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Precision Medicine and Men's Health

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Abstract

Precision medicine can greatly benefit men's health by helping to prevent, diagnose, and treat prostate cancer, benign prostatic hyperplasia, infertility, hypogonadism, and erectile dysfunction. For example, precision medicine can facilitate the selection of men at high risk for prostate cancer for targeted prostate-specific antigen screening and chemoprevention administration, as well as assist in identifying men who are resistant to medical therapy for prostatic hyperplasia, who may instead require surgery. Precision medicine-trained clinicians can also let couples know whether their specific cause of infertility should be bypassed by sperm extraction and *in vitro* fertilization to prevent abnormalities in their offspring. Though precision medicine's role in the management of hypogonadism has yet to be defined, it could be used to identify biomarkers associated with individual patients' responses to treatment so that appropriate therapy can be prescribed. Last, precision medicine can improve erectile dysfunction treatment by identifying genetic polymorphisms that regulate response to medical therapies and by aiding in the selection of patients for further cardiovascular disease screening.

Keywords

andrology, biologic determinants of health, genetics, health screening, physiological and endocrine disorders

Precision Medicine

In his 2015 State of the Union address, President Obama called for a national $215 million investment in precision medicine to develop preventive and therapeutic strategies tailored to individual patients' needs (Collins & Varmus, 2015; Mullard, 2015). The U.S. National Research Council's now preferred term for what has also been called "personalized" medicine (Katsnelson, 2013), precision medicine seeks to categorize patients according to susceptibility to specific diseases or responses to particular therapies, so interventions can target only those individuals who would most benefit from them (Office of the White House Press Secretary, 2015).

Precision medicine aims to increase collaboration between clinicians and their colleagues in anatomic and clinical pathology, as well as medical genetics. Pathologists can contribute their knowledge of genomics, proteomics, and metabolomics to enable the precise characterization of the molecular phenotypes of individual patients. In addition, medical geneticists and genetic counselors can diagnose and manage hereditary disorders to improve patient care. So far, precision medicine has primarily focused on identifying specific tumoral genetic signatures to customize anticancer therapies for patients using a "precision oncology" paradigm (Tsao et al., 2005). The White House's new initiative will extend precision medicine beyond its current primary focus on cancer diagnosis and therapy (Garraway, Verweij, & Ballman, 2013).

Although precision medicine will likely be most useful in treating cancers in the near future, it will have a major impact on men's health as our understanding of molecular biology and pathophysiology advances (Porche, 2015). In this commentary, we discuss the role of precision medicine in treating disorders of the male reproductive system, specifically prostate cancer (CaP), benign prostatic hyperplasia (BPH), infertility, hypogonadism, and erectile dysfunction (ED).

Prostate Cancer

The prevention, screening, diagnosis, and treatment of CaP, the most prevalent cancer in men, remains a thorny

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dilemma for physicians (Malvezzi, Bertuccio, Levi, Vecchia, & Negri, 2014). The estimated heritability of CaP is 42% (95% confidence interval [29, 50]; Lichtenstein et al., 2000). Genome-wide association (GWA) studies have identified more than 70 single-nucleotide polymorphisms that can predict CaP risk when incorporated into polygenic risk scores (Amin Al Olama et al., 2015; Eeles et al., 2014). Genetic susceptibility data, such as BRCA genotype, may also aid in choosing men for targeted prostate-specific antigen screening (Bancroft et al., 2014) and may also help end the over-treatment of men at low risk for disease (Schröder et al., 2012). Furthermore, genetic techniques may enable identification of men who would respond well to chemopreventive medications—for example, 5-α reductase inhibitors, nonsteroidal anti-inflammatory agents, selective estrogen receptor modulators, and statins—thus obviating the need for treating nonresponders (Schmitz-Dräger, Schöffski, Marberger, Sahin, & Schmid, 2014).

CaP is a heterogeneous group of diseases with unique genetic and proteomic signatures (Rubin, Maher, & Chinnaiyan, 2011). Molecular phenotyping techniques have identified at least seven molecular subtypes of CaP that vary in their risk for metastatic progression (Attard & Beltran, 2015). Assays of androgen-receptor signaling, aurora kinase A gain, BRCA gene aberrations, ERG:TMPRSS2 fusion, PTEN and RB1 loss, and mRNA signatures are available to risk stratify patients and assess for sensitivity to chemical castration, taxanes, and PARP inhibitors (Attard et al., 2015; Beltran et al., 2011; Boström et al., 2015; de Leeuw et al., 2015; Ferraldeschi et al., 2015; Fong et al., 2009). A separate, non-gene-based application that exemplifies precision-medicine treatment is the autologous cellular immunotherapy sipuleucel-T, which in effect programs the immune system to target and eliminate neoplastic cells, thus extending overall survival by up to 4 months in metastatic, castration-resistant CaP (Kantoff et al., 2010).

Benign Prostatic Hyperplasia

The attributes that qualify precision medicine for oncology also do so for treatment of benign diseases of dysregulated cell growth such as BPH (Bechis, Otsetov, Ge, & Olumi, 2014). Like CaP, BPH may be conceptualized as a heterogeneous group of diseases with unique molecular signatures, varying growth rates, and degrees of aggressiveness (Prakash et al., 2002). Furthermore, GWA studies have revealed associations between particular single-nucleotide polymorphisms and BPH risk and severity that could be used to stratify patients into risk groups for tailored pharmacogenomic therapy (Helfand, Hu, Loeb, McVary, & Catalona, 2013). Advances in our understanding of prostatic smooth-muscle regulation by α(1)-adrenoreceptors (α1ARs) and androgen-signaling pathways will also make the precision-medicine treatment of BPH a reality.

The expression of α1AR subtypes varies among symptomatic BPH patients, and expression-level differences may help predict which patients will respond to subtype-selective α1AR antagonists (Kojima, Sasaki, Hayashi, Tsujimoto, & Kohri, 2009). For example, epigenetic silencing of 5AR2 gene expression associated with increased body mass index and age is a risk marker for disease progression and medical therapy failure (Bechis et al., 2015). In up to 30% of men with BPH, silencing of the 5AR2 gene by DNA methylation is associated with resistance to medical therapy with finasteride (Niu et al., 2011). In such patients, a more aggressive treatment regimen, such as transurethral resection of the prostate, to improve symptoms may be indicated. Use of these data in the evaluation of patients with new-onset BPH could be used to justify early surgical intervention in certain cases, obviating the need for years of office visits for failed medical therapies (Bechis et al., 2014).

Male Infertility

Precision medicine promises to improve the management of male factor infertility, which accounts for 40% to 50% of cases of infertility among couples. Typically, a man with a lack of sperm in the ejaculate, azoospermia, should undergo diagnostic genetic testing to determine the desirability of surgical sperm retrieval (Hwang, Lipshultz, & Lamb, 2011). The current guidelines suggest screening identification of Y-chromosome microdeletions and karyotyping in men with severe testicular failure. Men with Klinefelter syndrome (47,XXY) and AZFc deletions can have foci of spermatogenesis in the testis, which makes sperm retrieval and the fathering of biological children with intracytoplasmic sperm injection possible. However, men with AZFa or AZFb deletions cannot father biological children because they lack spermatogenesis within their testis (Pryor et al., 1997). This information can help counsel men with AZFa or AZFb deletions to use donor sperm or adopt children.

Since up to 1,188 mammalian genes affect male fertility (most of which were identified in rodent studies), the aforementioned examples are but a few of precision medicine's potential uses (Lin & Matzuk, 2014; Matzuk & Lamb, 2008). As diagnostic genetic testing becomes more widely available throughout the United States, pathologists, medical geneticists, and genetic counselors will more frequently inform couples and their physicians on whether their specific cause of infertility should be bypassed by sperm extraction and *in vitro* fertilization to prevent future genetic mutations in their offspring (Alukal & Lamb, 2008). To this end, risk models will need to be

developed to translate this genetic information into the risk of developing traits that exhibit complex inheritance through the interaction of multiple genes. Precision medicine will also assist in the development of sperm biomarkers that will predict which sperm could better fertilize eggs (Palermo, Neri, & Rosenwaks, 2015).

The advantages of utilizing precision medicine to guide management of infertility are not merely academic. They will greatly benefit the reproductive health of couples as well as heighten their understanding of their infertility. Genetic diagnostics will provide specific names and causes for cases of infertility now deemed idiopathic. As our understanding of the molecular mechanisms of male factor infertility continues to improve, providers will be able to better predict the likelihood of natural pregnancy, streamline treatment selection, and predict treatment response.

Hypogonadism

Precision medicine's role in the management of hypogonadism has yet to be defined. Current diagnostic criteria for hypogonadism are imprecise, and most symptomatic men are treated with testosterone (T) gels, injectables, or implants at different serum T thresholds with mixed results (Lunenfeld et al., 2015). T deficiency's diagnostic cut points are somewhat arbitrary relative to symptoms, and a true threshold is unlikely to exist for most patients (Bernie, Scovell, & Ramasamy, 2014). Precision medicine may identify ideal T levels for individual patients based on metabolic markers, which can improve treatment. Depending on the interaction between T administration's dose and frequency and the patient's molecular phenotype, men may experience side effects ranging from mood swings, hypertension, and polycythemia, to more serious myocardial infarctions and strokes (Center for Drug Evaluation and Research, 2015). Precision medicine could identify biomarkers or genetic polymorphisms that will minimize T therapy side effects and help predict which men would have adverse cardiovascular events. This approach, an example of a pharmacogenomics, would ensure that the right patient receives the right drug at the right time.

Results from GWA studies suggest that a variety of heritable genetic polymorphisms affect the synthesis, metabolism, and action of sex hormones and contribute to variations in circulating serum levels of dehydroepiandrosterone, T, and sex hormone-binding globulin (Vandenput & Ohlsson, 2014). Genetic influences can regulate up to two thirds of the variation in serum T levels (Harris, Vernon, & Boomsma, 1998; Kuijper et al., 2007; Meikle, Stanish, Taylor, Edwards, & Bishop, 1982; Ring et al., 2005). For example, polymorphisms in the aromatase gene CYP19A1, which encodes the enzyme that converts T to estrogen, affect free T levels (Travis et al., 2009). Precise identification of such a polymorphism in the hypogonadal patient could prompt the clinician to prescribe an aromatase inhibitor, such as anastrozole or letrozole, rather than exogenous T therapy, to increase T levels.

Precision medicine could also include the screening of men for CAG repeats in the androgen receptor gene, which may determine which patients will benefit most from T therapy (Francomano, Greco, Lenzi, & Aversa, 2013). A study investigating the length of these repeats in patients who developed hypogonadotropic hypogonadism after undergoing pituitary surgery reported that response to therapy was inversely correlated with the number of repeats (Tirabassi, Delli Muti, Corona, Maggi, & Balercia, 2014). The association between CAG repeats and response to T therapy was also confirmed in a nonsurgical patient population with late-onset hypogonadism (Stanworth, Akhtar, Channer, & Jones, 2014). This finding suggests that screening for this polymorphism prior to prescribing T could help clinicians select the appropriate dose, frequency, and type of T therapy.

Erectile Dysfunction

Precision medicine could improve the treatment of ED, one of the most common and bothersome health concerns among aging men. Researchers are investigating whether specific genetic polymorphisms can predict patient response to PDE5 inhibitors such as sildenafil (Hatzimouratidis & Hatzichristou, 2008). Identifying such polymorphisms before therapy would allow the clinician to choose the correct type, dose, and frequency of PDE5 inhibitor or potentially an alternative therapy. PDE5 inhibitors are expensive, so such a screening program could be cost-effective. In fact, its utility has already been demonstrated in patients suffering from pulmonary hypertension (Sekine et al., 2014). Patients who possess a polymorphism in the gene that encodes the G-protein β3 subunit will more likely benefit from sildenafil than those without the mutation.

Precision medicine may allow for genetic prediction of ED occurrence and its side effects (Lopushnyan & Chitaley, 2012). It may not only identify genetic predictors and biomarkers for the development of ED, but also predictors of CaP treatment-related radiotherapy and radical prostatectomy associated ED for improvement of treatment decision making (Clavell-Hernandez & Wang, 2015). In addition, precision medicine could in theory assess for predictors of priapism and other adverse side effects from common medical therapies for ED such as cyanopsia (blue vision) and lower back pain caused by sildenafil and tadalafil.

More important, precision medicine could help health practitioners decide which patients with ED need further

screening for cardiovascular disease (Rodriguez, Al Dashti, & Schwarz, 2005). This dilemma is commonly faced by urologists, who are often the only health care providers evaluating men (Hanno, 2007). Of note, a recent cost-benefit analysis concluded that screening for coronary disease in men with ED can be cost-effective for secondary prevention (Pastuszak et al., 2015). Furthermore, concomitant diabetes, hypertension, and increased aortic stiffness and coronary artery calcification are associated with increased coronary risk in patients suffering from ED (Vlachopoulos, Ioakeimidis, & Stefanadis, 2015). We must determine whether there are genes that predict an association between ED and cardiovascular risk and, if so, whether they merit screening (Lee et al., 2008). Identifying genes that link ED and cardiovascular risk may help identify the patients who would gain the most from further workup and management.

Conclusions

A precision medicine approach to men's health will be advantageous in the diagnosis of and therapy for many conditions. To expand the current therapeutic options available to clinicians, collaboration among basic scientists, clinicians, engineers, pathologists, statisticians, and patients to develop patient-specific biomarkers is critical (Collins & Varmus, 2015). To properly implement precision medicine, we need to conduct translational research, solicit more male participation in clinical and genetics research, and enable underserved communities to access precision-medicine technologies so that all men have equitable access to them. We are optimistic that this nascent field will grow and change markedly in the years to come to the benefit of men and their families worldwide.

Declaration of Conflicting Interests

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References

Alukal, J. P., & Lamb, D. J. (2008). Intracytoplasmic sperm injection (ICSI)—What are the risks? *Urologic Clinics of North America*, *35*, 277-288. doi:10.1016/j.ucl.2008.01.004

Amin Al Olama, A., Benlloch, S., Antoniou, A. C., Giles, G. G., Severi, G., Neal, D., . . . Easton, D. F. (2015). Risk analysis of prostate cancer in PRACTICAL, a multinational consortium, using 25 known prostate cancer susceptibility loci. *Cancer Epidemiology, Biomarkers & Prevention*, *24*, 1121-9.

Attard, G., & Beltran, H. (2015). Prioritizing precision medicine for prostate cancer. *Annals of Oncology*, *26*, 1041-42.

Attard, G., de Bono, J. S., Logothetis, C. J., Fizazi, K., Mukherjee, S. D., Joshua, A. M., . . . Ryan, C. J. (2015). Improvements in radiographic progression-free survival stratified by ERG gene status in metastatic castration-resistant prostate cancer patients treated with abiraterone acetate. *Clinical Cancer Research*, *21*, 1621-1627. doi:10.1158/1078-0432.CCR-14-1961

Bancroft, E. K., Page, E. C., Castro, E., Lilja, H., Vickers, A., Sjoberg, D., . . . Eeles, R. A. (2014). Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: Results from the initial screening round of the IMPACT study. *European Urology*, *66*, 489-499. doi:10.1016/j.eururo.2014.01.003

Bechis, S. K., Otsetov, A. G., Ge, R., & Olumi, A. F. (2014). Personalized medicine for the management of benign prostatic hyperplasia. *Journal of Urology*, *192*, 16-23. doi:10.1016/j.juro.2014.01.114

Bechis, S. K., Otsetov, A. G., Ge, R., Wang, Z., Vangel, M. G., Wu, C.-L., . . . Olumi, A. F. (2015). Age and obesity promote methylation and suppression of 5-alpha reductase 2—Implications for personalized therapy in benign prostatic hyperplasia. *Journal of Urology*, *194*, 1031-37.

Beltran, H., Rickman, D. S., Park, K., Chae, S. S., Sboner, A., MacDonald, T. Y., . . . Rubin, M. A. (2011). Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. *Cancer Discovery*, *1*, 487-495. doi:10.1158/2159-8290.CD-11-0130

Bernie, A. M., Scovell, J. M., & Ramasamy, R. (2014). Comparison of questionnaires used for screening and symptom identification in hypogonadal men. *Aging Male*, *17*, 195-198. doi:10.3109/13685538.2014.963041

Boström, P. J., Bjartell, A. S., Catto, J. W. F., Eggener, S. E., Lilja, H., Loeb, S., . . . Cooperberg, M. R. (2015). Genomic predictors of outcome in prostate cancer. *European Urology*, *68*, 1033-44.

Center for Drug Evaluation and Research. (2015, March). *FDA drug safety communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use*. Retrieved from http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm

Clavell-Hernandez, J., & Wang, R. (2015). Penile rehabilitation following prostate cancer treatment: Review of current literature, *17*, 916-22.

Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. *New England Journal of Medicine*, *372*, 793-795. doi:10.1056/NEJMp1500523

de Leeuw, R., Berman-Booty, L. D., Schiewer, M. J., Ciment, S. J., Den, R. B., Dicker, A. P., . . . Knudsen, K. E. (2015). Novel actions of next-generation taxanes benefit advanced stages of prostate cancer. *Clinical Cancer Research*, *21*, 795-807. doi:10.1158/1078-0432.CCR-14-1358

Eeles, R., Goh, C., Castro, E., Bancroft, E., Guy, M., Al Olama, A. A., . . . Kote-Jarai, Z. (2014). The genetic epidemiol-

ogy of prostate cancer and its clinical implications. *Nature Reviews. Urology*, *11*, 18-31. doi:10.1038/nrurol.2013.266

Ferraldeschi, R., Nava Rodrigues, D., Riisnaes, R., Miranda, S., Figueiredo, I., Rescigno, P., . . . de Bono, J. (2015). PTEN protein loss and clinical outcome from castration-resistant prostate cancer treated with abiraterone acetate. *European Urology*, *67*, 795-802. doi:10.1016/j.eururo.2014.10.027

Fong, P. C., Boss, D. S., Yap, T. A., Tutt, A., Wu, P., Mergui-Roelvink, M., . . . de Bono, J. S. (2009). Inhibition of poly(ADP-Ribose) polymerase in tumors from BRCA mutation carriers. *New England Journal of Medicine*, *361*, 123-134. doi:10.1056/NEJMoa0900212

Francomano, D., Greco, E. A., Lenzi, A., & Aversa, A. (2013). CAG repeat testing of androgen receptor polymorphism: Is this necessary for the best clinical management of hypogonadism? *Journal of Sexual Medicine*, *10*, 2373-2381. doi:10.1111/jsm.12268

Garraway, L. A., Verweij, J., & Ballman, K. V. (2013). Precision oncology: An overview. *Journal of Clinical Oncology*, *31*, 1803-1805. doi:10.1200/JCO.2013.49.4799

Hanno, P. (2007). The urologist as a gatekeeper. *Nature Clinical Practice. Urology*, *4*(6), 289. doi:10.1038/ncpuro0818

Harris, J. A., Vernon, P. A., & Boomsma, D. I. (1998). The heritability of testosterone: A study of Dutch adolescent twins and their parents. *Behavior Genetics*, *28*, 165-171.

Hatzimouratidis, K., & Hatzichristou, D. G. (2008). Looking to the future for erectile dysfunction therapies. *Drugs*, *68*, 231-250.

Helfand, B. T., Hu, Q., Loeb, S., McVary, K. T., & Catalona, W. J. (2013). Genetic sequence variants are associated with severity of lower urinary tract symptoms and prostate cancer susceptibility. *Journal of Urology*, *189*, 845-848. doi:10.1016/j.juro.2012.11.044

Hwang, K., Lipshultz, L. I., & Lamb, D. J. (2011). Use of diagnostic testing to detect infertility. *Current Urology Reports*, *12*, 68-76. doi:10.1007/s11934-010-0154-0

Kantoff, P. W., Higano, C. S., Shore, N. D., Berger, E. R., Small, E. J., Penson, D. F., . . . Schellhammer, P. F. (2010). Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *New England Journal of Medicine*, *363*, 411-422. doi:10.1056/NEJMoa1001294

Katsnelson, A. (2013). Momentum grows to make "personalized" medicine more "precise." *Nature Medicine*, *19*, 249-249. doi:10.1038/nm0313-249

Kojima, Y., Sasaki, S., Hayashi, Y., Tsujimoto, G., & Kohri, K. (2009). Subtypes of alpha1-adrenoceptors in BPH: Future prospects for personalized medicine. *Nature Clinical Practice. Urology*, *6*, 44-53. doi:10.1038/ncpuro1276

Kuijper, E. a. M., Lambalk, C. B., Boomsma, D. I., van der Sluis, S., Blankenstein, M. A., de Geus, E. J. C., & Posthuma, D. (2007). Heritability of reproductive hormones in adult male twins. *Human Reproduction*, *22*, 2153-2159. doi:10.1093/humrep/dem145

Lee, Y.-C., Lin, H.-H., Wang, C.-J., Liu, C.-C., Wu, W.-J., Huang, C.-H., & Chang, L.-L. (2008). The associations among GNB3 C825T polymorphism, erectile dysfunction, and related risk factors. *Journal of Sexual Medicine*, *5*, 2061-2068. doi:10.1111/j.1743-6109.2008.00938.x

Lichtenstein, P., Holm, N. V., Verkasalo, P. K., Iliadou, A., Kaprio, J., Koskenvuo, M., . . . Hemminki, K. (2000). Environmental and heritable factors in the causation of cancer—Analyses of cohorts of twins from Sweden, Denmark, and Finland. *New England Journal of Medicine*, *343*, 78-85. doi:10.1056/NEJM200007133430201

Lin, Y.-N., & Matzuk, M. M. (2014). Genetics of male fertility. *Human Fertility: Methods in Molecular Biology*, *1154*, 25-37. doi:10.1007/978-1-4939-0659-8_2

Lopushnyan, N. A., & Chitaley, K. (2012). Genetics of erectile dysfunction. *Journal of Urology*, *188*, 1676-1683. doi:10.1016/j.juro.2012.07.008

Lunenfeld, B., Mskhalaya, G., Zitzmann, M., Arver, S., Kalinchenko, S., Tishova, Y., & Morgentaler, A. (2015). Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. *Aging Male*, *18*, 5-15. doi:10.3109/13685538.2015.1004049

Malvezzi, M., Bertuccio, P., Levi, F., Vecchia, C. L., & Negri, E. (2014). European cancer mortality predictions for the year 2014. *Annals of Oncology*, *25*, 1650-1656. doi:10.1093/annonc/mdu138

Matzuk, M. M., & Lamb, D. J. (2008). The biology of infertility: Research advances and clinical challenges. *Nature Medicine*, *14*, 1197-1213. doi:10.1038/nm.f.1895

Meikle, A. W., Stanish, W. M., Taylor, N., Edwards, C. Q., & Bishop, C. T. (1982). Familial effects on plasma sex-steroid content in man: Testosterone, estradiol and sex-hormone-binding globulin. *Metabolism: Clinical and Experimental*, *31*, 6-9.

Mullard, A. (2015). $215 million precision-medicine initiative takes shape. *Nature Reviews. Drug Discovery*, *14*(3), 155. doi:10.1038/nrd4569

Niu, Y., Ge, R., Hu, L., Diaz, C., Wang, Z., Wu, C.-L., & Olumi, A. F. (2011). Reduced levels of 5-α reductase 2 in adult prostate tissue and implications for BPH therapy. *Prostate*, *71*, 1317-1324. doi:10.1002/pros.21348

Office of the White House Press Secretary. (2015, January 30). *Fact sheet: President Obama's Precision Medicine Initiative*. Retrieved from www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative

Palermo, G. D., Neri, Q. V., & Rosenwaks, Z. (2015). To ICSI or not to ICSI. *Seminars in Reproductive Medicine*, 33, 92-102. doi:10.1055/s-0035-1546825

Pastuszak, A. W., Hyman, D. A., Yadav, N., Godoy, G., Lipshultz, L. I., Araujo, A. B., & Khera, M. (2015). Erectile dysfunction as a marker for cardiovascular disease diagnosis and intervention: A cost analysis. *Journal of Sexual Medicine*, *12*, 975-984. doi:10.1111/jsm.12848

Porche, D. J. (2015). Precision Medicine Initiative. *American Journal of Men's Health*, *9*, 177. doi:10.1177/1557988315574512

Prakash, K., Pirozzi, G., Elashoff, M., Munger, W., Waga, I., Dhir, R., . . . Getzenberg, R. H. (2002). Symptomatic and asymptomatic benign prostatic hyperplasia: Molecular differentiation by using microarrays. *Proceedings of the National Academy of Sciences of the United States of America*, *99*, 7598-7603. doi:10.1073/pnas.112191399

Pryor, J. L., Kent-First, M., Muallem, A., Van Bergen, A. H., Nolten, W. E., Meisner, L., & Roberts, K. P. (1997). Microdeletions in the Y chromosome of infertile men. *New England Journal of Medicine*, *336*, 534-539. doi:10.1056/NEJM199702203360802

Ring, H. Z., Lessov, C. N., Reed, T., Marcus, R., Holloway, L., Swan, G. E., & Carmelli, D. (2005). Heritability of plasma sex hormones and hormone binding globulin in adult male twins. *Journal of Clinical Endocrinology & Metabolism*, *90*, 3653-3658. doi:10.1210/jc.2004-1025

Rodriguez, J. J., Al Dashti, R., & Schwarz, E. R. (2005). Linking erectile dysfunction and coronary artery disease. *International Journal of Impotence Research*, *17*(Suppl. 1), S12-S18. doi:10.1038/sj.ijir.3901424

Rubin, M. A., Maher, C. A., & Chinnaiyan, A. M. (2011). Common gene rearrangements in prostate cancer. *Journal of Clinical Oncology*, *29*, 3659-3668. doi:10.1200/JCO.2011.35.1916

Schmitz-Dräger, B. J., Schöffski, O., Marberger, M., Sahin, S., & Schmid, H.-P. (2014). Risk adapted chemoprevention for prostate cancer: An option? *Recent Results in Cancer Research*, *202*, 79-91. doi:10.1007/978-3-642-45195-9_10

Schröder, F. H., Hugosson, J., Roobol, M. J., Tammela, T. L. J., Ciatto, S., Nelen, V., . . . Auvinen, A. (2012). Prostate-cancer mortality at 11 years of follow-up. *New England Journal of Medicine*, *366*, 981-990. doi:10.1056/NEJMoa1113135

Sekine, A., Tanabe, N., Sugiura, T., Shigeta, A., Jujo, T., Nishimura, R., . . . Tatsumi, K. (2014). Polymorphism of the G protein β3 subunit gene influences the efficacy of sildenafil in patients with pulmonary hypertension. *Internal Medicine*, *53*, 291-297.

Stanworth, R. D., Akhtar, S., Channer, K. S., & Jones, T. H. (2014). The role of androgen receptor CAG repeat polymorphism and other factors which affect the clinical response to testosterone replacement in metabolic syndrome and type 2 diabetes: TIMES2 sub-study. *European Journal of Endocrinology/European Federation of Endocrine Societies*, *170*, 193-200. doi:10.1530/EJE-13-0703

Tirabassi, G., Delli Muti, N., Corona, G., Maggi, M., & Balercia, G. (2014). Androgen receptor gene CAG repeat polymorphism independently influences recovery of male sexual function after testosterone replacement therapy in postsurgical hypogonadotropic hypogonadism. *Journal of Sexual Medicine*, *11*, 1302-1308. doi:10.1111/jsm.12493

Travis, R. C., Schumacher, F., Hirschhorn, J. N., Kraft, P., Allen, N. E., Albanes, D., . . . Hunter, D. J. (2009). 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 Epidemiology, Biomarkers & Prevention*, *18*, 2734-2744. doi:10.1158/1055-9965.EPI-09-0496

Tsao, M.-S., Sakurada, A., Cutz, J.-C., Zhu, C.-Q., Kamel-Reid, S., Squire, J., . . . Shepherd, F. A. (2005). Erlotinib in lung cancer—Molecular and clinical predictors of outcome. *New England Journal of Medicine*, *353*, 133-144. doi:10.1056/NEJMoa050736

Vandenput, L., & Ohlsson, C. (2014). Genome-wide association studies on serum sex steroid levels. *Molecular and Cellular Endocrinology*, *382*, 758-766. doi:10.1016/j.mce.2013.03.009

Vlachopoulos, C., Ioakeimidis, N., & Stefanadis, C. (2015). Biomarkers, erectile dysfunction, and cardiovascular risk prediction: The latest of an evolving concept. *Asian Journal of Andrology*, *17*, 17-20. doi:10.4103/1008-682X.143250