Chapter 1

How Has Men's Health Changed over the Past Two Decades?

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1.1 Introduction

Men's health has emerged as a distinct discipline within medicine and has experienced significant changes and advances within the last 20 years. Common medical conditions affecting men include heart disease, diabetes, hypertension, and kidney disease. Male-specific disorders include prostate and testicular problems, erectile dysfunction (ED), hypogonadism, and male factor infertility. In order to strike a balance for a healthy society, it is of equal importance to discuss issues related to the health of men as well as to that of women, and to understand the differences between them. In this chapter we aim to discuss how men's health has evolved over the past two decades and the role of the urologist in bringing men's health to the forefront. Just as the field has improved over the past 20 years, we expect that there will be significant gains over the next few decades quarterbacked by the urologist.

1.2 Health Disparities

Men's health disparities are differences in health outcomes that are determined by cultural, economic, and environmental factors associated with socially defined identities and group memberships [1]. More attention is needed toward addressing men's health and to optimize efforts to educate men regarding their healthcare needs. These health disparities are perhaps best exemplified by life expectancy and preventable disease.

Globally, the average male life expectancy at birth has increased from 65 years to approximately 70 years within the last two decades [2]. Despite this increase, there is not a single country where male life expectancy exceeds that of females, and by 2030 it is expected that male life expectancy will lag behind female life expectancy by at least seven years [3]. There are a number of reasons for gendered differences in life expectancy, including biological differences as well as cultural and behavioral ones linked to different social expectations of men and women. These social expectations include use of and access to health care. Males, for example, are more likely than females to die prematurely from noncommunicable and preventable disease, the major risk factors of which include tobacco use, unhealthy diets, and alcohol abuse.

Studies examining gender differences in preventive-care services have shown that men utilize general healthcare services as well as preventive-care services to a much lower degree than women. Specifically, it has been shown that men undergo blood pressure, cholesterol, dental checks, and also get the influenza vaccine in lower numbers compared to women [4]. Additionally, gender differences exist within specific health conditions, a phenomenon that can again be potentially explained by socioeconomic, environmental, genetic, and even physiological factors. The incidence of cardiovascular disease, for example, is higher in men than in women of similar age, a gender difference that is more prominent at a younger age and partly explained by the protective effects of sex hormones [5,6]. Furthermore, studies have demonstrated that men, compared to women, are more likely to be overweight or obese, more likely to consume fast food, high-sugar beverages, and alcohol, and are less likely to be knowledgeable about nutrition [7]. In order for some of these gender disparities to be understood, it is crucial to evaluate the primary motivators for men seeking physician evaluation and care.

1.3 Drivers for Seeking Health Care

It is estimated that 25% of men in the US population had no visits to the doctor in the past 12 months, compared with 12% of women, a difference that persists even after correcting for the use of healthcare services that are specific for women. This discrepancy in utilization has been present historically, and certainly over the last 20 years. It is thought to be influenced by a combination of variables, including mental distress, physical illness, perceived symptoms, poor subjective health, and propensity to use services. Women have higher levels of all of these variables, leading to the increased healthcare utilization among them [8].

Men commonly attribute their reluctance to visit a physician to busy schedules, fear of finding out something is wrong, and discomfort of physical exams (prostate, testicular). As such, healthcare utilization among men is typically governed by acuity or urgency of illness or injury, need for a specific procedure (e.g., vasectomy), or spousal persuasion. One of the major reasons that young women visit a physician is for family planning. Traditionally, family planning has focused on providing contraception to women as there are numerous reversible options available. This burden may be shifting to men, however, as international surveys have highlighted that men are interested in male contraceptive options, and there has

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been an increase in clinical research to this end [9]. This may be a potential new driver for men to seek physician care.

Contemporary men's health aims to shift the paradigm to preventative men's health care by emphasizing the importance of well visits, wellness checks, and men's health maintenance. Insurance incentives are one way this paradigm shift may be taking place. Through the Affordable Care Act from 2010 to 2015, for instance, people gaining coverage were more likely to be male (10.3 million or 54%). Additionally, the majority of people gaining coverage were in the 19–34 age group (8.7 million or 45%) [10]. With these incentives and potential drivers in place, clinics specific to men's health have emerged.

1.4 Men's Health Centers

There has been an emergence of medical clinics that have focused on ED and low testosterone ("low T") and branded themselves as "men's health centers." These centers have embraced the men's health platform and have largely been cash-based, taking advantage of the profitability surrounding ED and low T. Most of these centers are not staffed by healthcare professionals with academic training in male endocrinology, sexual medicine, or preventative medicine, and are built on the basis of optimizing men's health via testosterone, supplements, and intra-cavernosal injections [11].

Treatments for low testosterone have been gaining attractiveness since the early 2000s, heavily influenced by direct-to-consumer marketing. From 2001 to 2011, testosterone use in the United States tripled, and consequently, hundreds of testosterone clinics emerged. Rather than offering a traditional medical office visit comprised of history-taking, physical exam, and appropriate lab and imaging studies, these clinics offer memberships with frequent testosterone injections and lab monitoring. Likely as a result, total testosterone sales increased 12-fold globally, rising from $150 million in 2000 to $1.8 billion in 2011 [11]. Additionally, total testosterone use among men over 30 increased from 0.52% in 2002 to 3.20% in 2013. These for-profit low T clinics constitute the original iteration of men's health centers, providing patients with various forms of testosterone replacement therapy, often without a clear indication. These clinics, however, lack the follow-up that is required in patients receiving testosterone therapy and the detailed evaluation necessary for these patients regarding factors such as prostate cancer risk and fertility implications [11].

Over the last decade, men's health clinics have evolved beyond merely testosterone and ED to include a variety of issues and disciplines, including urologic diseases, nutrition, sports medicine, mental health, sleep medicine, cardiology, and dermatology. Academic centers, which have multidisciplinary teams equipped to address a wide variety of men's health issues, began establishing men's health clinics of their own in response. These academic centers now provide a comprehensive approach to men's health, with physicians managing sexual, endocrine, surgical, physical performance, and psychological issues. Fellowship training programs in men's health have emerged in various academic centers in response to the growing attention toward the subject, with the number of programs growing from 8 to 19 within the last decade [11]. With the growing attention toward men's health and the expanding training programs to facilitate experts in the field there has been a heightened interest in male urologic health, especially with the advent of new treatment options for hypogonadism, Peyronie's disease, and ED.

1.5 Men's Health Advocacy

The general interest in men's health was cast into the international spotlight by the "Movember" movement. Established in 2006 as a global charity, the Movember Foundation has become an annual event characterized by the growing of mustaches during the month of November to raise awareness of and funds to deliver innovative research for men's health issues such as prostate cancer, testicular cancer, mental health, and suicide prevention. The foundation also launched the Global Action Plan Prostate Cancer Active Surveillance initiative, creating the largest worldwide collaboration integrating patient data from men with prostate cancer on active surveillance. Similar to the "Pinktober" campaign focused on breast cancer that exploits pink ribbons as a strong visual tag, Movember exploits mustaches as a visual tag to maximize online visibility and to associate the movement specifically with improving men's health. This similarity between the two movements has caused some to question whether Movember is the "pink ribbon for men." The Movember Foundation has been able to raise over $900 million for men's health over the last 16 years [12].

1.6 Men's Health and Urology

Many of the reasons men seek healthcare are related to sexual function or reproductive health, often making urologists the first doctor a patient will see in many years. This puts urologists in an important position to quarterback men's health initiatives and to establish the patient–physician relationship that is essential for the patient to return to the physician's office. In fact, there has been evolving synergistic work between primary care physicians and urologists regarding men's health over the last two decades, as they began to recognize and embrace the relationship between the two fields. Primary care physicians interested in men's health are adept at medically managing a variety of men's health conditions such as BPH, hypogonadism, and ED as well as the comorbidities that can affect these. Urologists are often consulted for advanced medical and surgical management. There have been significant advances in many arenas over the last 20 years in men's urologic health, including prostate cancer, testicular pathology, infertility, and prosthetics.

1.6.1 Prostate Cancer

Prostate cancer is the most commonly diagnosed solid-organ malignancy in men in the USA and the second most common worldwide. Within the last 20 years, extensive research in the

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field of prostate cancer has resulted in important discoveries and modifications that have influenced our understanding of the disease and its management. Historically, most patients with low-risk prostate cancer were treated with either radical prostatectomy or radiotherapy-based treatment. However, conservative management of low-risk prostate cancer with active surveillance has become one of the most common management approaches.

There have been several advancements made for patients requiring definitive management of their prostate cancer. The last two decades has seen the advent of robot-assisted laparoscopic radical prostatectomy become the most commonly utilized surgical approach for prostate cancer. From 2004 to 2010, the number of patients treated with robotic radical prostatectomy versus open increased from 8% to 67%, a trend that continues to increase and evolve [13]. Prostate radiotherapy (RT) techniques have also experienced improvement in delivery, efficacy, safety, and efficiency. Techniques such as three-dimensional conformal RT, intensity-modulated RT, stereotactic body RT, robotic RT, high-dose-rate brachytherapy, and hypofractionation, to name a few, are revolutionizing the field [14,15]. In nearly every facet of prostate cancer management, tremendous progress has been made and continues to be made with promising techniques on the horizon.

1.6.2 Chronic Testicular Pain

Chronic testicular pain has been a challenging condition for both primary care providers and urologists to address. The condition may occur from previous scrotal surgery, infection, trauma, referred pain, or may be idiopathic. However, the etiology and pathophysiology of testicular pain have remained poorly understood since the term "orchialgia" was defined in the 1970s, contributing to the difficulty in treatment. More recently it was found that Wallerian degeneration of the autonomic nerves that travel along the spermatic cord may play a role in chronic testicular pain [16].

It is important to initially obtain a comprehensive history and physical exam and rule out underlying medical and anatomic causes such as tumors, intermittent torsion, active infection, and varicocele [17]. First-line therapy for chronic testicular pain is focused on conservative and medical management such as analgesics, anti-inflammatory agents, antibiotics, physical therapy, and avoidance of activities that evoke pain. When conservative management fails, surgical options are available depending on the cause of the testicular pain. Over the past two decades studies have demonstrated that a vasovasostomy is effective in the treatment of postvasectomy pain syndrome. When pain is diffuse involving the testicle or epididymis, microsurgical spermatic cord denervation (MSCD) offers a minimally invasive option with minimal morbidity and success rates of 70–80%. Surgical procedures such as orchiectomy and epididymectomy have been historically described as options for treating chronic testicular pain; however, they have variable success rates and are often considered to be a last resort. Though introduced in the 1970s, the technique of MSCD has been continuously developed and refined over the last 20 years and has become a primary surgical intervention for this patient population [17–20].

Though MSCD has gained much popularity, approximately 12–16% of patients will have persistent pain after denervation. In these patients, ultrasound guided targeted micro-cryoablation of the ilioinguinal and genitofemoral nerve fibers, which has been developed within the last 10 years, has proven effective. Similar to cryoablation, pulsed radiofrequency ablation of the cord has been recently developed for this patient population and is another potential treatment option [21].

1.6.3 Erectile Dysfunction

1.6.3.1 Phosphodiesterase Type 5 Inhibitors

Viagra (sildenafil) revolutionalized the field of sexual medicine after its introduction to the market as the first oral treatment for ED. Following approval from the US Food and Drug Administration (FDA) for the treatment of ED in March 1998, the "blue pill" made its first appearance in pop culture on the cover of *TIME* magazine in May 1998 and has since had a tremendous impact on men's health. In fact, just 7 years following its market launch, more than 750,000 physicians had prescribed sildenafil to more than 23 million men [22]. Prior to its use, men had the option of testosterone optimization, vacuum erection devices, injection therapies, or surgery. The ability to use an oral medication for ED quickly made sildenafil and other phosphodiesterase type 5 (PDE5) inhibitors, such as tadalafil, vardenafil, and avanafil the first-line treatments of choice for ED.

1.6.3.2 Intracavernosal Injection Therapy

In the 25–50% of patients who do not respond to noninvasive therapies or for those whom PDE5 inhibitors are contraindicated, alternative therapies such as intracavernosal injection (ICI) therapy may be considered. The most commonly used and studied ICI agents currently include prostaglandin-E1 (alprostadil), papaverine, phentolamine, and combination therapy [23]. Various urological bodies have issued guidelines on the management of ED over the past 20 years, many of them recommending ICI therapy as a second-line treatment option for patients who do not respond to PDE5 inhibitors. However, some bodies, such as the American Urological Association (AUA), have come to recommend that male patients should be offered information on all treatment modalities prior to selecting a treatment option. Additionally, within the last 5 years, the AUA and the European Association of Urology (EAU) have produced guidelines advising combination therapy, such as Trimix (alprostadil, papaverine, and phentolamine), as a better alternative to monotherapy [24,25].

1.6.3.3 Prosthetics

The field of prosthetic urology has made significant strides in the past 20 years. Malleable devices and inflatable penile prostheses (IPP) are the currently available penile implants.

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Infection rates have been dramatically reduced to 1–2% with the introduction of antibiotic-coated prosthetics, either inhibizone (AMS) or an antibiotic of choice (Coloplast) to adhere to the hydrophilic coating. There have also been improvements in components of the IPP by introduction of the one-touch release button in the pump, more compact and concealable reservoirs, no-crimp tubing, and the introduction of valves that prevent auto-inflation and lockout. The evolution of IPP has continued over the last 10 years with various technologies in development, including mechanized cylinder inflation via battery-operated pumps to eliminate problems associated with manual manipulation of the scrotal pump, and more compact devices to eliminate the need for tubing and connections, leading to lower infection rates and mechanical failures [26]. Battery-operated and heat-activated prostheses are currently undergoing research and development and are on the horizon for prosthetic urology.

1.6.3.4 Future of ED Treatment

Regenerative medicine therapies are being explored in the men's health practice as a way to restore erectile function. Low-intensity extracorporeal shock wave therapy, a technology introduced to medicine in 1978, is another noninvasive treatment that has continued to be developed, and in the last 10 years has proven to have positive effects on erectile function when applied to the penile shaft of men who responded to pharmacotherapy [27,28]. Platelet-rich plasma contains a high concentration of growth factors such as vascular endothelial growth factor, platelet-derived growth factor, and insulin growth factor [29]. Early clinical trials have suggested a small but clinically relevant improvement in ED through the endothelial nitric oxide synthase pathway [30,31]. Mesenchymal stem cells possess regenerative abilities and promote cell growth and survival through the release of a variety of cytokines [32]. Clinical trials have demonstrated safety and minor improvement in erectile function after the injection of stem cells [33]. Other techniques such as wrapping the neurovascular bundle with dehydrated amnion/chorion membrane during radical prostatectomy have emerged to help improve nerve recovery as these grafts are full of growth factors and cytokines [34]. Despite having sound translational evidence behind these therapies, there is still a paucity of data from human studies and further trials need to be completed before their routine clinical use can be recommended.

1.6.4 Fertility

Approximately 15% of couples fail to conceive after one year of trying, and male factor infertility accounts for about half of these cases. In recent years, increasing environmental pollution and psychological stresses have resulted in a decline in sperm counts worldwide [35]. Etiologic factors in male infertility include congenital, acquired, and idiopathic causes.

1.6.4.1 Semen Analysis

As modern statistical analysis has been utilized to examine the metrics of the parameters of the semen analysis over the last two decades, it has become clear that the semen analysis should be used as a part of, not as a complete male evaluation. The World Health Organization updated criteria in 2010 to help delineate a "normal" semen analysis. With the evolution of computers and the development of computer-assisted semen analysis equipment, machines have been able to measure standard semen parameters. Within the last decade, newer assays have been developed including testing for reactive oxygen species and sperm DNA fragmentation. These assays are still being studied and continue to undergo refinement but may prove to be informative in individual cases.

1.6.4.2 In Vitro Fertilization (IVF)

The first IVF birth in 1978 opened the door for the utilization of advanced reproductive technologies (ART) worldwide. One of the most important advances since 1978 in the trajectory of IVF was the ability to insert a single sperm into an ovum and achieve a live birth. This technique, known as intracytoplasmic sperm injection (ICSI), made biological parenthood possible when only a few sperm are available in the ejaculate or retrieved from the testis. The use of ICSI worldwide has steadily grown, representing 67% of all ART cases performed in 60 countries, according to the International Committee Monitoring Assisted Reproductive Technologies for 2008–2010, and revolutionized the treatment of infertility since the first ICSI report in 1992 [36,37]. Currently, ICSI is the preferred insemination protocol, with many centers using it in >90% of their insemination cycles [38].

First described in 1998, microdissection testicular sperm extraction (microTESE) has transformed sperm extraction in men with azoospermia and is useful when used in conjunction with ICSI [39]. In the past two years, microTESE has been reported to yield up to a 90% sperm retrieval rate from dilated seminiferous tubules [40]. The development of microTESE used in conjunction with ICSI has given many men with nonobstructive azoospermia the hope of biological parenthood. However, current methods of sperm retrieval via microTESE specimens are labor-intensive, inefficient, and expensive, so there is strong interest in improving the process. Novel sorting methods have therefore been developed over the last decade and continue to be cultivated. These methods include microfluidics, magnetic-activated cell sorting, and fluorescence-activated cell sorting [41]. In the last 20 years, studies on carriers and single-sperm freezing methods have tremendously improved the recovery and activity rates of sperm after cryopreservation, and there is large developmental potential of these procedures [35].

1.6.4.3 Microsurgical Advances

Since the microsurgical subinguinal approach to varicocelectomy was described in 1985, the technique has exploded worldwide and has resulted in excellent outcomes with lower complication rates than nonmicrosurgical approaches [38]. In the past five years, improved outcomes for both intrauterine insemination and IVF have been shown

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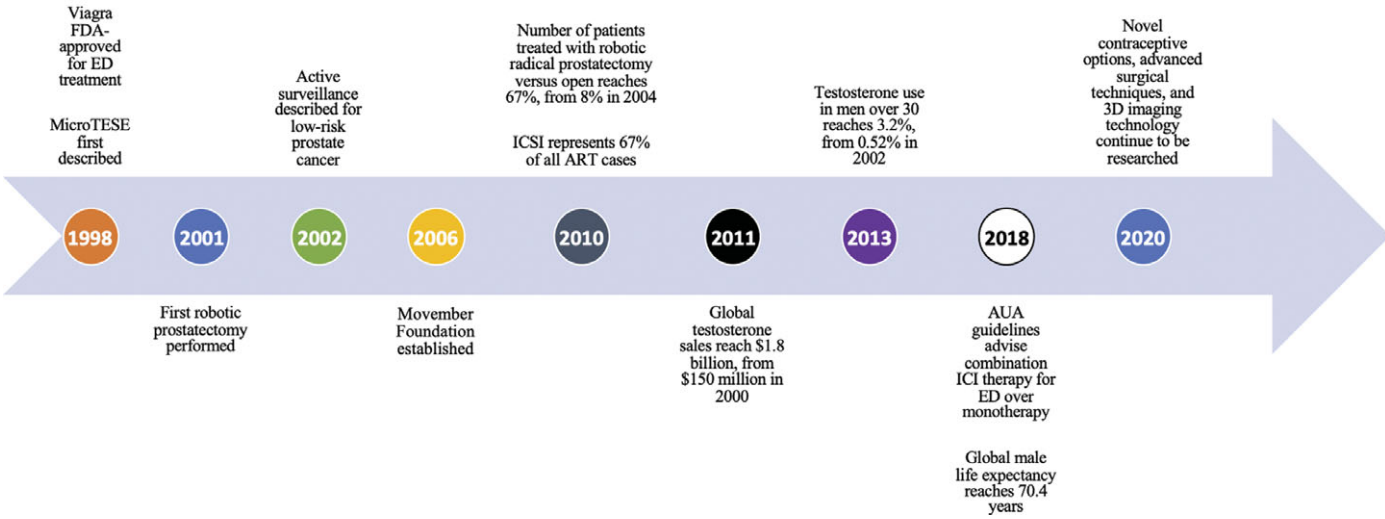

Figure 1.1 Progress and achievements in men's health over the last two decades

in men who first undergo microsurgical varicocelectomy. In fact, recent studies illustrate that both men with low sperm counts and those requiring TESE do indeed benefit from microsurgical varicocele repair even in instances when ART is required [42].

Microsurgical techniques have also been applied to men with obstructive azoospermia, with the first reported microsurgical vasectomy reversal using vasovasostomy in the 1970s [43]. As vasectomy reversal remains the standard of care for men desiring fertility after sterilization, the technique has been constantly refined throughout the past two decades. Currently, vasectomy reversal results in return of sperm to the ejaculate in 85–99% of men, with pregnancy rates from 40% to 80%, depending on time since vasectomy and female age. Additionally, with the constant advancement of technology, techniques such as robotic vasectomy reversal and video microsurgery are emerging. Though the cost-effectiveness of these novel techniques can be debated, literature within the last 20 years has shown that, compared to going directly to IVF/ICSI, vasectomy reversal is significantly more cost-effective than IVF/ICSI in sterilized males by a significant margin [44]. This phenomenon may also be due in part to the increasing accessibility of vasectomies, as five states have passed laws within the last 10 years that require state-regulated health insurance plans to also cover vasectomies at no additional cost to the patient.

1.7 Conclusion

The past 20 years have seen major innovations and refinements with men's health. The next 20 years will likely prove to be even more fruitful for the discipline. Things on the horizon include novel contraceptive options, advanced surgical technologies, incorporation of novel three-dimensional imaging capture in various urologic settings, and the continued advancement of men's health as a whole (Figure 1.1).

References

1. Griffith DM. Biopsychosocial approaches to men's health disparities research and policy. *Behav Med.* 2016;42(3):211–215. doi:10.1080/08964289.2016.1194158.
2. The World Bank. Life expectancy at birth, male (years). 2019. https://data.worldbank.org/indicator/SP.DYN.LE00.MA.IN. Accessed October 25, 2022.
3. Mortality GBD, Causes of Death Collaboration. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;385(9963):117–171. doi:10.1016/S0140-6736(14)61682-2.
4. Vaidya V, Partha G, Karmakar M. Gender differences in utilization of preventive care services in the United States. *J Womens Health (Larchmt).* 2012;21(2):140–145. doi:10.1089/jwh.2011.2876.
5. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. *Ann Intern Med.* 1976;85(4):447–452. doi:10.7326/0003-4819-85-4-447.
6. Vitale C, Fini M, Speziale G, Chierchia S. Gender differences in the cardiovascular effects of sex hormones. *Fundam Clin Pharmacol.* 2010;24(6):675–685. doi:10.1111/j.1472-8206.2010.00817.x.
7. Yahia N, Wang D, Rapley M, Dey R. Assessment of weight status, dietary habits and beliefs, physical activity, and nutritional knowledge among university students. *Perspect Public Health.* 2016;136(4):231–244. doi:10.1177/1757913915609945.
8. Koopmans GT, Lamers LM. Gender and health care utilization: the role of mental distress and help-seeking propensity. *Soc Sci Med.* 2007;64(6):1216–1230. doi:10.1016/j.socscimed.2006.11.018.

9. Roth MY, Amory JK. Beyond the condom: frontiers in male contraception. *Semin Reprod Med*. 2016;34(3):183–190. doi:10.1055/s-0036-1571435.
10. Garrett B, Gangopadhyaya A. Who gained health insurance coverage under the ACA, and where do they live? 2016. www.urban.org/sites/default/files/publication/86761/2001041-who-gained-health-insurance-coverage-under-the-aca-and-where-do-they-live.pdf. Accessed October 19, 2022.
11. Houman JJ, Eleswarapu SV, Mills JN. Current and future trends in men's health clinics. *Transl Androl Urol*. 2020;9(Suppl 2):S116–S122. doi:10.21037/tau.2019.08.33.
12. Cacciamani GE, Stern MC, Medina LG, Gill K, Sotelo R, Gill IS. Cancer awareness crusades-pink ribbons and growing moustaches. *Lancet Oncol*. 2019;20(11):1491–1492. doi:10.1016/S1470-2045(19)30639-4.
13. Lowrance WT, Eastham JA, Savage C, et al. Contemporary open and robotic radical prostatectomy practice patterns among urologists in the United States. *J Urol*. 2012;187(6):2087–2092. doi:10.1016/j.juro.2012.01.061.
14. Catton CN, Lukka H, Martin J. Prostate cancer radiotherapy: an evolving paradigm. *J Clin Oncol*. 2018;36(29):2909–2913. doi:10.1200/JCO.2018.79.3257.
15. Podder TK, Fredman ET, Ellis RJ. Advances in radiotherapy for prostate cancer treatment. *Adv Exp Med Biol*. 2018;1096:31–47. doi:10.1007/978-3-319-99286-0_2.
16. Tan WP, Levine LA. What can we do for chronic scrotal content pain? *World J Mens Health*. 2017;35(3):146–155. doi:10.5534/wjmh.17047.
17. Calixte N, Tojuola B, Kartal I, et al. Targeted robotic assisted microsurgical denervation of the spermatic cord for the treatment of chronic orchialgia or groin pain: a single center, large series review. *J Urol*. 2018;199(4):1015–1022. doi:10.1016/j.juro.2017.10.030.
18. Levine LA. Microsurgical denervation of the spermatic cord. *J Sex Med*. 2008;5(3):526–529. doi:10.1111/j.1743-6109.2007.00762.x.
19. Levine LA, Matkov TG, Lubenow TR. Microsurgical denervation of the spermatic cord: a surgical alternative in the treatment of chronic orchialgia. *J Urol*. 1996;155(3):1005–1007. doi:10.1016/s0022-5347(01)66369-9.
20. Tatem A, Kovac JR. Chronic scrotal pain and microsurgical spermatic cord denervation: tricks of the trade. *Transl Androl Urol*. 2017;6(Suppl 1):S30–S36. doi:10.21037/tau.2017.05.17.
21. Calixte N, Brahmbhatt J, Parekattil S. Chronic testicular and groin pain: pathway to relief. *Curr Urol Rep*. 2017;18(10):83. doi:10.1007/s11934-017-0722-7.
22. Martin AL, Huelin R, Wilson D, Foster TS, Mould JF. A systematic review assessing the economic impact of sildenafil citrate (Viagra) in the treatment of erectile dysfunction. *J Sex Med*. 2013;10(5):1389–1400. doi:10.1111/jsm.12068.
23. Duncan C, Omran GJ, Teh J, Davis NF, Bolton DM, Lawrentschuk N. Erectile dysfunction: a global review of intracavernosal injectables. *World J Urol*. 2019;37(6):1007–1014. doi:10.1007/s00345-019-02727-5.
24. Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA guideline. *J Urol*. 2018;200(3):633–641. doi:10.1016/j.juro.2018.05.004.
25. Wespes E, Amar E, Hatzichristou D, et al. EAU guidelines on erectile dysfunction: an update. *Eur Urol*. 2006;49(5):806–815. doi:10.1016/j.eururo.2006.01.028.
26. Gurtner K, Saltzman A, Hebert K, Laborde E. Erectile dysfunction: a review of historical treatments with a focus on the development of the inflatable penile prosthesis. *Am J Mens Health*. 2017;11(3):479–486. doi:10.1177/1557988315596566.
27. Vardi Y, Appel B, Kilchevsky A, Gruenwald I. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. *J Urol*. 2012;187(5):1769–1775. doi:10.1016/j.juro.2011.12.117.
28. Fojecki GL, Tiessen S, Osther PJ. Extracorporeal shock wave therapy (ESWT) in urology: a systematic review of outcome in Peyronie's disease, erectile dysfunction and chronic pelvic pain. *World J Urol*. 2017;35(1):1–9. doi:10.1007/s00345-016-1834-2.
29. Epifanova MV, Gvasalia BR, Durashov MA, Artemenko SA. Platelet-rich plasma therapy for male sexual dysfunction: myth or reality? *Sex Med Rev*. 2020;8(1):106–113. doi:10.1016/j.sxmr.2019.02.002.
30. Matz EL, Pearlman AM, Terlecki RP. Safety and feasibility of platelet rich fibrin matrix injections for treatment of common urologic conditions. *Investig Clin Urol*. 2018;59(1):61–65. doi:10.4111/icu.2018.59.1.61.
31. Musicki B, Palese MA, Crone JK, Burnett AL. Phosphorylated endothelial nitric oxide synthase mediates vascular endothelial growth factor-induced penile erection. *Biol Reprod*. 2004;70(2):282–289. doi:10.1095/biolreprod.103.021113.
32. Caplan AI, Correa D. The MSC: an injury drugstore. *Cell Stem Cell*. 2011;9(1):11–15. doi:10.1016/j.stem.2011.06.008.
33. Bahk JY, Jung JH, Han H, Min SK, Lee YS. Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: preliminary report of 7 cases. *Exp Clin Transplant*. 2010;8(2):150–160.
34. Patel VR, Samavedi S, Bates AS, et al. Dehydrated human amnion/chorion membrane allograft nerve wrap around the prostatic neurovascular bundle accelerates early return to continence and potency following robot-assisted radical prostatectomy: propensity score-matched analysis. *Eur Urol*. 2015;67(6):977–980. doi:10.1016/j.eururo.2015.01.012.
35. Liu S, Li F. Cryopreservation of single-sperm: where are we today? *Reprod Biol Endocrinol*. 2020;18(1):41. doi:10.1186/s12958-020-00607-x.
36. Dyer S, Chambers GM, de Mouzon J, et al. International Committee for Monitoring Assisted Reproductive Technologies world report: Assisted Reproductive Technology 2008, 2009 and 2010. *Hum Reprod*. 2016;31(7):1588–1609. doi:10.1093/humrep/dew082.
37. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet*. 1992;340(8810):17–18. doi:10.1016/0140-6736(92)92425-f.
38. Niederberger C, Pellicer A, Cohen J, et al. Forty years of IVF. *Fertil Steril*. 2018;110(2):185–324 e5. doi:10.1016/j.fertnstert.2018.06.005.

39. Schlegel PN, Li PS. Microdissection TESE: sperm retrieval in non-obstructive azoospermia. *Hum Reprod Update*. 1998;4(4):439. doi:10.1093/humupd/4.4.439.

40. Caroppo E, Colpi EM, Gazzano G, et al. The seminiferous tubule caliber pattern as evaluated at high magnification during microdissection testicular sperm extraction predicts sperm retrieval in patients with non-obstructive azoospermia. *Andrology*. 2019;7(1):8–14. doi:10.1111/andr.12548.

41. Mangum CL, Patel DP, Jafek AR, et al. Towards a better testicular sperm extraction: novel sperm sorting technologies for non-motile sperm extracted by microdissection TESE. *Transl Androl Urol*. 2020;9(Suppl 2):S206–S214. doi:10.21037/tau.2019.08.36.

42. Kirby EW, Wiener LE, Rajanahally S, Crowell K, Coward RM. Undergoing varicocele repair before assisted reproduction improves pregnancy rate and live birth rate in azoospermic and oligospermic men with a varicocele: a systematic review and meta-analysis. *Fertil Steril*. 2016;106(6):1338–1343. doi:10.1016/j.fertnstert.2016.07.1093.

43. Silber SJ. Microscopic technique for reversal of vasectomy. *Surg Gynecol Obstet*. 1976;143(4):631.

44. Lee R, Li PS, Goldstein M, Tanrikut C, Schattman G, Schlegel PN. A decision analysis of treatments for obstructive azoospermia. *Hum Reprod*. 2008;23(9):2043–2049. doi:10.1093/humrep/den200.