Kaiser Permanente Research Brief

Men's health

This brief summarizes the contributions of Kaiser Permanente Research since 2007 on the topic of men's health. Although men's health encompasses a wide range of health issues, this brief will focus on specific conditions affecting men (such as prostate cancer, testicular cancer, benign prostatic hyperplasia, and erectile dysfunction), as well as certain conditions for which men have specific or elevated risks (such as infertility, hypogonadism, bladder cancer, cardiovascular disease, back pain, and opioid use disorders).

Men in the United States are at risk for a variety of acute and chronic health problems. Approximately 1 in 9 will be diagnosed with prostate cancer at some point, making it the second-most common cancer among American men, and the American Cancer Society estimated that over 30,000 men died of this disease in 2019.¹ Testicular cancer is less common than prostate cancer, affecting 1 in every 250 males, but it typically affects much younger men and boys, with an average age at diagnosis of just 33.¹ In addition, more than three-quarters of the 80,000 Americans who will be diagnosed with bladder cancer this year are men, and nearly 13,000 men were expected to die from this cancer in 2019.¹ Men are also more likely than women to suffer from common chronic illnesses. Cardiovascular disease causes 1 of every 4 deaths in men, and a large majority of sudden cardiac events occur in men.² Furthermore, men are more likely than women to be diagnosed with opioid use disorders.³

Many of the health problems men face can significantly affect quality of life.

Kaiser Permanente Publications Related to Men's Health since 2007



Source: Kaiser Permanente Publications Library and PlumX metrics, as of May 13, 2021.

- a Number of citing journal articles, according to Scopus.
- b Number of references in PubMed guidelines.
- c Citations in DynaMed Plus, a point-of-care clinical reference tool.

Benign prostatic hyperplasia (BPH), a noncancerous enlargement of the prostate gland often leading to urinary health problems, is a very common condition, affecting more than 14 million men.⁴ Erectile dysfunction also affects approximately 20% of men, and becomes more common with age: One study estimated that ED is experienced by 5% of men under 40, but 70%

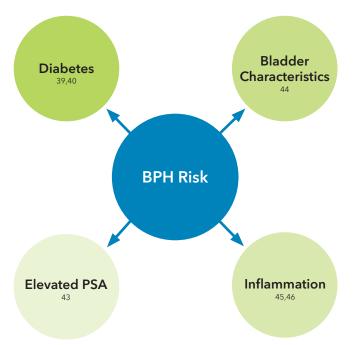
This brief summarizes a selection of the publications contained within the Kaiser Permanente Publications Library, which indexes journal articles and other publications authored by individuals affiliated with Kaiser Permanente. The work described in this brief originated from across Kaiser Permanente's 8 regions and was supported by a wide range of funding sources including internal research support as well as both governmental and nongovernmental extramural funding. of men 70 and older.⁵ ED often occurs in men with low testosterone, or hypogonadism, which is estimated to affect 6% of Americans.^{6,7} Infertility is an issue for 1 in 6 couples in the United States, and male infertility is implicated in two-thirds of all cases.⁸ Moreover, while low back pain is more common in women,⁹ men are much more likely to be prevented from working by this pain.¹⁰

Men's health is an active area of study for Kaiser Permanente Research. Scientists across the organization have used our rich, comprehensive, longitudinal data to advance knowledge in the areas of understanding risk, improving patient outcomes, and translating research findings into policy and practice. We have published more than 400 articles related to men's health since 2007.¹¹ Together, these articles have been cited nearly 12,500 times. These articles are the product of observational studies, randomized controlled trials, meta-analyses, and other studies led by Kaiser Permanente scientists. Our unique environment - a fully integrated care and coverage model in which our research scientists, clinicians, medical groups, and health plan leaders collaborate - lets us contribute generalizable knowledge on men's health, and many other topics of research.

Understanding Risk

For which health problems are men at increased risk?

Men experience a variety of unique health problems, and our research has explored risk factors associated with these conditions. Our scientists have done extensive work on the genetic causes of male cancers such as prostate cancer,¹²⁻²⁵ and have also found other health conditions to be associated with increased risks of these cancers. including obesity,²⁶ infertility,²⁷ sexually transmitted diseases,²⁸ and inflammatory illness.²⁹⁻³¹ In addition, our research has demonstrated links between lifestyle factors and cancer risks. Smoking tobacco (alone³² or in conjunction with cannabis³³) and poor diet³⁴ may be associated with cancer risk in men. Conversely, the use of statins^{35,36} and certain medications for benign prostatic hyperplasia³⁷ may protect against the development of prostate cancer.



These and other risk factors have also been implicated in the development of BPH, and in reproductive or sexual problems in men. Kaiser Permanente research has found that men with type 2 diabetes are at increased risk of both ED³⁸ and urination problems suggestive of BPH,^{39,40} while men who smoke are at elevated risk of ED⁴¹ but not urinary retention.⁴² Other risk factors for BPH include elevated levels of PSA (prostate-specific antigen),⁴³ certain bladder characteristics,⁴⁴ and inflammation.^{45,46} Use of statins, however, was found to be protective against the risk of BPH.⁴⁷ Low levels of testosterone are associated with erectile dysfunction,⁴⁸ as is advancing age.⁴⁹ Our scientists have also identified a genetic link⁵⁰ to the development of ED. Other factors associated with ED and other forms of reproductive dysfunction include exposures to BPA (bisphenol A, an industrial chemical found in plastic)⁵¹⁻⁵⁴ and the use of nonsteroidal anti-inflammatory drugs,⁵⁵ opioids,⁵⁶ and multiple medications.⁵⁷ Our research has also linked BPA exposure, 58,59 opioid use,^{60,61} and genetic factors^{13,62,63} to the risk of low testosterone. Finally, Kaiser Permanente research into cardiovascular risks has found androgen deprivation therapy for prostate cancer^{64,65} to be linked to metabolic illness in men, and lifestyle factors including poor physical fitness have been linked to atherosclerosis.⁶⁶ Younger men who experience ED may also be at higher risk for cardiovascular events.67



Are there subgroups of men who are at particularly high risk for these health problems?

Studies done at Kaiser Permanente have explored racial and ethnic disparities in diseases commonly experienced by men. Although Black men may be at risk of faster elevations in PSA,⁶⁸ evidence suggests that prostate cancer is identified more often¹⁹ and treated more aggressively⁶⁹ in white men. Black men with localized prostate cancer are more likely to reject, and less likely to complete, radiotherapy.^{70,71} Our scientists have also found lower risks of ED in Black and Asian American men,⁷² and elevated risks for urinary problems in Asian American men and Latinos.⁷³ Although the reasons for these disparities are unclear, our researchers have found that racial disparities in access to care may be less common among Kaiser Permanente members,⁷⁴ compared to men outside our system.⁷⁵

What are the consequences of health conditions common to men?

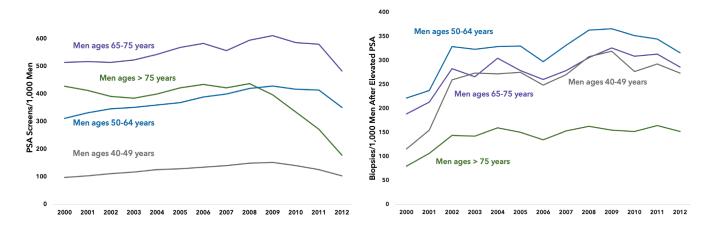
Another line of research has focused on the health risks that may result from the health problems that men often face. Although many of these conditions carry risks of mortality, they may also have significant effects on quality of life. Anxiety and other psychological problems also occur commonly in men with these diagnoses.⁷⁶⁻⁷⁹ BPH can significantly affect bladder function, and the fertility and sexual function problems these men often experience can impact personal relationships.⁸⁰ A study of health-related quality of life following prostate surgery in our members found that these patients frequently suffer short-term sexual dysfunction, as well as longer-term urinary incontinence.⁸¹ Conservatively-managed patients, however, may be at risk for greater health-related anxiety.⁷⁹ These findings have been echoed in a study of quality of life following radiation treatment for prostate cancer.⁸²

Improving Patient Outcomes

What prevention or early intervention strategies are effective in mitigating the health risks faced by men?

Kaiser Permanente researchers have studied numerous interventions for preventing health problems experienced by men. Early screening for prostate cancer has been associated with reduced mortality,⁸³⁻⁸⁷ and prompt follow-up on abnormal PSA results using electronic health records⁸⁸ may further improve outcomes. However, screening guidelines have become more targeted in recent years due to concerns about high false-positive rates and the significant heterogeneity of the disease; this has led to declining use of PSA tests in all age groups over time.^{89, 90} Our scientists have also conducted genomic research involving PSA, which may be used to refine screening through the use of molecular genetic

As guidelines for PSA screening in prostate cancer have changed, screening rates in older men have declined, even though rates of biopsies remain steady.⁸⁹



testing.⁹¹⁻⁹³ We have also found that social support increases the likelihood of receiving appropriate screening.⁹⁴

Some of our preventive programs at Kaiser Permanente aim to address underlying causes of men's health problems. For example, although the reduction of cardiovascular and lung disease is the primary goal of smoking cessation programs, these programs have also been shown to reduce ED.⁴¹ Kaiser Permanente research has also addressed risk assessment and prevention strategies for specific cancers. Research conducted by our scientists has helped clinicians to understand the significance of microscopic hematuria (small amounts of blood in the urine) for the risk of bladder cancer: Although such cancer is rare in patients with microscopic hematuria, male sex is a risk factor for such a diagnosis, and is part of a Hematuria Risk Index developed by Kaiser Permanente researchers and clinicians to gauge patient risk and decrease unnecessary use of invasive testing.⁹⁵ Research on 5-alpha-reductase inhibitors in the treatment of BPH has also explored the effectiveness of these medications for preventing death from prostate cancer³⁷ and other causes.⁹⁶

What are the key factors in effective treatment of the common health problems experienced by men?

A significant area of research at Kaiser Permanente involves the effectiveness and safety of treatments for men's health problems. One

area of focus surrounds the decision-making process regarding active treatment (such as surgery, radiation) versus conservative management of prostate cancer, in which the risks of complications must be weighed against the likelihood of long-term disease progression.97,98 These decisions are often associated with significant anxiety,^{77,79,99,100} and our scientists have studied risk stratification approaches intended to match lower-risk men with less invasive treatments.¹⁰¹⁻¹⁰⁵ Recent studies have found that supporting men's decisions about surveillance. either through web-based education and coaching^{103,106} or individualized risk prediction,¹⁰⁵ reduces anxiety and improves the quality of decisions. Kaiser Permanente researchers have also studied genetic and other factors associated with poor responses to many forms of prostate cancer treatment.^{107,108} Our scientists have conducted numerous evaluations of available tests for prostate cancer occurrence and progression, which enables clinicians to choose the most effective among these tests.¹⁰⁹⁻¹¹⁴

Our scientists have also worked to improve care for patients with bladder cancer by studying patient and clinician factors associated with various types of urinary diversion procedures.^{115,116} The Be-Well Study being conducted by Kaiser Permanente researchers is exploring the role of diet and other lifestyle factors in the care of patients with bladder cancer.^{117,118} In keeping with Kaiser Permanente's broader focus on total patient health,

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Two years after prostate cancer treatment, quality-of-life scores related to sexual function remain low, but scores related to urinary incontinence are only affected for patients undergoing robotic prostatectomy.⁸¹

	Androgen Deprivation		Robotic Prostatectomy		Radiation Therapy	
	Sexual Function	Urinary Incontinence	Sexual Function	Urinary Incontinence	Sexual Function	Urinary Incontinence
Baseline	42	86	63	92	50	89
1 Month	25	83	15	30	36	79
12 Months	17	81	27	66	36	84
24 Months	13	82	33	66	35	84



another focus concerns compliance with recommended preventive health care services while treating male-specific health conditions.¹¹⁹⁻¹²¹ Despite concerns that patients' overall health management would suffer after a diagnosis of prostate cancer, 2 studies conducted among our members found that delivery of preventive services (including colon cancer screening and flu shots) increased following such diagnoses.^{119,120} In response to evidence that guidelines for testosterone therapy are frequently not followed, our researchers have also studied the safety of these treatments. One study, conducted outside of Kaiser Permanente, found that testosterone therapy increased the risk of nonfatal myocardial infarction in some men,¹²² while another study conducted with Kaiser Permanente members found that testosterone reduced cardiovascular risks.¹²³ More recent work has found no evidence of a relationship between testosterone therapy and prostate cancer risk.124

What are the key components of approaches to reduce disparities in care and outcomes experienced by men?

Kaiser Permanente has effectively reduced racial and ethnic disparities in men's health through the use of systems, including its Complete Care program,¹²⁵ to ensure the delivery of recommended care.¹²⁶⁻¹²⁸ PSA screening rates in Kaiser Permanente are higher among ethnic minority populations⁷⁴ compared to American men generally,⁷⁵ as are the rates of timely biopsies after abnormal PSA test results¹²⁹ and the quality of prostate cancer care.¹³⁰⁻¹³² Evidence also exists that our efforts have reduced disparities in the incidence of cardiovascular disease between groups defined by race or ethnicity.¹³³

Translating Research Findings Into Policy and Practice

How has Kaiser Permanente research related to men's health contributed to changes in policy and practice?

Kaiser Permanente is a learning health care organization that works to systematically use research to inform and improve practice. Research, clinical,

and operational partners within Kaiser Permanente have tested a range of interventions to reduce the risk of common men's health problems, and to improve the outcomes men experience. Our work on the use of microscopic hematuria evaluation in bladder cancer management⁹⁵ led directly to changes in national practice guidelines.¹³⁴ Kaiser Permanente researchers in Northern California have used artificial intelligence techniques to identify men with medical-record information suggestive of testicular cancer, leading to improved monitoring and care.¹³⁵ In addition, our researchers in Southern California have supported the implementation of PSA SureNet, which leverages our electronic medical records to ensure that men with elevated PSA test results receive appropriate clinical management.^{88,136} Kaiser Permanente's electronic health record system has also been used to rapidly implement changes in prostate cancer screening guidelines, and to develop a prostate cancer risk calculator to guide decision-making in men with abnormal PSA test or physical exam results.137

Kaiser Permanente research contributes not only to policy and practice change within our own care delivery system but has also advanced national understanding of men's health. To date, Kaiser Permanente's research on men's health since 2007 has been cited 48 times within recent consensus statements and clinical practice guidelines published by a wide range of entities, including the American Cancer Society,¹³⁸ the American Academy of Family Physicians,¹³⁹ the American Urological Association,¹⁴⁰ and a joint guideline involving the American Urological Association, American Society for Radiation Oncology, and Society of Urologic Oncology.¹⁴¹ In addition, Kaiser Permanente researchers and clinician scientists have directly contributed as authors of the prostate cancer screening guidelines published by the U.S. Preventive Services Task Force.85,86

Kaiser Permanente is also an established leader in the field of men's health research. The California Men's Health Study is a multi-year study of men's health issues conducted in a diverse group of nearly 85,000 male Kaiser Permanente members.^{33-35,72,142-146} Many participants in the CMHS have subsequently chosen to enter the Kaiser Permanente Research Bank, a long-term





genetic research effort.¹⁴⁷ We are also involved in the National Cancer Institute's Community Oncology Research Program¹⁴⁸ and its Genitourinary Cancers Steering Committee,¹⁴⁹ and in the NRG Oncology collaboration.¹⁵⁰⁻¹⁵² Our scientists are leaders in important National Cancer Institute-sponsored research, including the Be-Well Study¹¹⁸ and the Breast and Prostate Cancer Cohort Consortium.^{13,17,62,63}

Kaiser Permanente's nearly 185 research scientists and more than 1,530 support staff are based at 9 research centers. There are currently 2,355 studies underway, including clinical trials. Since 2007, our research scientists and clinicians have published nearly 19,000 articles. Kaiser Permanente currently serves approximately 12.5 million members in 8 states and the District of Columbia.

This brief was written by Nicholas P. Emptage, Anna C. Davis, and Elizabeth A. McGlynn. It is available online from <u>about.kaiserpermanente.org/our-story/health-research/research-briefs</u>. The authors wish to thank Stephen Van Den Eeden for his contributions to the development of this brief.





References

- 1. American Cancer Society. Cancer Facts & Figures, 2019. Atlanta, GA: American Cancer Society;2019.
- 2. Centers for Disease Control and Prevention. Men and Heart Disease Fact Sheet. 2017; <u>https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_men_heart.htm</u>. Accessed April 15, 2019.
- 3. Center for Behavioral Health Statistics and Quality. 2016 National Survey on Drug Use and Health: Detailed Tables. Rockville, MD: Substance Abuse and Mental Health Services Administration;2017.
- 4. National Institute of Diabetes and Digestive and Kidney Diseases. Prostate Enlargement (Benign Prostatic Hyperplasia). 2014; https://www.niddk.nih.gov/health-information/urologic-diseases/prostate-problems/prostate-enlargement-benign-prostatic-hyperplasia. Accessed April 15, 2019.
- 5. Selvin E, Burnett AL, Platz EA. Preval ence and risk factors for erectile dysfunction in the US. *Am J Med.* 2007;120(2):151-157.
- Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab. 2007;92(11):4241-4247.
- Araujo AB, O'Donnell AB, Brambilla DJ, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 2004;89(12):5920-5926.
- 8. American Society for Reproductive Medicine. *Defining Infertility*. Birmingham, AL American Society for Reproductive Medicine;2014.
- Shmagel A, Foley R, Ibrahim H. Epidemiology of Chronic Low Back Pain in US Adults: Data From the 2009-2010 National Health and Nutrition Examination Survey. Arthritis Care Res (Hoboken). 2016;68(11):1688-1694.
- 10. Centers for Disease Control and Prevention. A NIOSH Look at Data from the Bureau of Labor Statistics: Worker Health by Industry and Occupation. Cincinnati, OH: National Institute for Occupational Safety and Health;2001.
- KPPL Search, conducted on May 13, 2021: ((dc.subject.mesh:"prostatic neoplasms" OR dc.subject.mesh:"-11. prostate hyperplasia" OR dc.subject.mesh:"prostatism" OR dc.subject.mesh:"Prostatic Diseases" OR dc.subject.mesh:"testicular neoplasms" OR dc.subject.mesh:"scrotum" OR dc.subject.mesh:"testis" OR dc.subject. mesh:"men's health" OR dc.subject.mesh:"erectile dysfunction" OR dc.subject.mesh:"impotence, vasculogenic" OR dc.subject.mesh:"penile erection" OR dc.subject.mesh:"penis" OR dc.subject.mesh:"infertility, male" OR dc.subject.mesh:"semen" OR dc.subject.mesh:"vasectomy" OR dc.subject.mesh:"Epididymitis" OR dc.subject.mesh:"Penile Diseases" OR dc.subject.mesh:"Spermatic Cord Torsion" OR dc.subject. mesh:"Cryptorchidism" OR dc.subject.mesh:"Orchitis") OR (title:"prostate cancer"~4 OR title:"prostatectomy" OR title:"androgen deprivation therapy" OR title:"prostate antigen"~3 OR title:"prostate carcinoma"~4 OR title:"prostatic enlargement" OR title:"prostatic hyperplasia" OR title:"prostatitis" OR title:"Sildenafil " OR title:"testicular cancer"~4 OR title:"testicular tumors"~4 OR title:"testicular seminoma" OR title:"neoplasia testis" OR title:"paratesticular adenomatoid tumor" OR title:"erectile dysfunction" OR abstract:"erectile dysfunction" OR title:"peyronie's disease" OR title:"vasectomy" OR title:"circumcision") OR ((title:men OR title:male) NOT (title:women OR title:female)) OR (citation:"Am J Mens Health" OR citation:"Harv Mens Health Watch" OR citation:"J Mens Health")) AND dc.type:"Journal Article" AND dc.date.issued:[2007 2021].
- 12. Kaulfuss S, Grzmil M, Hemmerlein B, et al. Leupaxin, a novel coactivator of the androgen receptor, is expressed in prostate cancer and plays a role in adhesion and invasion of prostate carcinoma cells. *Mol Endocrinol.* 2008;22(7):1606-1621.
- 13. Travis RC, Schumacher F, Hirschhorn JN, et al. CYP19A1 genetic variation in relation to prostate cancer risk and circulating sex hormone concentrations in men from the Breast and Prostate Cancer Cohort Consortium. *Cancer Epidemiol Biomarkers Prev.* 2009;18(10):2734-2744.
- 14. Yeager M, Chatterjee N, Ciampa J, et al. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. *Nat Genet*. 2009;41(10):1055-1057.
- Lou H, Yeager M, Li H, et al. Fine mapping and functional analysis of a common variant in MSMB on chromosome 10q11.2 associated with prostate cancer susceptibility. *Proc Natl Acad Sci U S A*. 2009;106(19):7933-7938.
- 16. Koutros S, Schumacher FR, Hayes RB, et al. Pooled analysis of phosphatidylinositol 3-kinase pathway variants and risk of prostate cancer. *Cancer Res.* 2010;70(6):2389-2396.
- 17. Schumacher FR, Cheng I, Freedman ML, et al. A comprehensive analysis of common IGF1, IGFBP1 and IGFBP3 genetic variation with prospective IGF-I and IGFBP-3 blood levels and prostate cancer risk among Caucasians. *Hum Mol Genet*. 2010;19(15):3089-3101.
- 18. Berndt SI, Sampson J, Yeager M, et al. Large-scale fine mapping of the HNF1B locus and prostate cancer risk. *Hum Mol Genet*. 2011;20(16):3322-3329.
- Hoffmann TJ, Van Den Eeden SK, Sakoda LC, et al. A large multi-ethnic genome-wide association study of prostate cancer identifies novel risk variants and substantial ethnic differences. *Cancer Discov.* 2015;5(8):878-891.



- 20. Weinmann S, Van Den Eeden SK, Haque R, et al. Immunohistochemical Expression of ERG in the Molecular Epidemiology of Fatal Prostate Cancer Study. *Prostate*. 2013;73(13):1371-1377.
- 21. Sehrawat A, Gao L, Wang Y, et al. LSD1 activates a lethal prostate cancer gene network independently of its demethylase function. *Proc Natl Acad Sci USA*. 2018;115(18):E4179-E4188.
- 22. Emami NC, Kachuri L, Meyers TJ, et al. Association of imputed prostate cancer transcriptome with disease risk reveals novel mechanisms. *Nat Commun.* 2019;10(1):3107. Epub 2019-3107.
- 23. Du Z, Hopp H, Ingles SA, et al. A Genome-wide Association Study of Prostate Cancer in Latinos. *Int J Cancer.* 2019.
- 24. Conti DV, Darst BF, Moss LC, et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. *Nat Genet.* 2021;53(1):65-75.
- 25. Emami NC, Cavazos TB, Rashkin SR, et al. A Large-Scale Association Study Detects Novel Rare Variants, Risk Genes, Functional Elements, and Polygenic Architecture of Prostate Cancer Susceptibility. *Cancer Res.* 2021;81(7):1695-1703.
- 26. Haque R, Van Den Eeden SK, Wallner LP, et al. Association of body mass index and prostate cancer mortality. *Obes Res Clin Pract.* 2014;8(4):e374-381.
- 27. Walsh TJ, Schembri M, Turek PJ, et al. Increased risk of high-grade prostate cancer among infertile men. *Cancer*. 2010;116(9):2140-2147.
- Cheng I, Witte JS, Jacobsen SJ, et al. Prostatitis, sexually transmitted diseases, and prostate cancer: the California Men's Health Study. PLoS ONE. 2010;5(1):e8736.
- Moore A, Huang WY, Danforth K, et al. Prospective evaluation of serum IL-16 and risk of prostate cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Cancer Causes Control. 2018;29(4-5):455-464.
- 30. Roddam AW, Allen NE, Appleby P, et al. Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies. *Ann Intern Med.* 2008;149(7):461-471.
- 31. Travis RC, Appleby PN, Martin RM, et al. A meta-analysis of individual participant data reveals an association between circulating levels of IGF-I and prostate cancer risk. *Cancer Res.* 2016;76(8):2288-2300.
- 32. Weinmann S, Shapiro JA, Rybicki BA, et al. Medical history, body size, and cigarette smoking in relation to fatal prostate cancer. *Cancer Causes Control.* 2010;21(1):117-125.
- Thomas AA, Wallner LP, Quinn VP, et al. Association Between Cannabis Use and the Risk of Bladder Cancer: Results From the California Men's Health Study. Urology. 2015;85(2):388-392.
- 34. McMahon DM, Burch JB, Hébert JR, et al. Diet-related inflammation and risk of prostate cancer in the California Men's Health Study. *Ann Epidemiol.* 2019;29:30-38.
- 35. Flick ED, Habel LA, Chan KA, et al. Statin use and risk of prostate cancer in the California Men's Health Study cohort. *Cancer Epidemiol Biomarkers Prev.* 2007;16(11):2218-2225.
- 36. Breau RH, Karnes RJ, Jacobson DJ, et al. The association between statin use and the diagnosis of prostate cancer in a population based cohort. *J Urol.* 2010;184(2):494-499.
- 37. Wallner LP, DiBello JR, Li BH, et al. 5-Alpha Reductase Inhibitors and the Risk of Prostate Cancer Mortality in Men Treated for Benign Prostatic Hyperplasia. *Mayo Clin Proc.* 2016;91(12):1717-1726.
- 38. Burke JP, Jacobson DJ, McGree ME, et al. Diabetes and sexual dysfunction: results from the Olmsted County study of urinary symptoms and health status among men. *J Urol.* 2007;177(4):1438-1442.
- 39. Van Den Eeden SK, Ferrara A, Shan J, et al. Impact of type 2 diabetes on lower urinary tract symptoms in men: a cohort study. *BMC Urol.* 2013;13:12.
- 40. Sarma AV, Burke JP, Jacobson DJ, et al. Associations between diabetes and clinical markers of benign prostatic hyperplasia among community-dwelling Black and White men. *Diabetes Care*. 2008;31(3):476-482.
- 41. Safavy S, Kilday PS, Slezak JM, et al. Effect of a Smoking Cessation Program on Sexual Function Recovery Following Robotic Prostatectomy at Kaiser Permanente Southern California. *Perm J.* 2017;21:16-138.
- 42. Sarma AV, Jacobson DJ, St Sauver JL, et al. Smoking and acute urinary retention: the Olmsted County study of urinary symptoms and health status among men. *Prostate*. 2009;69(7):699-705.
- 43. Rhodes T, Jacobson DJ, McGree ME, et al. Benign Prostate Specific Antigen Distribution and Associations With Urological Outcomes in Community Dwelling Black and White Men. J Urol. 2012;187(1):87-91.
- 44. Rule AD, St Sauver JL, Jacobson DJ, et al. Three-dimensional ultrasound bladder characteristics and their association with prostate size and lower urinary tract dysfunction among men in the community. *Urology*. 2009;74(4):908-913.
- 45. St Sauver JL, Jacobson DJ, McGree ME, et al. Longitudinal association between prostatitis and development of benign prostatic hyperplasia. *Urology*. 2008;71(3):475-479.
- 46. St Sauver JL, Sarma AV, Jacobson DJ, et al. Associations between C-reactive protein and benign prostatic hyperplasia/lower urinary tract symptom outcomes in a population-based cohort. *Am J Epidemiol.* 2009;169(11):1281-1290.
- 47. St Sauver JL, Jacobsen SJ, Jacobson DJ, et al. Statin use and decreased risk of benign prostatic enlargement and lower urinary tract symptoms. *BJU Int.* 2011;107(3):443-450.



- Gades NM, Jacobson DJ, McGree ME, et al. The associations between serum sex hormones, erectile function, and sex drive: the Olmsted County Study of Urinary Symptoms and Health Status among Men. J Sex Med. 2008;5(9):2209-2220.
- 49. Gades NM, Jacobson DJ, McGree ME, et al. Longitudinal evaluation of sexual function in a male cohort: the Olmsted county study of urinary symptoms and health status among men. *J Sex Med.* 2009;6(9):2455-2466.
- 50. Jorgenson E, Matharu N, Palmer MR, et al. Genetic variation in the SIM1 locus is associated with erectile dysfunction. *Proc Natl Acad Sci USA*. 2018;115(43):11018-11023.
- 51. Li D, Zhou Z, Qing D, et al. Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. *Hum Reprod.* 2010;25(2):519-527.
- 52. Li DK, Zhou Z, Miao M, et al. Relationship between urine bisphenol-A level and declining male sexual function. *J Androl.* 2010;31(5):500-506.
- 53. Li DK, Zhou Z, Miao M, et al. Urine bisphenol-A (BPA) level in relation to semen quality. *Fertil Steril.* 2011;95(2):625-630.
- 54. Song X, Miao M, Zhou X, et al. Bisphenol A Exposure and Sperm ACHE Hydroxymethylation in Men. Int J Environ Res Public Health. 2019;16(1):01.
- 55. Gleason JM, Slezak JM, Jung H, et al. Regular nonsteroidal anti-inflammatory drug use and erectile dysfunction. J Urol. 2011;185(4):1388-1393.
- 56. Deyo RA, Smith DH, Johnson ES, et al. Prescription Opioids for Back Pain and Use of Medications for Erectile Dysfunction. *Spine*.38(11):909-915.
- 57. Londono DC, Slezak JM, Quinn VP, et al. Population-based study of erectile dysfunction and polypharmacy. *BJU Int.* 2012;110(2):254-259.
- Liu X, Miao M, Zhou Z, et al. Exposure to bisphenol-A and reproductive hormones among male adults. Environ Toxicol Pharmacol. 2015;39(2):934-941.
- 59. Zhou Q, Miao M, Ran M, et al. Serum bisphenol-A concentration and sex hormone levels in men. *Fertil Steril.* 2013;100(2):478-482.
- 60. Rubinstein AL, Carpenter DM. Association Between Commonly Prescribed Opioids and Androgen Deficiency in Men: A Retrospective Cohort Analysis. *Pain Med.* 2017;18(4):637-644.
- 61. Rubinstein AL, Carpenter DM, Minkoff JR. Hypogonadism in Men With Chronic Pain Linked to the Use of Long-acting Rather Than Short-acting Opioids. *Clin J Pain.* 2013;29(10):840-845.
- 62. Ahn J, Schumacher FR, Berndt SI, et al. Quantitative trait loci predicting circulating sex steroid hormones in men from the NCI-Breast and Prostate Cancer Cohort Consortium (BPC3). *Hum Mol Genet*. 2009;18(19):3749-3757.
- 63. Lindstrom S, Ma J, Altshuler D, et al. A large study of androgen receptor germline variants and their relation to sex hormone levels and prostate cancer risk. Results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. *J Clin Endocrinol Metab.* 2010;95(9):E121-127.
- 64. Tsai HT, Keating NL, Van Den Eeden SK, et al. Risk of Diabetes among Patients Receiving Primary Androgen Deprivation Therapy for Clinically Localized Prostate Cancer. *J Urol.* 2015;193(6):1956-1962.
- 65. Bradley MC, Zhou Y, Freedman AN, et al. Risk of diabetes complications among those with diabetes receiving androgen deprivation therapy for localized prostate cancer. *Cancer Causes Control.* 2018;29(8):785-791.
- Lee CD, Jae SY, Iribarren C, et al. Physical fitness and carotid atherosclerosis in men. Int J Sports Med. 2009;30(9):672-676.
- 67. Inman BA, Sauver JL, Jacobson DJ, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc.* 2009;84(2):108-113.
- 68. Sarma AV, St Sauver JL, Jacobson DJ, et al. Racial Differences in Longitudinal Changes in Serum Prostate-specific Antigen Levels: The Olmsted County Study and the Flint Men's Health Study. *Urology*. 2014;83(1):88-93.
- 69. Richert-Boe KE, Weinmann S, Shapiro JA, et al. Racial differences in treatment of early-stage prostate cancer. *Urology.* 2008;71(6):1172-1176.
- 70. Dee EC, Muralidhar V, Arega MA, et al. Factors influencing non-completion of radiotherapy among men with localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2020.
- 71. Dee EC, Arega MA, Yang DD, et al. Disparities in Refusal of Locoregional Treatment for Prostate Adenocarcinoma. JCO Oncol Pract. 2021:Op2000839.
- 72. Smith JF, Caan BJ, Sternfeld B, et al. Racial disparities in erectile dysfunction among participants in the California Men's Health Study. J Sex Med. 2009;6(12):3433-3439.
- 73. Van Den Eeden SK, Shan J, Jacobsen SJ, et al. Evaluating Racial/Ethnic Disparities in Lower Urinary Tract Symptoms in Men. *J Urol.* 2012;187(1):185-189.
- 74. Haque R, Van Den Eeden SK, Jacobsen SJ, et al. Correlates of prostate-specific antigen testing in a large multiethnic cohort. *Am J Manag Care*. 2009;15(11):793-799.



- 75. Martires KJ, Kurlander DE, Minwell GJ, et al. Patterns of cancer screening in primary care from 2005 to 2010. *Cancer.* 2014;120(2):253-261.
- 76. Clemens JQ, Meenan RT, O'Keeffe Rosetti MC, et al. Prevalence of and risk factors for prostatitis: population based assessment using physician assigned diagnoses. *J Urol.* 2007;178(4 Pt 1):1333-1337.
- 77. Miaskowski C, Paul SM, Cooper BA, et al. Predictors of the trajectories of self-reported sleep disturbance in men with prostate cancer during and following radiation therapy. *Sleep*. 2011;34(2):171-179.
- 78. Davis K, Bellini P, Hagerman C, et al. Physicians' Perceptions of Factors Influencing the Treatment Decision-Making Process for Men with Low-Risk Prostate Cancer. *Urology*. 2017;107:86-95.
- 79. Taylor KL, Luta G, Hoffman RM, et al. Quality of life among men with low-risk prostate cancer during the first year following diagnosis: the PREPARE prospective cohort study. *Transl Behav Med.* 2018;8(2):156-165.
- 80. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in america project: benign prostatic hyperplasia. *J Urol.* 2008;179(5 Suppl):S75-80.
- 81. Chien GW, Slezak JM, Harrison TN, et al. Health-related quality of life outcomes from a contemporary prostate cancer registry in a large diverse population. *BJU Int.* 2017;120(4):520-529.
- 82. Bruner DW, Pugh SL, Lee WR, et al. Quality of Life in Patients With Low-Risk Prostate Cancer Treated With Hypofractionated vs Conventional Radiotherapy: A Phase 3 Randomized Clinical Trial. *JAMA Oncol.* 2019.
- 83. Bergstralh EJ, Roberts RO, Farmer SA, et al. Population-based case-control study of PSA and DRE screening on prostate cancer mortality. *Urology*. 2007;70(5):936-941.
- Wallner LP, Jacobsen SJ. Prostate-specific antigen and prostate cancer mortality: a systematic review. Am J Prev Med. 2013;45(3):318-326.
- Bibbins-Domingo K, Grossman DC, Curry SJ. The US Preventive Services Task Force 2017 Draft Recommendation Statement on Screening for Prostate Cancer: An Invitation to Review and Comment. JAMA. 2017;317(19):1949-1950.
- U. S. Preventive Services Task Force, Grossman DC, Curry SJ, et al. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;319(18):1901-1913.
- 87. Alpert PF. New Evidence for the Benefit of PSA Screening: Data From 400,887 Kaiser Permanente Patients. *Urology.* 2018;118:119-126. Epub 2018-05-14.:119-126.
- Danforth KN, Smith AE, Loo RK, et al. Electronic Clinical Surveillance to Improve Outpatient Care: Diverse Applications within an Integrated Delivery System. EGEMS (Wash DC). 2014;2(1):1056.
- Wallner LP, Hsu JW, Loo RK, et al. Trends in prostate specific antigen screening, prostate biopsies, urology visits and prostate cancer treatments from 2000 to 2012. Urology. 2015;86(3):498-505.
- Presti J, Alexeeff S, Horton B, et al. Changes in Prostate Cancer Presentation Following the 2012 USPSTF Screening Statement: Observational Study in a Multispecialty Group Practice. J Gen Intern Med. 2019.
- 91. Hoffmann TJ, Passarelli MN, Graff RE, et al. Genome-wide association study of prostate-specific antigen levels identifies novel loci independent of prostate cancer. *Nat Commun.* 2017;8:14248.
- Eklund M, Nordström T, Aly M, et al. The Stockholm-3 (STHLM3) Model can Improve Prostate Cancer Diagnostics in Men Aged 50-69 yr Compared with Current Prostate Cancer Testing. Eur Urol Focus. 2018;4(5):707-710.
- 93. Stovsky M, Klein EA, Chait A, et al. Clinical Validation of IsoPSA, a Single Parameter, Structure-Based Assay for Improved Detection of High-Grade Prostate Cancer. *J Urol.* 2019.
- 94. Wallner LP, Sarma AV, Lieber MM, et al. Psychosocial factors associated with an increased frequency of prostate cancer screening in men ages 40 to 79 years: the Olmsted County study. *Cancer Epidemiol Biomarkers Prev.* 2008;17(12):3588-3592.
- Loo RK, Lieberman SF, Slezak JM, et al. Stratifying risk of urinary tract malignant tumors in patients with asymptomatic microscopic hematuria. *Mayo Clin Proc.* 2013;88(2):129-138.
- 96. Wallner LP, DiBello JR, Li BH, et al. The use of 5-alpha reductase inhibitors to manage benign prostatic hyperplasia and the risk of all-cause mortality. *Urology*. 2018.
- 97. Hoffman RM, Lobo T, Van Den Eeden SK, et al. Selecting Active Surveillance: Decision-Making Factors for Men with a Low-Risk Prostate Cancer. *Med Decis Making*. 2019.
- 98. Berry DL, Hong F, Blonquist TM, et al. Decision regret, adverse outcomes, and treatment choice in men with localized prostate cancer: Results from a multi-site randomized trial. *Urol Oncol.* 2020.
- 99. Dunn LB, Aouizerat BE, Cooper BA, et al. Trajectories of anxiety in oncology patients and family caregivers during and after radiation therapy. *Eur J Oncol Nurs.* 2012;16(1):1-9.
- 100. Taylor KL, Hoffman RM, Davis KM, et al. Treatment Preferences for Active Surveillance vs. Active Treatment Among Men with Low-Risk Prostate Cancer. *Cancer Epidemiol Biomarkers Prev.* 2016;25(8):1240-1250.
- 101. Chu WG, Kim BJ, Slezak J, et al. The effect of urologist experience on choosing active surveillance for prostate cancer. *World J Urol.* 2015;33(11):1701-1706.
- Kelly SP, Van Den Eeden SK, Hoffman RM, et al. Sociodemographic and clinical predictors of switching to active treatment among a large ethnically diverse cohort of men with low-risk prostate cancer on observational management. J Urol. 2016;196(3):734-740.



- 103. Berry DL, Hong F, Blonquist TM, et al. Decision Support with the Personal Patient Profile-Prostate: A Multi-Center Randomized Trial. J Urol. 2018;199(1):89-97.
- 104. Hoffman RM, Van Den Eeden SK, Davis KM, et al. Decision making processes among men with low-risk prostate cancer: a survey study. *Psychooncology*. 2018;27(1):325-332.
- 105. Huntley JH, Coley RY, Carter HB, et al. Clinical evaluation of an individualized risk prediction tool for men on active surveillance for prostate cancer. *Urology*. 2018;121:118-124.
- 106. Wilson LS, Blonquist TM, Hong F, et al. Assigning value to preparation for prostate cancer decision making: a willingness to pay analysis. *BMC Med Inform Decis Mak*. 2019;19(1):6. Epub 2019-2001.
- 107. Spratt DE, Alshalalfa M, Fishbane N, et al. Transcriptomic heterogeneity of androgen receptor (AR) activity defines a de novo low AR-active subclass in treatment naïve primary prostate cancer. *Clin Cancer Res.* 2019.
- 108. Wang K, Luo J, Yeh S, et al. The MAO inhibitors phenelzine and clorgyline revert enzalutamide resistance in castration resistant prostate cancer. *Nat Commun.* 2020;11(1):2689. Epub 2020-2606.
- Van Den Eeden SK, Lu R, Zhang N, et al. A Biopsy-based 17-gene Genomic Prostate Score as a Predictor of Metastases and Prostate Cancer Death in Surgically Treated Men with Clinically Localized Disease. *Eur Urol.* 2018;73(1):129-138.
- 110. Nichol MB, Wu J, Huang J, et al. Cost-effectiveness of Prostate Health Index for prostate cancer detection. *BJU Int.* 2012;110(3):353-362.
- 111. Glass AG, Leo MC, Haddad Z, et al. Validation of a Genomic Classifier for Predicting Post-Prostatectomy Recurrence in a Community Based Health Care Setting. *J Urol.* 2016;195(6):1748-1753.
- 112. Spratt DE, Yousefi K, Deheshi S, et al. Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease. J Clin Oncol. 2017;35(18):1991-1998.
- 113. Spratt DE, Zhang J, Santiago-Jiménez M, et al. Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer. J Clin Oncol. 2018;36(6):581-590.
- 114. Van den Broeck T, Moris L, Gevaert T, et al. Validation of the Decipher Test for Predicting Distant Metastatic Recurrence in Men with High-risk Nonmetastatic Prostate Cancer 10 Years After Surgery. *Eur Urol Oncol.* 2019.
- 115. Kwan ML, Leo MC, Danforth KN, et al. Factors That Influence Selection of Urinary Diversion Among Bladder Cancer Patients in 3 Community-based Integrated Health Care Systems. *Urology*. 2019;125:222-229.
- 116. Leo MC, Gilbert SM, Wendel CS, et al. Development of a Goal Elicitation Measure to Support Choice about Urinary Diversion by Patients with Bladder Cancer. *J Urol.* 2019;202(1):83-89.
- 117. Kwan ML, Garren B, Nielsen ME, Tang L. Lifestyle and nutritional modifiable factors in the prevention and treatment of bladder cancer. *Urol Oncol.* 2019;37(6):380-386.
- 118. Kwan ML, Kushi LH, Danforth KN, et al. The Be-Well Study: a prospective cohort study of lifestyle and genetic factors to reduce the risk of recurrence and progression of non-muscle-invasive bladder cancer. *Cancer Causes Control.* 2019;30(2):187-193.
- Wallner LP, Slezak JM, Loo RK, et al. Ten-Year Trends in Preventive Service Use Before and After Prostate Cancer Diagnosis: A Comparison with Noncancer Controls. *Perm J.* 2017;21:16-184.
- 120. Wallner LP, Slezak JM, Quinn VP, et al. Quality of preventive care before and after prostate cancer diagnosis. J Mens Health. 2015;11(5):14-21.
- 121. Haque R, UlcickasYood M, Xu X, et al. Cardiovascular disease risk and androgen deprivation therapy in patients with localised prostate cancer: a prospective cohort study. *Br J Cancer*. 2017;117(8):1233-1240.
- 122. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS ONE*. 2014;9(1):e85805.
- 123. Cheetham TC, An J, Jacobsen SJ, et al. Association of Testosterone Replacement With Cardiovascular Outcomes Among Men With Androgen Deficiency. *JAMA Intern Med.* 2017;177(4):491-499.
- 124. Walsh TJ, Shores MM, Krakauer CA, et al. Testosterone treatment and the risk of aggressive prostate cancer in men with low testosterone levels. *PLoS ONE*. 2018;13(6):e0199194. Epub 0192018-0199106.
- 125. Kanter MH, Lindsay G, Bellows J, Chase A. Complete care at Kaiser Permanente: transforming chronic and preventive care. *Jt Comm J Qual Patient Saf.* 2013;39(11):484-494.
- 126. Inkelas M, Brown AF, Vassar SD, et al. Enhancing Dissemination, Implementation, and Improvement Science in CTSAs through Regional Partnerships. *Clin Transl Sci.* 2015;8(6):800-806.
- 127. Henry SL, Shen E, Ahuja A, et al. The Online Personal Action Plan: A Tool to Transform Patient-Enabled Preventive and Chronic Care. *Am J Prev Med.* 2016;51(1):71-77.
- 128. Sharp AL, Baecker AS, Shen E, et al. Effect of a HEART Care Pathway on Chest Pain Management Within an Integrated Health System. *Ann Emerg Med.* 2019.
- 129. Reading SR, Porter KR, Hsu JY, et al. Racial and Ethnic Variation in Time to Prostate Biopsy after an Elevated Screening Level of Serum PSA. *Urology*. 2016;96:121-127.
- 130. Sassani P, Blumberg JM, Cheetham TC, et al. Black men have lower rates than white men of biochemical failure with primary androgen-deprivation therapy. *Perm J.* 2011;15(3):4-8.



- 131. Porter KR, Hsu JW, Chien GW, et al. Racial and ethnic differences in time to treatment for patients with localized prostate cancer. *Urology*. 2013;81(2):283-287.
- 132. Reading SR, Porter KR, Slezak JM, et al. Racial and Ethnic Variation in Health-Related Quality of Life Scores Prior to Prostate Cancer Treatment. *Sex Med.* 2017;5(4):e219-e228.
- 133. Rana JS, Liu JY, Moffet HH, et al. Ethnic Differences in Risk of Coronary Heart Disease in a Large Contemporary Population. *Am J Prev Med.* 2016;50(5):637-641.
- 134. American College of Obstetricians and Gynecologists. Committee Opinion No. 703 Summary: Asymptomatic Microscopic Hematuria in Women. *Obstet Gynecol.* 2017;129(6):1153-1154.
- 135. Rare Cancer Carefully Tracked and Treated [press release]. April 25, 2018.
- 136. Kaiser Permanente's 'SureNet' Improves Patient Safety, Closes Care Gaps [press release]. August 21, 2018.
- 137. Presti J, Alexeeff S, Horton B, et al. Prospective development of a prostate cancer risk calculator in a racially diverse population: The Kaiser Permanente Prostate Cancer Risk Calculator. *Urol Oncol.* 2020.
- 138. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin.* 2010;60(2):70-98.
- 139. American Academy of Family Physicians. Prostate Cancer Clinical Preventive Service Recommendation. 2018; https://www.aafp.org/patient-care/clinical-recommendations/all/prostate-cancer.html. Accessed May 2, 2019.
- 140. Burnett AL, Nehra A, Breau RH, et al. Erectile Dysfunction: AUA Guideline. J Urol. 2018;200(3):633-641.
- 141. Sanda MG, Chen RC, Crispino T, et al. *Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline*. Linthicum, MD: American Urological Association;2017.
- 142. Enger SM, Van den Eeden SK, Sternfeld B, et al. California Men's Health Study (CMHS): a multiethnic cohort in a managed care setting. *BMC Public Health.* 2006;6:172.
- 143. Chao C, Slezak JM, Caan BJ, Quinn VP. Alcoholic beverage intake and risk of lung cancer: the California Men's Health Study. *Cancer Epidemiol Biomarkers Prev.* 2008;17(10):2692-2699.
- 144. Wallner LP, Slezak JM, Loo RK, et al. Progression and treatment of incident lower urinary tract symptoms among men in the California Men's Health Study. *BJU Int.* 2015;115(1):127-133.
- Hechter RC, Chao C, Jacobsen SJ, et al. Clinical effectiveness of pneumococcal polysaccharide vaccine in men: California Men's Health Study. *Vaccine*. 2012;30(38):5625-5630.
- 146. Ahmed AT, Quinn VP, Caan B, et al. Generational status and duration of residence predict diabetes prevalence among Latinos: the California Men's Health Study. BMC Public Health. 2009;9:392.
- 147. Kaiser Permanente. Kaiser Permanente Research Bank. 2019; <u>https://researchbank.kaiserpermanente.org/</u>. Accessed May 2, 2019.
- 148. National Cancer Institute. NCORP: About. 2019; https://ncorp.cancer.gov/about/. Accessed May 2, 2019.
- 149. National Cancer Institute. Genitourinary Cancers Steering Committee Roster. 2019; <u>https://www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn/genitourinary/roster</u>. Accessed May 2, 2019.
- 150. Lukka HR, Pugh SL, Bruner DW, et al. Patient reported outcomes in NRG Oncology RTOG 0938, evaluating two ultrahypofractionated regimens for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2018.
- 151. Valicenti RK, Pugh SL, Trabulsi EJ, et al. First Report of NRG Oncology/Radiation Therapy Oncology Group 0622: A Phase 2 Trial of Samarium-153 Followed by Salvage Prostatic Fossa Irradiation in High-Risk Clinically Nonmetastatic Prostate Cancer After Radical Prostatectomy. Int J Radiat Oncol Biol Phys. 2018;100(3):695-701.
- Thor M, Deasy JO, Paulus R, et al. Tolerance doses for late adverse events after hypofractionated radiotherapy for prostate cancer on trial NRG Oncology/RTOG 0415. *Radiother Oncol.* 2019;135:19-24. Epub 2019-03-05.:19-24.

