The most ideal approach would be for all patients to see an andrologist and continence specialist before RP or be seen in preoperative 'survivorship' seminars, based on discussing possible consequences and optimising functional recovery after treatment. Such seminars should be run by the teams involved in managing sexual function and continence postoperatively. Patients should be given a simple, one page sheet outlining the possible consequences of their intended treatment, be that radiotherapy or surgery, on sexual function and continence. In the same way that patients are given a key contact for their cancer care, they should have access to a key contact for their functional recovery. In addition to follow-up visits with the operating surgeon, focusing on the oncological outcome, a separate follow-up based on functional outcome with an andrologist and continence specialist would focus on functional recovery.

There has been a drive to develop high-volume cancer centres of excellence, with pooled resources to allow excellence in imaging, pathology, as well as surgical and non-surgical treatments. The most utopian approach would see these centres also having andrology and continence specialists focused on the management of all postoperative functional consequences, including the ability to undertake penile implant and artificial sphincter surgery as required.

The progress in developing such an infrastructure has been slow. Research on optimising functional recovery has not been as extensive as the focus on diagnosis and treatment in prostate cancer, which can dominate many urology journals and meetings. This imbalance needs to be addressed, to provide not only the best treatment for prostate cancer, but also the best management of the consequences of treatment, aimed at improving quality of life after surgery.

Conflict of Interest

None.

Majid Shabbir

Guy's Hospital, London, UK

References

1 **Deveci S, Gotto GT, Alex B, O'Brien K, Mulhall JP.** A survey of patient expectations regarding sexual function following radical prostatectomy. *BJU Int* 2016; 118: 641–5

2 **Schroeck FR, Krupski TL, Sun L et al.** Satisfaction and regret after open retropubic or robot-assisted laparoscopic radical prostatectomy. *Eur Urol* 2008; 54: 785–93

3 **Crawford ED, Bennett CL, Stone NN et al.** Comparison of perspectives on prostate cancer: analyses of survey data. *Urology* 1997; 50: 366–72

HOXB13 mutations and prostate cancer risk

For the first time, Storebjerg et al. [1] describe the prevalence of the *HOXB13* G84E mutation in a Danish population and its association with prostate cancer risk and features indicative of clinically aggressive disease in a cohort of men undergoing radical prostatectomy. In this study, the prostate cancer risk mutation was seen in 0.49% of controls with an ~5-fold increase in risk of prostate cancer among carriers. The homeobox transcription factor gene *HOXB13*, is located on the long arm of chromosome 17 (17q21), and belongs to a superfamily of genes considered critical to animal embryonic development, characterised by a highly-conserved DNA-binding domain. In 2012, our research team described the association of a rare recurrent *HOXB13* mutation, substituting adenine for guanine in the second position of codon 84 resulting in the replacement of glycine by glutamic acid, with prostate cancer and found that the carrier frequency was ~20-times higher among men with early onset disease and multiple affected close relatives compared with men presumed without disease [2]. Since then, numerous studies have confirmed this association with estimates of risk overall varying from ~3 to 9-fold, and generally a greater risk seen among men diagnosed before the age of 60 years and among those with a positive family history of disease among first-degree relatives [3]. The G84E mutation is almost exclusively found in men of Northern European descent with evidence suggesting that it is a relatively recent (circa 1790s) founder mutation in the population, and considered to be of moderate penetrance (estimated lifetime risk among carriers 35–65%) [4]. The same germline mutation has also been preliminarily reported to be associated with cancers of the breast, colon, bladder, and leukaemia, but requires further investigation [5,6].

The findings from this study [1], both for the prevalence of the mutation, as well as its magnitude of association with prostate cancer, are comparable to prior reports in Northern European populations. Furthermore, among the 995 cases, the mutation frequency was significantly

© 2016 The Authors

associated with features predictive of progression after surgery (high PSA level, positive surgical margins, higher pathological Gleason score, and non-organ confined disease) suggesting that genetic evaluation of men with a strong family history would identify a subset of men that would benefit from early screening and intervention in the same manner as are male carriers of known founder mutations in *BRCA2* [7]. The observation between *HOXB13* and clinical features indicative of aggressive disease has been less consistent compared with studies of risk overall and the exact mechanism whereby the gene contributes to malignant progression in the prostate is not well-understood. There is some suggestion that the gene may operate both as a tumour suppressor, as early studies reported its suppression of androgen receptor activity, and as an oncogene as *HOXB13* overexpression has been seen in androgen-independent tumours [8].

Currently, most countries (including the USA) do not recommend use of PSA screening for men at average risk for prostate cancer. However, given the significant risk of prostate cancer in men carrying a single copy of the *HOXB13* G84E allele, should these male mutation carriers be screened for prostate cancer with PSA testing and DRE? If so, how do we identify these men and at what age should testing commence? Unfortunately, many G84E carriers may not be identified by family history, which raises the question about when is the risk of disease significant enough to warrant population level testing? As Nordic countries, including Denmark, have a higher frequency of *HOXB13* G84E allele in the general population, research directed toward understanding the benefit of genetic testing followed by prostate cancer early detection strategies should be considered.

Conflicts of Interest

Dr Cooney reports no conflicts of interest. However, Dr Cooney has a patent application relating to *HOXB13* that is pending.

Kathleen A. Cooney* **and Jennifer L. Beebe-Dimmer**†

**Departments of Internal Medicine and Urology, The University of Michigan, Comprehensive Cancer Center, Ann Arbor, and †Department of Oncology, Wayne State University School of Medicine, Karmanos Cancer Institute, Detroit, MI, USA*

References

1 **Storebjerg TM, Høyer S, Kirkegaard P et al**. Prevalence of the *HOXB13* G84E mutation in Danish men undergoing radical prostatectomy and its correlations with prostate cancer risk and aggressiveness. *BJU Int* 2016; 118: 646–53

2 **Ewing CM, Ray AM, Lange EM et al**. Germline mutations in HOXB13 and prostate-cancer risk. *N Engl J Med* 2012; 366: 141–9

3 **Beebe-Dimmer JL, Isaacs WB, Zuhlke KA et al**. Prevalence of the *HOXB13* G84E prostate cancer risk allele in men treated with radical prostatectomy. *BJU Int* 2014; 113: 830–5

4 **Chen Z, Greenwood C, Isaacs WB et al**. The G84E mutation of *HOXB13* is associated with increased risk for prostate cancer: results from the reduce trial. *Carcinogenesis* 2013; 34: 1260–4

5 **Alanee S, Couch F, Offit K**. Association of a *HOXB13* variant with breast cancer. *N Engl J Med* 2012; 367: 480–1

6 **Beebe-Dimmer JL, Hathcock M, Yee C et al**. The *HOXB13* G84E mutation is associated with an increased risk for prostate cancer and other malignancies. *Cancer Epidemiol Biomarkers Prev* 2015; 24: 1366–72

7 **National Comprehensive Cancer Network (NCCN), NCCN Clinical Practice Guidelines in Oncology.** Genetic/Familial High-risk Assessment: Breast and Ovarian (Version 2.2015). Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 12-27-2015

8 **Shah N, Sukumar S**. The Hox genes and their roles in oncogenesis. *Nat Rev Cancer* 2010; 10: 361–71

© 2016 The Authors