifen group (50%). Ralph (1992) reported that 80% of patients had pain improvement; this proportion is comparable to the placebo group in Teloken (1999).

Based on these studies, tamoxifen does not appear to improve pain, curvature, or plaque. Body of evidence strength is Grade C based on one RCT with a high risk of bias, one randomized design without a placebo group, and one observational study. Total sample size administered tamoxifen was <100 patients.

Procarbazine. Three observational studies examined the effects of procarbazine.[35,41,42] Procarbazine does not appear to reliably improve curvature or reduce plaque. Adverse events were common and included gastric disturbances, nausea, anxiety, and headache. Body of evidence strength is Grade C given the observational designs.

Omega-3 fatty acids. Omega-3 fatty acids were evaluated in one RCT.[43] Responses of the active treatment group and of the placebo group were statistically indistinguishable with regard to measures of curvature, plaque, and pain. Body of evidence strength is Grade B based on one high-quality RCT.

Vitamin E + propionyl-L-carnitine. One RCT evaluated the effects of vitamin E alone, L-carnitine alone, and vitamin E + L-carnitine in comparison to placebo (Safarinejad 2007). Responses of all four groups were statistically similar in terms of curvature, plaque, and pain, suggesting that none of these

substances reliably improves symptoms compared to placebo. Body of evidence strength is Grade B based on one high-quality RCT.

Guideline Statement 7.

Clinicians should not offer electromotive therapy with verapamil. *(Moderate Recommendation; Evidence Strength Grade C)*

Discussion. One RCT (Greenfield 2007)[44] and one observational study (Pirozzi-Farina 1997)[45] evaluated verapamil delivered via electromotive drug administration (EMDA). In the RCT, electromotive verapamil (delivered at home) provided minimal benefit compared to placebo with the two groups statistically indistinguishable with regard to curvature decreases and the percent of patients who improved. Pirozzi-Farina (1997) reported that some patients experienced curvature improvement and that most patients with pain reported improvement; however, this design lacks controls for PD natural history or placebo effects and these findings have limited utility. Overall, the Panel interpreted these data to indicate that there is no compelling evidence that verapamil delivered electromotively is an effective treatment for PD. The Recommendation is Moderate given the substantial burden associated with administration of this treatment in the absence of a body of convincing evidence demonstrating efficacy. Body of evidence strength is Grade C based on one small high-quality RCT (<25 patients exposed to verapamil) and one observational study.

Guideline Statement 8.

Clinicians may administer intralesional collagenase clostridium histolyticum in combination with modeling by the clinician and by the patient for the reduction of penile curvature in patients with stable Peyronie's disease, penile curvature >30° and <90°, and intact erectile function (with or without the use of medications). *(Moderate Recommendation; Evidence Strength Grade B)*

Discussion. The Panel emphasizes that the use of intralesional collagenase + clinician/patient modeling is appropriate only in the patient with stable disease with curvature > 30 degrees and < 90 degrees who has intact erectile function with or without the use of medications. In addition, the Panel notes that, to-date, clinical trials have not evaluated the use of collagenase in patients with hourglass deformity, ventral curvature, calcified plaque, or plaque located proximal to the base of the penis; outcomes for these patient subgroups are unknown. Further, the Panel notes that intralesional collagenase is a therapy for curvature; it does not treat pain or ED. The best evidence for the use of intralesional collagenase in combination with modeling to treat curvature is provided by four RCTs.[46-48] Additional evidence is provided by an open-label study.[49] The earliest RCT (Gelbard 1993) evaluated single injections of various doses and followed patients for three months post-treatment. Gelbard (2012) focused on up to 6 injections of 10,000 U over 18 weeks, evaluated the importance of modeling performed by the clinician, and followed patients for 4.5 months post-treatment end. The two Gelbard (2013) trials, known as the IMPRESS I and IMPRESS II trials, focused on up to 8 injections of 10,000 U over 24 weeks, and followed patients for an additional 7.5 months after treatment for a total follow up duration of one year. In these two trials, modeling was performed by the clinician after each treatment cycle and patients were instructed to perform modeling at home three times/day between treatment cycles and to attempt to straighten the penis without pain during erection. In these two studies, all patients experienced modeling (e.g., there were no placebo/sham only groups). The IMPRESS I and IMPRESS II are the definitive trials that established the current FDA-approved intralesional collagenase plus modeling protocol.

The patients treated in the 2012 trial had average PD symptom duration from 25 to 36 months across 4 treatment groups (collagenase only – n=57; collagenase + clinician modeling – n=54; placebo + clinician modeling – n=20; placebo only – n=16); average baseline curvature ranged from 48.9 degrees to 54.7 degrees. Exclusion criteria included severe pain with penile palpation by the clinician, ED that was unresponsive to PDE5 inhibitors, and lack of full erectile response to prostaglandin E1 during curvature measurement. At 36 weeks of follow-up, curvature reductions of 27.1% in the collagenase only group, 32.4% in the collagenase + clinician modeling group, and 27.9% in the placebo only group were reported. Curvature in the placebo + clinician modeling group increased by 2.5%. The average magnitude of curvature reduction was 14.7 degrees in the collagenase only group, 17.7 degrees in the collagenase + clinician modeling group, and 13.7 degrees in the placebo only group. The placebo + clinician modeling group had an average curvature increase of 1.3 degrees. The authors note that findings for the placebo only group were heavily influenced by a patient subset that experienced large curvature reductions during the study. Only patients in the collagenase + clinician modeling group reported statistically significant reductions in bother scores on the Peyronie's Disease Questionnaire (PDQ).

Patients in the IMPRESS I and II trials had average PD symptom durations of 57.6 and 40.8 months in the placebo + clinician/patient modeling groups (final Ns of 104 and 107) and of 46.8 and 50.4 months in the

collagenase + clinician/patient modeling groups (final Ns of 199 and 202). Average baseline curvature was 49.0 and 49.6 degrees in the placebo + clinician/patient modeling groups and 48.8 and 51.3 degrees in the collagenase + clinician/patient modeling groups. Patients were required to have stable disease. Exclusion criteria were more extensive than in the 2012 trial and included curvature <30 degrees or >90 degrees, isolated hourglass deformity without curvature, calcified plaque, plaque causing curvature proximal to the penis base, ED unresponsive to PDE5 inhibitors, and lack of full erectile response to prostaglandin E1 or Trimix during curvature measurement. At one year of follow-up, in the collagenase groups, curvature was reduced by mean 17 degrees (mean 34% overall; mean reduction of 17.8 degrees in IMPRESS I and mean 16.2 degrees in IMPRESS II); in the placebo + modeling groups curvature was reduced by mean 9.3 degrees (mean 18.2%; mean 10 degrees in IMPRESS I and mean 8.5 degrees in IMPRESS II). PDQ bother scores were significantly reduced in the collagenase + modeling groups but not in the placebo + modeling groups. However, approximately one-third of patients did not complete the PDQ at one or both measurement points and the PDQ has not been fully validated psychometrically. These issues create uncertainty regarding the meaning of the PDQ findings. IIEF overall satisfaction scores were significantly improved (from mean 5.6 to 6.6) among patients who received collagenase but not among patients who received placebo (from mean 5.6 to 6.0; combined analysis of patients from both trials; differences not statistically significant when trials were analyzed separately). The open-label study (Levine 2015) used essentially the same inclusion/exclusion criteria and injection protocol; it included patients who received placebo in the IMPRESS trials (n=23) and patients who participated in a pharmacokinetics study (n=20), but most patients were newly-enrolled (n=305). Approximately one-third of patients were missing PDQ data, limiting analysis to 238 patients. At week 36, curvature reduction was similar to the magnitude reported in the active treatment arms of the RCTs (mean 18.3 degrees); PDQ bother scores were significantly reduced. IIEF overall satisfaction scores improved (non-significantly) by 1.1 points.

The Panel notes that, based on the inclusion and exclusion criteria for the IMPRESS trials, the use of collagenase has only been evaluated in patients with stable disease with curvature > 30 degrees and < 90 degrees, without isolated hourglass deformity or calcified plaque or plaque located proximal to the base of the penis, and with intact erectile function (with or without use of PDE5s). In addition, the Panel emphasizes that intralesional collagenase is a therapy for curvature; it does not treat pain or ED. Intralesional collagenase is not appropriate in patients who meet curvature and plaque inclusion criteria but whose primary concerns are pain and/or ED. Further, patients should be thoroughly counseled regarding the expected average curvature reduction of 17 degrees. Clinicians should bear in mind that the average difference between the collagenase and placebo groups, although statistically significant, was only 7.7 degrees and that IIEF overall satisfaction scores improved by one point. The magnitude of treatment effect beyond placebo, therefore, is modest; this modest effect should be considered carefully in the context of potential adverse events, some of which can be serious (see guideline statement below). The Panel also notes that provision of collagenase is contingent on completion of a certification procedure provided by the manufacturer.

Body of evidence strength is Grade B. The Gelbard (2012) trial and the IMPRESS I and II trials (Gelbard 2013) are of high quality, but in the absence of replication by another group of investigators, some uncertainty remains regarding whether findings will reliably generalize across practitioners, settings, and patients. In addition, whether curvature improvements are maintained long-term remains unknown as the longest trials ended at one year of follow-up. The Recommendation is moderate given the modest size of curvature reduction in the context of a low risk of serious adverse events.

Guideline Statement 9.

Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional collagenase regarding potential occurrence of adverse events, including penile ecchymosis, swelling, pain, and corporal rupture. *(Clinical Principle)*

Discussion. It is critical for patients to have realistic expectations regarding the potential for adverse events to occur with use of intralesional collagenase. In the IMPRESS I and II trials, 84.2% of patients in the collagenase groups and 36.3% of patients in the placebo groups experienced at least one adverse event after up to 4 treatment cycles (the authors note that these adverse events were those that occurred in 1% or more of collagenase-treated patients and at a greater incidence than in the placebo group). The most common adverse events in both groups were penile ecchymosis (collagenase group: 80.0%; placebo group: 26.0%), penile swelling (collagenase group: 55.0%; placebo group: 3.2%) and penile pain (collagenase group: 45.4%; placebo group: 9.3%). Additional adverse events reported in <5% of collagenase-treated patients were blood blister, penile blister, erythema, general pruritus, painful erection, ED, skin discoloration, procedural pain, injection site vesicles, localized edema, dyspareunia, injection site pruritus,

nodule, and suprapubic pain. Most adverse events were considered mild or moderate by the investigators and resolved without intervention. Six of 551 (1.1%) collagenase-treated patients experienced serious adverse events; these were corporal rupture in three patients and penile hematoma in three patients. The three cases of corporal rupture occurred during intercourse (one case occurred in a patient who had intercourse during the required 14-day no-intercourse post-treatment period); all three were surgically repaired. Of the three cases of hematoma, one spontaneously healed, one was treated with aspiration, and one was surgically addressed. The manufacturer additionally notes that in 1,044 collagenase-treated patients (551 from the IMPRESS trials and the remainder from unpublished, uncontrolled trials), corporal rupture occurred in five patients (0.5%) and in nine patients (0.9%) a combination of penile ecchymosis or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported. Whether these nine patients had corporal rupture is not clear. Of the 1,044 patients, severe penile hematoma was reported in 39 (3.7%). In the open-label study, 85.3% of patient had treatment-related adverse events.[49] The most common adverse event was penile hematoma (in 50.7% of patients), with injection site pain, injection site hematoma, penile pain, and penile swelling reported in approximately 25% of patients. Three patients experienced serious adverse events – two severe penile hematomas and one corporal rupture. Both cases of hematoma resolved without intervention; the corporal rupture occurred during sexual activity and was surgically repaired. Patients should be carefully counseled regarding the likelihood of mild, moderate, and serious adverse events, what to do should an adverse event occur, and how to recognize an adverse event that requires urgent medical attention.

Guideline Statement 10.

Clinicians may administer intralesional interferon α-2b to patients with Peyronie's disease. ***(Moderate Recommendation; Evidence Strength Grade C)***

Discussion. Intralesional interferon α-2b was evaluated in one RCT reported in two papers,[50,51] one randomized design without a placebo group,[34] and in eight observational studies.[52-59] The multi-center RCT required that patients had PD symptoms for >12 months with curvature of at least 30 degrees; patients with calcified plaques were excluded. Patients were administered 5 MU interferon α-2b (final n = 50) every 2 weeks for 12 weeks (total of 6 injections) compared to placebo (final n = 53).[50,51] Curvature, plaque size, penile pain, erectile function (with the IIEF) and penile hemodynamics were measured at baseline and at study completion. Statistically significant improvements were documented in all outcomes except for IIEF scores (both groups improved similarly). Average curvature reduction was 13.5 degrees in the interferon group compared to 4.5 degrees in the placebo group. Average plaque size reduction was 2.6 cm^2 in the interferon group compared to 0.9 cm^2 in the placebo group. Penile pain resolved in 21 of 31 (67.7%) patients in the interferon group who reported pain at baseline but in only 9 of 32 (28.1%) of patients in the placebo group who entered the study with pain. Penile duplex Doppler ultrasound (PDDU) revealed significant improvements in peak systolic velocity (PSV) and mean resistive index in the interferon group but not in the placebo group. The proportion of men with normal vascular status increased significantly in the interferon group (from 31.5% to 57.8%) but remained the same in the placebo group (25% at both measurement points).

An additional randomized design compared vitamin E 400 IU twice daily for 24 weeks, interferon 5MU weekly for 12 weeks, and interferon 5MU weekly (for 12 weeks) + vitamin E 400 IU twicy daily (for 24 weeks).[34] In contrast to the placebo-controlled RCT, this study did not document statistically significant improvement in any measured parameter, including curvature, plaque size or pain. However, there are important differences in the patient population evaluated. In this study patients had early stage PD of <6 months duration in contrast to the RCT patients who had average symptom duration of 20 months and may have been more likely to have stable disease. Although there did not appear to be effects on curvature or plaque size, pain resolved in more patients who were administered interferon alone (71%) or interferon + vitamin E (83.3%) compared to vitamin E alone (50%). These differences were not significant given the small sample size of 10 per group. The Panel interpreted these findings to indicate that intralesional interferon may be most appropriate for the patient with stable disease.

Patient inclusion criteria and dosing regimens varied considerably across the eight observational studies. Most studies reported curvature decreases (Astorga 2000 – mean 14.2 degrees; Trost 2013 – mean 9 degrees) and/or rates of curvature improvement >60%.[53-59] Similar findings were reported for plaque size decreases and/or rates of plaque size improvement. The observational studies all reported large percentages of patients with improved pain post-treatment, ranging from 80% to 100%. Judge & Wisniewski (1997) included a placebo/sham group to which patients did not appear to be randomized; no patients in this group exhibited curvature improvement, plaque reduction, or pain improvement. The Panel notes that the overall conclusions of this group of studies regarding effects of intralesional interferon on curvature and plaque are consistent with the RCT and

findings with regard to pain are consistent with Inal (2006).

The Panel notes that, based on the RCT inclusion and exclusion criteria, the use of intralesional interferon is appropriate in the patient with stable disease with curvature > 30 degrees and without calcified plaque. In addition, the Panel notes that intralesional interferon appears to be effective for curvature, plaque size, pain, and some vascular outcomes. Patients should be thoroughly counseled regarding the expected average curvature reduction of 13.5 degrees. Clinicians should bear in mind that the average difference between the interferon and placebo groups, although statistically significant, was 9 degrees. The magnitude of treatment effect beyond placebo, therefore, is modest but does appear to occur in the context of improvements in other PD outcomes (i.e., plaque size, pain, vascular outcomes).

Body of evidence strength is Grade C based on one RCT of moderate quality and one other randomized design with somewhat divergent findings. The Recommendation is moderate given the modest size of treatment effects in the setting of frequent minor adverse events (see Guideline Statement 9).

Guideline Statement 11.

Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional interferon α-2b about potential adverse events, including sinusitis, flu-like symptoms, and minor penile swelling. *(Clinical Principle)*

Discussion. Patients should be counseled that from 40 to 100% of patients who received intralesional interferon reported sinusitis; flu-like symptoms of fever, chills, and arthralgia; and minor penile swelling with ecchymosis. These symptoms were effectively treated with over-the-counter nonsteroidal anti-inflammatory medications and did not last longer than 48 hours. In addition, the Panel notes that use of oral hydration is helpful to mitigate these transient symptoms.

Guideline Statement 12.

Clinicians may offer intralesional verapamil for the treatment of patients with Peyronie's disease. *(Conditional Recommendation; Evidence Strength Grade C)*

Discussion. The Panel notes that the evidence for the use of intralesional verapamil is weak; clinicians should carefully consider whether the use of this treatment is appropriate given the substantial uncertainty regarding its efficacy and the availability of other treatments that are clearly more effective. Intralesional verapamil was evaluated in nine randomized designs, including two RCTs, and eight observational studies. This literature is challenging to interpret given the varied patient inclusion criteria, including the focus on patients in the active disease stage with dynamic and evolving symptoms; varied treatment protocols; and the conflicting findings reported. The two RCTs enrolled patients with moderately long disease durations – mean 16 months in Rehman (1998)[60] and mean 21.3 months in Shirazi (2009).[61] In Rehman (1998), at baseline, patients had mean curvature of 37.7 degrees in the verapamil group and mean 33.6 degrees in the placebo group. In Shirazi (2009), the curvatures were greater, with mean curvature of 49.7 degrees in the verapamil group and 45.6 degrees in the placebo group. Dosing regimens varied considerably, with patients administered 10 – 27 mg intralesional verapamil weekly for 6 months in Rehman (1998) and 10 mg verapamil twice weekly for 12 weeks in Shirazi (2009). Rehman (1998) reported significant decreases in plaque length, width, and volume in the verapamil group but not in the placebo group with a trend ($p = 0.07$) for a curvature reduction in the verapamil group but not the placebo group. All patients who had pain at baseline were pain-free at study end. In contrast, Shirazi (2009) reported that both groups exhibited similar small curvature decreases, plaque area decreases, and pain improvement rates.

The other randomized designs compared verapamil 10 mg in different volumes (4 ml, 10 ml, 20 ml),[62] intralesional verapamil alone compared to intralesional verapamil plus oral anti-oxidants,[63] verapamil delivered both intralesionally and by EMDA with or without various oral supplements,[64,65] intralesional verapamil to oral pentoxifylline and the two treatments combined,[66] verapamil 10 mg + dexamethasone 4 mg intralesionally compared to by EMDA,[67] and verapamil 10 mg intralesional compared to hyperthermia.[68] Cavallini (2007) reported that as injection volume increased, curvature and plaque area exhibited greater decreases with the largest reductions in the 20 ml group. Favilla (2014) reported that patients in the verapamil only and the verapamil + oral anti-oxidants exhibited similar improvements in curvature and plaque volume. The group that received anti-oxidants reported larger improvements on the IIEF-15 and its subscales. Note that these patients were in the acute phase in which symptoms are dynamic and the study did not include a no-treatment or natural history control group. Paulis & Cavallini (2013) reported that verapamil delivered intralesionally as well as via EMDA with or without an herb and anti-oxidant supplement resulted in greater curvature reduction and plaque improvement in the supplemented group; pain improvement rates were >85% in both groups. In Paulis (2013) both groups were administered verapamil intralesionally + via EMDA

with an additional topical treatment (diclofenac) and oral anti-oxidants. The groups differed only in terms of whether they received vitamin E. The group that received vitamin E reported larger improvements in curvature and plaque and had a greater pain improvement rate (95%) compared to the non-vitamin E group (81%). In Paulis & Cavallini & Giorgio (2013), an observational study, one group was administered verapamil intralesionally via EMDA with an additional topical treatment (diclofenac) and oral anti-oxidants, including vitamin E, and one group had no treatment. When the 18 month treatment period concluded, the active treatment group exhibited curvature and plaque volume reductions and decreased pain; the no treatment group experienced increased curvature and plaque volume and new onset of pain in previously pain -free patients. Alizadeh (2014) reported that patients administered oral pentoxifylline, intralesional verapamil, or the two treatments combined exhibited similar curvature and plaque volume improvements; the combined group had somewhat greater pain reductions and ED improvement than did the pentoxifylline only group. However, this study is difficult to fully evaluate because no data are provided that convey magnitude – only proportions of patients who improved for each outcome. Mehrsai (2013) reported that verapamil + dexamethasone delivered by EMDA resulted in greater plaque reductions than the same substances delivered intralesionally. In contrast, Perugia (2005) reported minimal curvature reduction in the verapamil group but large curvature reduction in the hyperthermia group, similar plaque size reductions in both groups, and 100% pain improvement rates in both groups. Because this group of studies did not include placebo groups, patient inclusion criteria varied, and most studies evaluated combination treatments, definitive interpretation is difficult.

An additional group of seven observational studies evaluated intralesional verapamil[69-73] and intralesional verapamil compared to extracorporeal shock wave therapy (ESWT) or combined treatment.[74,75] Most studies reported that intralesional verapamil reduced curvature; findings with regard to plaque were mixed. The four studies that reported on pain noted that most or all patients had pain improvement or resolution.[71,72,74,75] The overwhelming weakness of these studies, however, is the failure to control for change over time in PD symptoms independent of treatment or for placebo effects. Pain is particularly susceptible to placebo effects; findings with regard to pain from these studies are of unknown validity.

The Panel interpreted these data to mean that clinicians who consider the use of intralesional verapamil as a treatment for symptoms of PD should fully consider the weakness of the evidence demonstrating its efficacy. In particular, clinicians should be aware that the lack of control for PD natural history in most of the available literature creates substantial uncertainty, particularly given the focus on patients in the acute phase with symptoms that are in a dynamic state. The Panel notes that the overall balance between benefits and risks/ burdens of intralesional verapamil, therefore, remains unclear given these concerns. Body of evidence strength is Grade C based on the conflicting findings from the two RCTs and the additional, largely unreplicated findings provided by the other randomized studies in the absence of adequate control groups.

Guideline Statement 13.

Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional verapamil about potential adverse events, including penile bruising, dizziness, nausea, and pain at the injection site. *(Clinical Principle)*

Discussion. Of the 17 studies that evaluated intralesional verapamil, four (including two RCTs) did not address adverse events.[60,61,67,70] Six studies reported that no adverse events occurred.[25,63-65,74,75] The remaining studies reported a range of minor adverse events, including penile bruising in 15% to 66% of patients,[62,69,71,73,] dizziness or nausea in 2% to 10% of patients,[66,68,72] loss of libido (10%),[68] weakness (16.7%),[66] transient pain at the injection site (2%),[72] and sweating (23.3%).[66] Patients should be counseled regarding the possibility of these adverse events.

Guideline Statement 14.

Clinicians should not use extracorporeal shock wave therapy (ESWT) for the reduction of penile curvature or plaque size. *(Moderate Recommendation; Evidence Strength Grade B)*

Discussion. Nineteen studies evaluated the effects of ESWT. Three studies were RCTs,[76-78] one was a randomized design without a placebo/sham group[79] and the remaining studies were observational designs.[80-94] In the randomized trials, patient inclusion criteria varied considerably from stable disease for >6 months without any prior PD treatment,[76] to stable disease for at least 3 months with previous unsuccessful oral treatment[77] to disease <12 months with pain and no previous PD treatment[78] to disease </= 12 months with pain and ED.[79] Treatment durations ranged from 4 to 6 weeks with typically 1 session per week; the number of shock waves (SWs) ranged from 2000 to 3000 and the mJ per mm^2 ranged from 0.25 to 0.29. Three trials followed patients for six months after treatment ended,[76,78,79] Hatzichristodoulou (2013) followed patients for approximately one month post-treatment. Sample sizes were approximately 50 per group in Hatzichristodoulou (2013), Palmieri (2009), and

Palmieri (2012). In Chitale (2010), sample sizes were smaller with n = 16 in the ESWT group and n = 20 in the placebo/sham group.

None of the randomized designs reported a benefit of ESWT on curvature and plaque. Chitale (2010) reported no effects of ESWT to improve curvature and that plaque size remained unchanged in both groups. Hatzichristodoulou (2013) reported that curvature was reduced similarly in the active and sham treatment groups, with statistically similar percentages of patients experiencing improvement and worsening of curvature and plaque. Palmieri (2009) reported small non-significant decreases in curvature and plaque for the ESWT group and small increases in curvature and plaque for the placebo/sham group. Palmieri (2012), which compared ESWT to ESWT + tadalafil, reported similar small curvature and plaque decreases for both groups. The observational studies reported conflicting findings, from no change in curvature to large curvature decreases and from zero patients experiencing curvature reduction to >75% of patients experiencing curvature reductions. Most observational studies that addressed plaque outcomes, however, were consistent with the randomized trial findings and reported no benefit of ESWT.[81,83,88,91,93]

The Panel interpreted these data to mean that ESWT does not reliably improve curvature or plaque in PD patients; ESWT, therefore, should not be used by clinicians for this purpose. Body of evidence strength is Grade B based on three RCTs (two of high quality – Chitale 2010 and Palmieri 2009; and one of moderate quality – Hatzichristodoulou 2013) and one other randomized design (Palmieri 2012).

Guideline Statement 15.

Clinicians may offer extracorporeal shock wave therapy (ESWT) to improve penile pain. (*Conditional Recommendation; Evidence Strength Grade B*)

Discussion. Four randomized designs, including three RCTs, addressed the effects of ESWT to decrease pain. Hatzichristodoulou (2013) reported that mean pain scores on a visual analog scale decreased more among ESWT patients (from baseline value of 4 to post-treatment value of 1.5) than among placebo/sham patients (from baseline value of 4 to post-treatment value of 3). In addition, 85% of ESWT patients with pain reported decreases compared to 48% of the placebo/sham group. Palmieri (2009) also reported that mean pain scores on a visual analog scale decreased more in the ESWT group (from 5.5 at baseline to 0.46 at 24 weeks) than in the placebo/sham group (from 5.2 at baseline to 2.7 at follow-up). Palmieri (2012), which compared ESWT to ESWT + tadalafil, reported similar large pain level decreases in both groups (ESWT only – from 5.2 at baseline to 0.45 at 24 weeks; ESWT + tadalafil – from 4.9 at baseline to 0.43 at 24 weeks). In Chitale (2010) both groups had similar pain level decreases on a visual analog scale but baseline pain levels were low (ESWT – baseline 1.5, post-treatment 0.5; Placebo/Sham – baseline 1.2, post-treatment 0.4), limiting the range of responses.

All but one of the observational studies that measured pain reported either decreases on a VAS, large percentages of patients reporting improvement, and/or increased percentages of patients reporting pain-free status at study end.[80,82-89,91-93] The exception was Poulakis (2006) which reported that ESWT patients had pain decreases (from baseline 6.0 on VAS to post-treatment value of 1.0) that were similar to those reported by a no-treatment control group (baseline 6.0 to 2.0 over the same period).[90]

The Panel interpreted these data to indicate that ESWT may reduce pain in PD patients. Body of evidence strength is Grade B based on three RCTs (two of high quality;[76,78] and one of moderate quality[77]) and one other randomized design.[79] The Recommendation is Conditional because the broader PD literature indicates that pain is the PD symptom that is most likely to resolve over time without intervention, the patient burden involved in obtaining ESWT treatment to treat pain may be substantial, and other treatments may be equally effective at alleviating pain. Further, ESWT is associated with frequent adverse events. These include localized petechial bleeding or bruising in from 5% to 90% of patients with most studies reporting rates of 50% or greater, urethral bleeding or transient hematuria in from 1.9% to 100% of patients with most studies reporting rates <10%, and minor ecchymosis in from 3.6% to 16% of patients. Importantly, although severe adverse events are infrequent, the most common severe adverse event is pain – reported in 1.9% to 4.0% of patients. Given that ESWT is recommended to treat pain but not other symptoms of PD, the clinician and patient must carefully weigh the risk of adverse events, particularly increased pain, against the potential benefit of pain relief.

Guideline Statement 16.

Clinicians should not use radiotherapy (RT) to treat Peyronie's disease. (Moderate Recommendation; Evidence Strength Grade C)

Discussion. Eight observational studies evaluated the use of radiotherapy (RT) to treat PD.[95-102] A wide range of RT doses was used, ranging from 2.2 Gy to 45 Gy, generally administered in 1.5 to 2.0 Gy fractions. Most studies followed patients for considerable periods with four studies reporting outcomes at >5 years post-

treatment. All studies were single group designs except for Furlow (1975), which provided data on two RT doses (one treatment of 2.2 to 5.5 Gy vs. two treatments with total 4.4 to 10.4 Gy) and a no-treatment comparison group. Inclusion criteria were minimally reported, with most papers indicating that patients had a diagnosis of PD.

With regard to effects on curvature, studies reported that from 6.3 to 52% of patients reported curvature improvement and from 2.0 to 28% of patients reported curvature worsening. However, Furlow (1975) noted that rates of curvature improvement were similar across the two RT groups (50% and 39%) and the no treatment control group (52%). From 13.3 to 66.4% of patients reported plaque improvement and from 0 to 6.0% reported plaque worsening. Again, Furlow (1975) noted that improvement rates for the RT groups (55% and 44%) were essentially the same as for the no treatment control group (58%). Pain improvement rates ranged from 54 to 100%, but Furlow (1975) reported that pain improvement rates were indistinguishable across the two RT groups (100% and 92.3%) and the no treatment control group (100%). Because PD is characterized by symptoms that change over time, some of which resolve without intervention and some of which (i.e., pain) are susceptible to placebo effects, observational designs are of limited utility to understand whether or not a treatment might be effective. This group of studies has the additional limitation of relying largely on subjective patient impressions of curvature and plaque changes – judgments known to be poorly correlated with objective measures— rather than using more rigorous measurement protocols. Further, the information provided by Furlow (1975) suggests that any changes in symptoms may be readily attributable to the passage of time. [96]

Given the potential risks of exposing patients to RT in the context of unproven benefits, the Panel interpreted these data to mean that RT should not be offered to patients with PD. Body of evidence strength is Grade C because of observational designs and poor measurement protocols. The Recommendation is Moderate given concerns that exposure to unnecessary radiation has unknown consequences and presents a potential moderate health risk in the setting of uncertain benefits.

Guideline Statement 17.

Clinicians should assess patients as candidates for surgical reconstruction based on the presence of stable disease. *(Clinical Principle)*

Discussion. Patients who are considering surgical reconstruction as a treatment for PD should be in the stable phase of the disease. Typically, PD lesions become stable at 12 to 18 months after symptom onset. The most common inclusion criteria for surgical studies are the presence of PD symptoms for at least 12 months and stable curvature for 3 to 6 months. It should be noted that this literature focuses almost entirely on patients with stable disease; surgical outcomes for patients with active disease are not known. The Panel, therefore, comments only on patients with stable disease. The pre-surgical evaluation should query the patient regarding when symptoms began to determine whether the patient is likely to be in the stable phase and should establish, by clinician follow-up or by patient report, that PD symptoms have been clinically unchanged for at least three months. In the Panel's expert opinion, the distinguishing features of stable disease are deformity and plaque(s) that are unchanging and non-progressive. Patients with stable disease may have pain, but typically pain is associated with erection only. The evaluation should establish and document through appropriate diagnostic methods (see Discussion under Guideline Statement 2): the location (e.g., proximal, mid, distal), direction of curvature (e.g., dorsal, lateral, ventral), and degree of curvature; the presence of other deformities such as indentation, hinge, narrowing, hourglass, or shortening; the presence, location, and extent of plaque(s), including whether any are calcified; the presence and degree of ED; the extent to which deformity and/or pain in the patient with normal erectile function interferes with intercourse for the patient and partner; and, the presence and degree of distress. This information is critical to appropriately counsel patients regarding the various options available and which options may be most suitable for a particular patient. This information also is needed to counsel patients regarding expected outcomes. For example, although most surgical strategies will improve or eliminate curvature, surgical therapies other than prosthesis implant generally do not restore erectile function in patients with ED that is unresponsive to pharmacotherapy or vacuum constriction devices. If the patient's priority is full sexual function, and he has ED refractory to pharmacotherapy, then he and his partner should be counseled to consider prosthesis implantation.

Guideline Statement 18.

Clinicians may offer tunical plication surgery to patients whose rigidity is adequate for coitus (with or without pharmacotherapy and/or vacuum device therapy) to improve penile curvature. *(Moderate Recommendation; Evidence Strength Grade C)*

Discussion. Sixty observational studies reported outcomes for 2,958 patients who had tunical plication

surgeries of various types. [9,11,103-161] This technique is the most common surgical strategy used to treat PD patients, representing approximately half of all surgeries conducted on PD patients (51.0% of 5,818 patients who underwent surgical reconstruction other than prosthesis surgery). Studies in which all patients had plication as well as grafting are included in this section.

The most commonly-reported outcome was the percent of patients who experienced curvature improvement post-surgery reported in 54 study arms. Forty-two study arms reported improvement rates of 90% or higher, with the majority of studies in this group reporting curvature improvement rates of 100%. Seven studies reported rates between 80 and 89%.[9,107,108,118,146,156,158] The remaining studies had curvature improvement rates that ranged from 42% to 79%.[104,119,136,139,143]

Other outcomes were only sparsely reported. For example, a subset of studies reported rates of ED pre- and post-surgery. However, only a few studies validly measured erectile function before and after surgery. In this group, Savoca (2000 & 2004) reported that at baseline no patient had ED as measured by nocturnal penile tumescence (NPT), color Doppler sonography, MRI and/or cavernosometry but that at mean 89 months follow-up 12.9% of 218 patients experienced ED as measured by the IIEF-5. Iacono (2012) and Kayigil & Okulku (2013) administered the IIEF-15 and all it subscales pre-operatively and at mean 24 and 18 months post-surgery, respectively, most subscales demonstrated improvement. Rolle (2005) administered the IIEF-5 pre- and post-operatively and at mean 12 months post-surgery scores had improved slightly (from mean 17.8 to mean 19). Cantoro (2014) also administered the IIEF-5 and reported that at mean 103 most post-surgery, 88.7% of patients maintained IIEF-5 scores >21 while 11.3% had scores between 10 and 21. None of these patients had ED pre-surgery. Brock (1993) evaluated patients pre-surgery, some of which had ED at baseline, and at mean 18 months post-surgery using Doppler sonography and intracavernosal injections; no change in erectile function occurred. Cormio (2002) evaluated patients with intracavernosal injections pre- and post-surgery; at mean 30 months post-surgery patient responses on the ICI test remained the same. It is difficult to draw conclusions regarding ED based on the few data available.

Thirty-three studies reported rates of persistent change in penile sensation. Twenty-one studies reported rates ranging from 0% to 10%,[104,109-111,117,118,121,123,125,128,130,133-137,142,147,153,160,161] three studies reported rates between 11% and 20%,[132,136,149,150] and the remaining nine studies reported rates from >20% to 66%.[11,127,138,143,144,148,154,157,158] Some studies reported changes in penile dimension but only a few studies actually measured SPL before and after surgery. Among these studies, Bokarica (2005) reported that shortening occurred in 100% of patients with an average decrease in length of 2.64 cm. Cantoro (2014) reported that shortening occurred in 100% of patients with 22.5% experiencing length reductions of 1.5 to 3 cm and 77.5% experiencing reductions of <1.5 cm. Savoca (2000) also reported that shortening occurred in 100% of patients and that it was "significant" (defined as 1.5 to 3 cm) in 14% of patients and "non-significant" (defined as <1.5 cm) in 86% of patients. Chung (2014) reported that shortening of ≥2 cm occurred in 22.2% of patients. Hudak (2013) reported on two groups of patients -- one group with simple curvature and one group with complex, biplanar curvature or curvature > 60 degrees. The percentage of men who experienced an SPL decrease was 11% in Group 1 and 23% in Group 2; however, mean pre- and post-operative SPLs were 14.6 cm and 14.5 cm for Group 1 (average decrease of 0.1 cm) and 14.6 cm and 14.6 cm for group 2. Adibi (2012) focused on men with complex deformity and reported that SPL was unchanged in 69%, increased an average 0.65 cm in 16%, and decreased 0.5 cm in 14%. Taylor & Levine (2008) reported a mean 0.6 cm increase in SPL from pre- to post-surgery with 18% of patients losing mean 1.2 cm in length and the remaining patients either remaining the same or gaining up to 3.5 cm. in length. Greenfield (2006) reported that patients lost a mean 0.36 cm post-surgery but patients with ventral curvature with or without a lateral component experienced significantly greater losses by percent (4.3 and 5.6% respectively) than did patients with dorsal (0.5%), lateral (1.0%) , or dorsal-lateral curvatures (1.1%). Dugi & Morey (2009) reported that SPL measurements did not differ pre- to post-surgery.

Forty-three study arms reported at least one category of adverse event. The number of studies that reported particular adverse events and the ranges for those adverse events are listed in Table 2. The incidence of serious adverse events, such as hematoma requiring reoperation or major skin necrosis, was low. The most frequently-reported AE was the presence of palpable or painful sutures; of the eleven studies that reported this AE, eight of them reported rates >10%.

Thirty-one studies reported patient satisfaction rates ranging from 41% to 100%.[11,77,103,114-116,118,120,121,125,127-132,136,137,144,147-151,153-159,161] Nineteen studies reported rates >80%. Only four studies reported partner satisfaction rates, which ranged from 50% to 88.4%.[137,144,147,158]

The Panel interpreted these data to indicate that for most patients plication surgery results in curvature

Table 2: Adverse Event Rates in Surgical Plication Studies			
	# of Studies Reporting	Minimum Percent	Maximum Percent
Urethral laceration	7	0.00	4.35
Urinary retention	4	1.40	16.70
UTI	2	0.60	0.64
Superficial skin necrosis minor	2	0.46	8.30
Skin necrosis major	1	0.46	0.46
Hematoma	9	0.00	10.91
Hematoma requiring reoperation	5	0.00	1.38
Wound infection	13	0.00	6.70
Chest infection	2	1.70	2.87
Palpable or painful suture	11	0.00	35.5
Suture granuloma	6	0.46	3.60
Phimosis	8	0.00	5.10
Persistent erectile or penile pain post-surgery	8	0.00	27.60

correction in the setting of a relatively low risk of serious adverse events. The Panel notes that because plication surgery is not a treatment for ED and because the consequences of plication surgery with regard to erectile function remain unclear, the most appropriate candidates for plication surgery are patients with intact erectile function or with ED responsive to oral medications or vacuum pump therapy or ICI therapy. The Panel emphasizes the importance of obtaining objective baseline measures of PD signs and symptoms in order to adequately counsel patients and rationally evaluate surgical outcomes. Hudak (2013) reported that while 84% of patients had no measurable decrease in SPL, 78% reported a perceived penile length reduction. Taylor & Levine (2008) reported that 69% of patients perceived a post-surgery loss in penile length but a loss could be documented in only 18%.

Body of evidence strength is Grade C given the observational designs, the range of patient inclusion criteria, the variations in plication surgery performed, and the range of follow-up durations. The Recommendation is Moderate given the clear benefit of plication surgery to ameliorate curvature in most patients in the setting of relatively few serious adverse events.

Guideline Statement 19.

Clinicians may offer plaque incision or excision and/or grafting to patients with deformities whose rigidity is adequate for coitus (with or without pharmacotherapy and/or vacuum device therapy) to improve penile curvature. *(Moderate Recommendation; Evidence Strength Grade C)*

Discussion. Eighty-eight observational studies reported outcomes for 2,585 patients who had plaque incision and/or excision and grafts.[11,106,108,127,129,132,135,136,139,142,162-239] In a few cases, these techniques were combined with additional procedures such as plication or concomitant Nesbit procedure (e.g., Trieber & Gilbert 1991; Taylor & Levine 2008). This set of techniques is the second most common surgical strategy used to treat PD patients, used in approximately 44% of the 5,818 PD patients who underwent surgical reconstruction other than prosthesis surgery.

Similar to other surgical procedures, the most commonly-reported outcome was the percent of patients who experienced curvature improvement; this information was reported in 72 study arms (some studies reported on more than one group of patients). Improvement rates ranged from 25% to 100% with 64 study arms reporting rates >80% and 57 study arms reporting rates >90%.

Thirty-six studies validly measured erectile function before and after surgery.[108,163,169,174,176,179-183,185,188,193,194,197,200,201,203,204,207,209,210,214-216,218-222,225,228,229,235,238,239] Findings from these studies are mixed, with some studies reporting no change in erectile function post-surgery, some reporting that erectile function deteriorated in some patients, and some reporting that erectile function improved in some patients.

Nineteen studies reported rates of persistent change in penile sensation ranging from 0% to 25%. Ten studies reported rates of 0%,[180,182,183,193,197,203,204,220,235,238] five reported rates of <5%,[163,194,207,214,225] and the remaining four studies reported rates that ranged from 9.8% to 25%.[181,185,210,215] Eleven studies measured SPL before and after surgery and reported rates of penile shortening from 0% to 63%. Four studies reported rates of 0%[200,220,235,238] and the remaining studies reported rates ranging from 15.4% to 63%.[163,169,181,207,214,221,228] Four studies reported the mean degree of shortening; these were 0.2 cm,[214] 0.5 cm,[169] 0.7 cm,[207] and 1.0 cm.[228] Several studies reported penile lengthening in 21% to 100% of patients with average increases ranging from 1.0 cm to 2.2 cm.[169,200,207,220,238]

Adverse events were sparsely reported in this

literature. The only adverse events reported by more than a few studies were hematoma rates reported by 12 studies (range 0 to 26%), with ten studies reporting rates <10%, and wound infection rates reported in 11 studies (range 0 to 9%), with eight studies reporting rates of 0%.

Patient satisfaction rates were reported in 12 studies and ranged from 40.9% to 93.3%; eight studies reported rates above 80%. Partner satisfaction rates were reported in four studies and ranged from 72% to 100%.

The Panel interpreted these data to indicate that, for most patients, plaque incision and/or excision with grafting results in curvature correction in the setting of a relatively low risk of serious adverse events. The Panel notes that because these surgical strategies are not treatments for ED and because the consequences of surgery with regard to erectile function remain unclear, the most appropriate candidates for surgery are patients with intact erectile function or with ED responsive to oral medications or vacuum pump therapy.

Body of evidence strength is Grade C given the observational designs, the range of patient inclusion criteria, the variations in surgical techniques performed, and the range of follow-up durations. The Recommendation is Moderate given the clear benefit of surgery to ameliorate curvature in most patients in the setting of relatively few serious adverse events.

Guideline Statement 20.

Clinicians may offer penile prosthesis surgery to patients with Peyronie's disease with erectile dysfunction (ED) and/or penile deformity sufficient to impair coitus despite pharmacotherapy and/or vacuum device therapy. *(Moderate Recommendation; Evidence Strength Grade C)*

Discussion. Forty-three observational studies reported on outcomes for 2,216 PD patients who had penile prosthesis surgery.[9,104,110,129,135,142,183,215,217,218,221,235,240-270] This literature is challenging to interpret because of: the observational designs; the small sample sizes (approximately half of the studies reported on <25 patients); the diversity of surgical techniques and prostheses employed; the fact that approximately half of the studies do not specify a prosthesis type or note that various prostheses were used; the large range of follow-up durations from immediately post-surgery to four to six years post-surgery; and the provision of limited information regarding patient characteristics, outcomes, and follow-up procedures. In addition to prosthesis implantation, most studies used other surgical procedures, including modeling, plication, plaque incision or excision, tunica albuginea incision, and/or grafts of various materials.

The most commonly-reported outcome was the percent of patients who reported curvature improvement post-surgery. Twenty-six studies reported this information.[9,104,110,129,142,183,221,235,241,242,245,247,249-255,257,262,264-267,270] All studies reported rates of >80% and twenty studies reported improvement rates of 100%. In addition, seven studies reported the percent of patients who experienced complete penile straightening with a range from 85 to 100%.[242,245,249,255,259,262,266]

Other penile outcomes were reported by a small number of studies. Although several studies reported penile shortening information based on patient perception, only three studies actually measured SPL before and after surgery. Usta (2003) reported on two groups of patients. No shortening occurred among patients who had the AMS 700CX or Mentor Alpha I implanted in combination with modeling, plaque incision/excision, and pericardial graft. Among patients who had the AMS 700CX or Mentor Alpha I implanted with modeling only, 6.4% experienced shortening (Usta 2003). Zucchi (2013) noted no shortening among patients who had the Virilis I implanted with plaque incision and pericardial graft. Montorsi (1996) reported that 30% of patients experienced shortening with implant of the AMS 700CX with or without plaque incision/excision and lyodura graft. Six studies that measured SPL reported penile lengthening data. Length increases ranged from 1.3 to 3.6 cm. These studies used different surgical procedures (Egydio 2013 – various unspecified prosthesis with pericardium graft for lengthening; Djordjevic & Kojovic 2013 – malleable or inflatable prosthesis with TA incision; Montorsi 2001 – AMS 700CS inflatable with TA incision; Austoni 2005 – soft silicon prosthesis with plaque incision/excision and saphenous vein graft; Sansalone 2012 – various inflatable prostheses with circumferential lengthening graft; Zucchi 2013 – Virilis I axial with plaque incision and pericardial graft).

Fourteen studies reported percentages of patients that experienced persistent changes in penile sensation ranging from 0 to 50%; seven studies reported rates of 5% or less.[215,235,240,245,246.255,269] Three studies reported rates of 7%[261] or 8%.[142,259] Two studies reported rates of 20% -- these studies used either circumferential lengthening procedures with graft (Sansalone 2012) or plaque incision with graft (Zucchi 2013). Marzi (1997) had a rate of 28.6% after using malleable prostheses with or without plaque excision. Montorsi (2001) reported a rate of 40% after implanting the AMS 700CX and using relaxing TA incisions.

Adverse events were sparsely reported in this

literature. Only half of the studies reported data on post-operative infection rates. Five studies reported rates of 0%,[241,245,250,257,258] seven studies reported rates of <3%[218,246,249,251,254,255,269] and eleven studies reported rates ranging from 3.5 to 12.0%.[135,240,242,244,249,252,253,258,261,262,267] One study (Rigaud & Berger 1995) reported a rate of 60%. This study had only 5 patients and used an unspecified inflatable prosthesis with circumferential lengthening GoreTex graft. Twenty-seven studies reported rates of infection that required surgical revision or prosthesis explant. Fifteen studies reported rates of 0 to 3%.[129,218,240,241,245,246,248-252,254,255,263,269] Eleven studies reported rates between 3.4% and 16.7%.[104,135,183,242,244,249,253,262,265,267,268] Rigaud & Berger (1995) reported a rate of 40%.

Revision rates for mechanical failure were reported by nineteen studies. Eleven studies reported rates of < 5%.[129,135,241,245,249,250,251,252,254,261,263] The remaining studies reported rates ranging from 6.0% to 33.3%.[110,243,244,246,253,268,269] The studies with the highest rates used either modeling or complex surgical procedures in addition to prosthesis implantation, however, other studies with equally complex procedures had revision rates <5%. Surgical complexity, therefore, is not a strong predictor of high revision rates. Revision rates for patient dissatisfaction or discomfort were reported by twelve studies. Seven studies reported rates of 5% or less.[249,250,251,253,255,267,268] The remaining studies reported rates ranging from 5.8% to 17%.[245,246,249,259,260] The highest rates were reported in Montorsi (1993) and Montorsi (1995). In both studies the Finney semi-rigid prosthesis was used and patients who had revision for dissatisfaction had replacement with AMX Ultrex models. Other adverse events associated with surgery, such as urethral laceration, urethral erosion, or hematoma, were addressed by five or fewer of the prosthetic surgery studies.

Twenty-four studies reported patient satisfaction rates.[110,129,217,221,235,240,242,243,245,246,248,249,250,251,255,257,259,260,261,262,266,267,268] All rates were above 70% except for Montorsi (1993) and Montorsi (1995) which had rates of 48% and 51% respectively. These study arms used the Finney semi-rigid prosthesis and had large numbers of patients who requested revision because of dissatisfaction with the device. Only six studies reported partner satisfaction rates.[235,240,257,259-,260,261] Rates ranged from 75 to 90% satisfied with the exception of rates from Montorsi (1993) and (1995) which used the Finney semi-rigid prosthesis. In these two study arms rates were 40% and 41% respectively – likely because a large number of patients had revisions for patient dissatisfaction.

The Panel interpreted these data to indicate that for the majority of patients penile prosthesis implant results in curvature correction and restoration of satisfactory sexual function in the context of surgical adverse event rates that are relatively low in most studies. Body of evidence strength is Grade C based on the observational designs. The Recommendation is Moderate given the clear benefits of surgery to ameliorate symptoms of PD with the relatively low risk in most studies of serious adverse events such as infection or the need for revision.

Guideline Statement 21.

Clinicians may perform adjunctive intra-operative procedures, such as modeling, plication or incision/grafting, when significant penile deformity persists after insertion of the penile prosthesis. *(Moderate Recommendation; Evidence Strength Grade C)*

Discussion. Of the 43 prosthetic surgery studies reviewed, 33 utilized intra-operative procedures such as modeling, plication, plaque incision or excision, TA incision, and/or grafting as adjunctive techniques to prosthesis insertion to achieve optimal curvature correction and penile dimensions. The Panel interpreted this literature to indicate that adjunctive procedures are frequently necessary to achieve patient and clinician goals for prosthesis surgery. The Panel notes that the available adverse event evidence suggests no correlation between surgical complexity and infection or revision rates or patient satisfaction. Therefore, the clinician may at his or her discretion employ the necessary techniques to achieve optimal surgical outcomes.

Body of evidence strength is Grade C given the observational study designs. The Recommendation is Moderate given the benefits of adjunctive procedures to maximize curvature reduction and penile dimensions in the setting of a low risk in most studies for serious adverse events.

Guideline Statement 22.

Clinicians should use inflatable penile prosthesis for patients undergoing penile prosthetic surgery for the treatment of Peyronie's disease. (Expert Opinion)

Discussion. In the Panel's experience, inflatable prostheses containing reinforced silicone or the material bioflex® result in fewer adverse events and are associated with high rates of patient satisfaction. It is the Panel's expert opinion that these types of prostheses should be used for PD patients. The Panel further notes that modeling to maximize curvature correction is difficult to accomplish with semi-rigid devices. Given that it is not possible to know whether

modeling is needed until the operation begins, the choice of a prosthesis that allows modeling is optimal.

Other Treatments.

The Panel identified the treatments reviewed below as possibly promising but for which insufficient evidence currently exists to support even a Conditional Recommendation for their use. In the Panel's view, the treatments in this category are unproven until a larger and/or more rigorous evidence base is available.

Oral Therapies. ***Colchicine.*** Five studies evaluated the effects of colchicine either alone or in combination with another oral treatment.[271-275] One study was a randomized design with a comparison group administered ibuprofen (Prieto Castro 2003). Although studies generally reported that large proportions of patients exhibited improvements in curvature, plaque, and pain, without controls for the natural history of PD these data remain of uncertain utility.

Pentoxifylline. One randomized design without a placebo control[66] and one observational study with a no treatment comparison group[276] reported on the effects of pentoxifylline. Alizadeh (2014) compared oral pentoxifylline to intralesional verapamil and combined treatment. Similar proportions of patients in each group experienced curvature and plaque improvement. More patients in the combined group experienced pain reduction and ED improvement than in the pentoxifylline only group. This study is difficult to interpret, however, because only proportion data are provided (no data reflecting magnitude of change are reported) and the study lacks a control for PD natural history. Smith (2011) reported that 92% of the pentoxifylline group had plaque improvement or stabilization compared to 44% of the no treatment group. The Panel judged that some uncertainty remains regarding the efficacy of pentoxifylline given the limited evidence base; replication in a randomized design is needed before pentoxifylline can be recommended as a PD treatment.

Potassium aminobenzoate. One RCT with a high risk of bias[277] and one observational study[278] evaluated the effects of potassium aminobenzoate. Similar proportions of patients experienced curvature improvement in the active and placebo arms of the RCT but plaque volume decreased more in the active treatment arm than in the placebo arm. The Panel judged that the efficacy of potassium aminobenzoate is unproven given the limited evidence base and the fact that <100 patients have been evaluated; replication in a high-quality randomized design is needed before it can be recommended as a PD treatment.

Co-enzyme Q10. Co-enzyme Q10 was evaluated in one RCT.[279] The authors reported that CoQ10 significantly reduced curvature and plaque size and increased IIEF-5 scores in the active treatment group compared to the placebo group. There were no effects on pain. The efficacy of CoQ10 is unproven given the existence of only one study and the fact that <100 patients were administered CoQ10; replication in a high -quality randomized design is needed before it can be recommended as a PD treatment.

Topical Therapies. ***Magnesium or verapamil.*** Topical magnesium or verapamil were evaluated in comparison to placebo in one RCT.[280] Topical verapamil improved curvature and reduced plaque compared to placebo. More patients experienced curvature improvement and plaque reduction in the verapamil group compared to the placebo group. The magnesium sulfate group had results comparable to the placebo group. In the open-label phase of this trial in which patients continued with topical verapamil, the improvements documented in the randomized phase continued. Uncertainty remains regarding the efficacy of topical verapamil given the existence of only one study and the fact that <20 patients were administered verapamil; replication in a high-quality randomized design with a larger sample size is needed before it can be recommended as a PD treatment.

Topical liposomal recombinant human superoxide dismutase (LrhSOD). Two studies examined the effects of topical LrhSOD – one crossover trial[281] and one observational study.[282] Topical LrhSOD for four weeks significantly reduced pain compared to placebo. In the open-label phase of this trial, pain improvement continued. Effects on curvature and plaque were not evaluated in the randomized phase but curvature improvements were noted in 23% of patients and plaque reductions in 47% of patients in the open-label phase. In the observational study, 25% of patients reported curvature improvement, 56% reported plaque improvement, and 100% reported pain improvement. Uncertainty remains regarding the efficacy of topical LrhSOD given the small body of evidence, and the fact that <60 patients were administered LrhSOD; replication in a high-quality randomized design with a larger sample size is needed before it can be recommended as a PD treatment.

Electromotive therapies. ***Electromotive verapamil + dexamethasone.*** Six studies, including two randomized designs without placebo control groups[67,283] and four observational studies evaluated electromotive verapamil + dexamethasone.[284-287] Di Stasi (2004) compared verapamil + dexamethasone electromotive to lidocaine electromotive. Mehrsai (2013) compared verapamil + dexamethasone electromotive to verapamil + dexamethasone intralesional. Verapamil + dexamethasone significantly reduced plaque volume and penile curvature compared to lidocaine

electromotive (Di Stasi 2004). Pain improved in both groups but the verapamil + dexamethasone group had longer periods of pain relief. When compared to intralesional verapamil + dexamethasone, electromotive verapamil + dexamethasone reduced plaque volume more and improved IIEF scores to a greater degree, but these changes were not statistically significant.[67] Electromotive treatment did, however, improve pain significantly more than did the intralesional treatment. The observational studies generally reported curvature improvements, plaque reductions, and pain improvement. These findings are suggestive that verapamil + dexamethasone may provide benefits to PD patients; however, the randomized designs evaluated <100 patients and lacked placebo groups. Replication with larger sample sizes with a placebo group to control for placebo effects is needed.

Intralesional Therapies. ***Intralesional LrhSOD.*** Three observational studies evaluated the effects of intralesional LrhSOD.[288-290] Given the absence of untreated controls, randomized designs, and/or placebo control groups, the studies cannot be interpreted because of the inability to account for change over time in disease state independent of treatment. Given the methodological limits of these studies, the small sample sizes, and the small number of studies, intralesional LrhSOD for treatment of PD remains unproven.

Other intralesional therapies. An additional group of studies examined other types of intralesional treatments. One small RCT[291] (n = 32 in the active treatment group) evaluated the effects of nicardipine and reported significant improvement in pain, plaque size, and IIEF-5 scores compared to placebo; both groups exhibited similar curvature improvements. These findings require replication. Additional observational studies evaluated intralesional parathyroid hormone,[292] intralesional dexamethasone,[293] intralesional betamethasone + hyaluronidase + lidocaine,[294] intralesional Iloprost,[295] and intralesional verapamil with or without intralesional dexamethasone and with or without lidocaine electromotive.[296] Most studies reported improvement in one or more signs and symptoms of PD. However, given the observational designs, small sample sizes, and lack of control for natural history of placebo effects, these findings require replication in randomized adequately-powered designs.

Combination Therapies. An additional group of studies evaluated combination therapies. These included: verapamil intralesional + oral L-carnitine;[297] verapamil intralesional + oral tamoxifen;[297] interferon intralesional + oral vitamin E;[298] verapamil intralesional + oral l-arginine + oral pentoxifylline;[299] verapamil intralesional + oral l-arginine + oral pentoxifylline + penile traction;[299] oral vitamin E with or without ICI treatments (papaverine, phentolamine, PGE1) and with or without oral colchicine;[300] and ultrasound + hydrocortisone.[301] These one-of-a-kind studies had small sample sizes and reported a mix of findings. All require replication in appropriately-powered randomized designs.

Mechanical Therapies. Several studies evaluated the effects of therapies categorized as mechanical. Three observational studies reported on the effects of penile traction for 4.5 to 5.0 hours a day[302-304] and reported curvature improvements. One observational study evaluated the use of the vacuum pump without the constriction ring[305] and also reported curvature improvement. One randomized study assessed hyperthermia (39 to 40 degrees C for 30 min twice weekly; the comparison group received intralesional verapamil) and reported curvature improvement and plaque reduction.[68] Sample sizes were small; these findings require replication in appropriately-powered randomized designs.

SECTION 7: RESEARCH NEEDS AND FUTURE DIRECTIONS

Given its prevalence and its significant psychosocial impact, better understanding of the pathophysiology of PD is greatly needed. In addition, this knowledge is critical to develop clinical therapies that are effective and safe. The absence of knowledge regarding what causes PD has two major consequences: it is not possible to advise men regarding risk factors and how the disease may be prevented and treatments remain focused on the alleviation of symptoms rather than on addressing causal mechanisms. Ideally, future treatments will be developed with full understanding of the scientific basis of the disease and that demonstrate consistent clinical effectiveness for most or all patients. Research endeavors in this field should continue to address multiple disciplinary areas including epidemiology, risk associations, pathophysiology, psychosocial assessment, diagnostics, clinical pharmacology and therapeutics, and health-related outcomes.

Basic scientific investigation effort should be geared toward elucidating the biologic mechanisms of PD. Current understanding of pathogenesis suggests the involvement of inflammatory factors, cytokines, growth factors and other molecular factors involved in tissue injury, fibrosis and abnormal wound healing. Ongoing scientific investigation that defines the molecular pathophysiology of this disorder can be expected to suggest molecular sites that can be targeted therapeutically. In acknowledgment of a likely genetic determinant or susceptibility for many individuals incurring PD, scientific focus should be intensified in

discovering the genetic factors related to this condition. Investigative work involving gene expression profiles and describing gene mutations of cellular proteins involved in tissue fibrosis and plaque calcification is most relevant. Such work also may lead to establishing biomarkers that can be applied for disease evaluation and related diagnostic procedures (e.g., predictors of progression, spontaneous recovery, and possibly treatment response). Purpose in the basic scientific arena also may encompass the application of emerging technologies which, while grounded within advancements in the scientific basis of PD, may yield opportunities for implementing revolutionary therapeutics in the field. Besides such advances in pharmacotherapy, gene therapy, stem cell therapy and regenerative medicine may all be considered as having potential future roles in this condition.

Clinical research is also central and can be expected to involve a translational process flowing from basic scientific discoveries. New drugs or therapies with a scientific foundation will need to be brought forward while adhering to rigorous clinical assessment methodology. Several considerations merit emphasis for clinical therapeutic development in PD in view of widespread deficiencies that were found in studies of therapies for this disease state.

First, studies must be undertaken with full appreciation for the fact that PD is characterized by symptoms that change over time and that some symptoms will resolve in the absence of treatment. In the absence of a control for the natural history of PD, findings from observational studies are of limited value. Journal editors and article reviewers may want to consider whether studies that do not meet methodological thresholds for making a meaningful contribution to the PD body of knowledge merit publication.

Second, some PD symptoms – such as pain -- are highly susceptible to placebo effects. It is not possible to know with certainty whether a new therapy reliably decreases pain in the absence of a placebo control group. Reports of pain relief from studies that were not designed to control for natural history of symptoms as well as placebo effects cannot move the PD treatment literature forward clinically.

Third, because patients may have highly variable courses with or without treatment, findings from studies that have small sample sizes – even well-designed studies – potentially lack generalizability because of the inherent instability of findings derived from small numbers of patients. Replication of findings is critical before new therapies can be offered with confidence.

Fourth, the quality of any empirical literature depends on its capacity for accurate measurement. PD studies must use validated measures of objective and subjective outcomes. Objectively measured outcomes, such as degree of curvature or plaque characteristics or penile dimensions or ED, are critically important to establish that a therapy is effective in reducing these manifestations of PD. Without this information, it is difficult to counsel patients regarding what to expect from specific therapeutic choices and whether a particular therapy is suitable for a specific patient given that patient's history, values, and treatment goals. A critical component of the patient experience of PD is subjective and includes pain and distress. Pain can be measured validly using visual analog scales. These scales provide reliable documentation of baseline symptoms and responses to treatment. At the time this guideline was created, measures of patient symptomatology and distress (i.e., the PDQ) were undergoing psychometric evaluation[306,307] but were not yet fully validated for use in clinical settings. Until a validated measure of distress is available, the Panel emphasizes the need to query patients regarding distress as part of baseline evaluation and follow-up. In addition, patient perceptions of changes in deformity and penile dimensions are not reliable indicators of objective changes, with many patients overestimating the degree of curvature and the extent of penile shortening (e.g., Bacal 2009; Hudak 2013; Taylor & Levine 2008; Matsushita 2014). Importantly, although patient perceptions of deformity may not predict objective measures of deformity, and patient distress is poorly correlated with objective measures of deformity (Hellstrom 2013), patient perceptions of deformity correlate with distress. Therefore, documentation of objective outcomes is critical to provide patients with information regarding actual changes in curvature and penile dimensions. Additionally, the assessment of benefit for a proposed therapy should be based on establishing clinically meaningful change measures, whether they are objectively or subjectively measured.

LIST OF ABBREVIATIONS

AE	**Adverse event**
AMS	**American Medical Systems**
AUA	**American Urological Association**
CCT	**Clinical controlled trial**
CESD	**Center for Epidemiological Studies Depression scale**
cm	**Centimeters**
CoQ10	**Co-enzyme Q10**
ED	**Erectile dysfunction**
EMDA	**Electromotive drug administration**
ES	**Evidence strength**
ESWT	**Extracorporeal shock wave therapy**
Gy	**Gray**
ICI	**Intracavernosal injection**
IIEF	**International Index of Erectile Function**
IMPRESS	**Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies**
LrhSOD	**Liposomal recombinant human superoxide dismutase**
mg	**Milligrams**
mJ	**Millijoules**
ml	**Milliliters**
mm	**Millimeter**
MRI	**Magnetic resonance imaging**
MU	**Million units**
NOQ	**Newcastle-Ottawa Quality Assessment Scale**
NPT	**Nocturnal penile tumescence**
PD	**Peyronie's disease**
PDDU	**Penile duplex Doppler ultrasound**
PDE5	**Phosphodiesterase type 5 inhibitor**
PDQ	**Peyronie's Disease Questionnaire**
PGC	**Practice Guidelines Committee**
PSV	**Geak systolic velocity**
QoL	**Quality of life**
RCT	**Randomized controlled trial**
RT	**Radiotherapy**
SPL	**Stretched penile length**
SWs	**Shock waves**
U	**Units**
VAS	**Visual analog scale**

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All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

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This document was written by the Peyronie's Disease Guidelines 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 representatives of urology, family medicine, clinical psychology, patient advocacy, 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 diagnosis and treatment of Peyronie's Disease.

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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 government 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.

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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.

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