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Authors

Gaylis, Franklin
Bree, Kelly K
Dato, Paul
et al.

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Low Penetrance Germline Genetic Testing: Role for Risk Stratification in Prostate Cancer Screening and Examples From Clinical Practice

Franklin Gaylis, MBBCh,[1–3] Kelly K. Bree, MD,[4] Paul Dato, MD,[2] Gerald L. Andriole, MD,[3,5] Christopher J. Kane, MD,[3,6] A. Karim Kader, MD, PhD[1,3]

[1]Department of Urology, University of California, San Diego, San Diego, CA; [2]Genesis Healthcare Partners, San Diego, CA; [3]Stratify Genomics, San Diego, CA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX; [5]Mary Culver Department of Surgery, Washington University School of Medicine, St. Louis, MO; [6]UC San Diego Health Physicians, San Diego, CA

Broad-based prostate-specific antigen (PSA) screening has saved lives but at a substantial human and financial cost. One way of mitigating this harm, while maintaining and possibly improving the benefit, is by focusing screening efforts on men at higher risk. With age, race, and family history as the only risk factors, many men lack any reliable data to inform their prostate cancer (PCa) screening decisions. Complexities including history of previous negative biopsies, interpretation of negative and/or equivocal mpMRI findings, and patient comorbidities further compound the already complicated decisions surrounding PCa screening and early detection. The authors present cases that provide real-world examples of how a single nucleotide polymorphism–based test can provide patients and providers with personalized PCa risk assessments and allow for development of improved risk-stratified screening regimens.

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KEY WORDS

Prostate cancer screening • Somatic DNA test • Germline DNA tests • Single nucleotide polymorphism DNA test • Risk stratification

Prostate cancer (PCa) is the most common solid organ malignancy affecting American men and the second leading cause of cancer-related mortality. In 2020, 192,000 new diagnoses of PCa and over 33,000 deaths from the disease are expected in the United States.[1] PCa screening and early detection is the subject of much debate. This stems from the acknowledged life-saving benefit in a few, contrasted by the harm in the many who struggle with a falsely elevated prostate-specific antigen (PSA) or the over-diagnosis and over-treatment of indolent disease. Therefore, the US Preventive Services Task Force recommended against screening in 2012. Subsequently, we have observed a substantial upward grade and stage migration and, more recently, a halt in the longstanding decline in PCa mortality for the first time since PSA screening was introduced 30 years ago.[1–3] These observations have led to a more critical approach to PCa screening and early detection, with many promoting a risk-adapted approach to identifying who should be screened, when to start, how often to screen, when to biopsy, and when to stop screening.[4–6] Given challenges with established risk factors (age, race, and family history [FH]), there has been an attempt to improve pre-screening risk stratification.

Thanks to breakthroughs in our understanding of the human genome, several classes of genetic tests have emerged to assist in screening and early detection of PCa. To understand the proper use and interpretation of these tests, a basic understanding of genetics is required (Figure 1). Somatic DNA tests such as Decipher (Decipher Biosciences, San Diego, CA) and Prolaris (Myriad Genetics, Salt Lake City, UT) look at the non-heritable genetic changes affecting gene expression and require tumor tissue to evaluate. Germline DNA tests examine heritable genetic changes to an individual's baseline DNA, so any tissue can be tested, and the result is the same at birth as it would be at death. There are two types of germline tests. Mutations are, by definition, rare genetic changes (occurring in less than 3% of the general population), inherited from a parent, that often lead to altered gene function or expression such as with BRCA1/2 testing (Myrisk [Myriad Genetics]; 23andMe Test [23andMe, Sunnyvale, CA]) resulting in a high risk of disease (high penetrant) if positive and no effect on risk if negative. The other type of germline test is the single nucleotide polymorphism (SNP)–based test. SNPs are single base pair DNA changes that distinguish individuals. There are over 300 million SNPs throughout the genome and, since 2007, dozens have been associated with PCa risk.[7] The effect of a single SNP is small (low penetrant). However, when numerous SNPs are

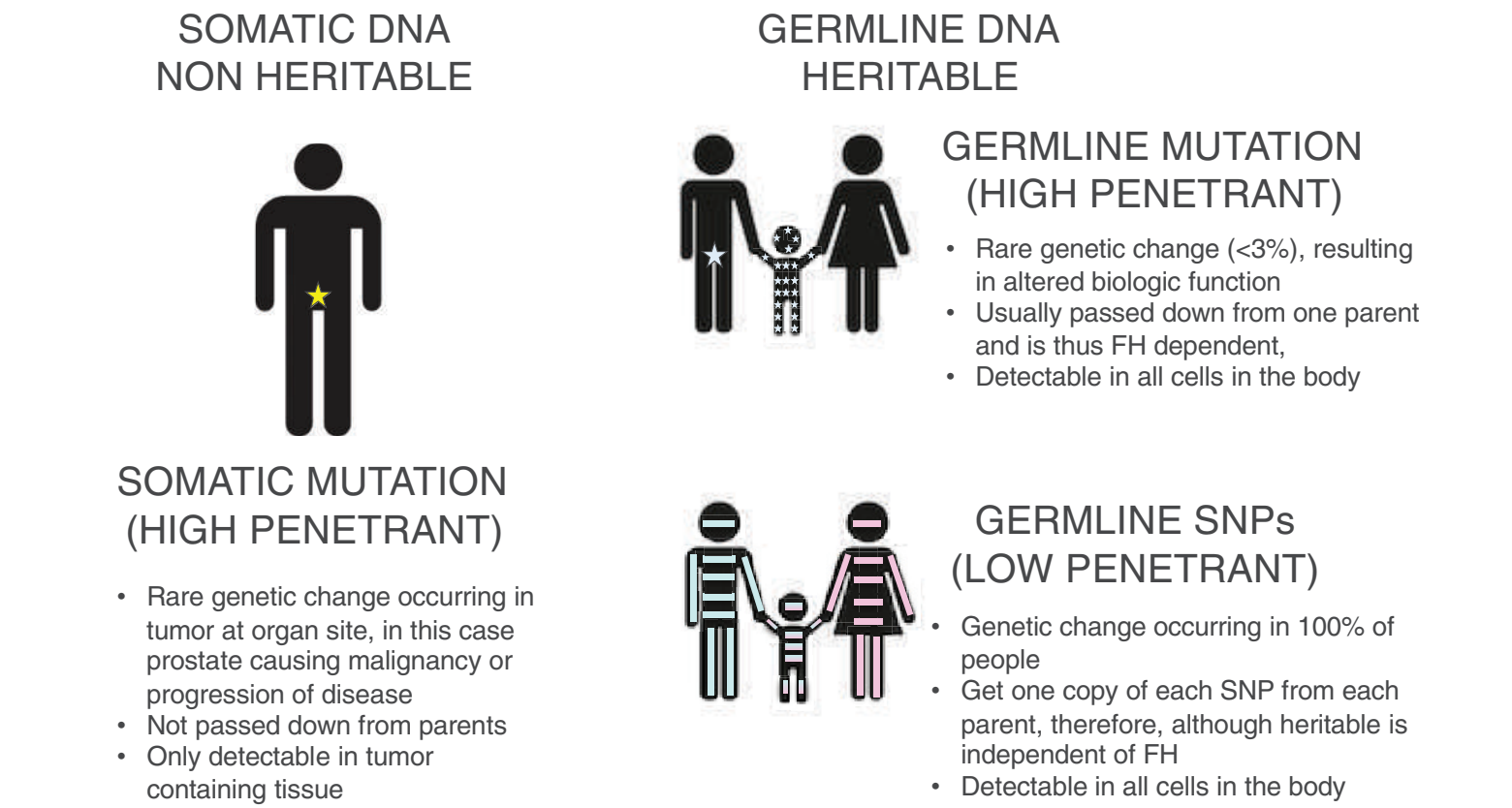

Figure 1. Classes of genetic tests currently being used for prostate cancer screening and early detection. FH, family history; SNP, single nucleotide polymorphism.

combined, a genetic score can be generated that results in improved risk prediction. Although SNPs are inherited, an individual receives one copy from each parent. Because there are dozens of SNPs analyzed, the chance that siblings or parents would have the same genetic score is almost impossible. Therefore, unlike germline mutation tests, SNP-based tests are independent of and complimentary to FH and provide actionable information on 100% of the population instead of 3%.

Prompt Prostate Genetic Score™ (PGS; Stratify Genomics, San Diego, CA) is a SNP-based test that provides an objective assessment of a man's lifetime risk of developing PCa. It is a simple buccal swab test that can be performed in a clinic or at home. SNPs included in this novel test are genotyped using next generation sequencing on the Illumina platform (Illumina Inc, San Diego, CA). A genetic score is calculated for each patient based on his genotype at the PCa-associated SNPs (which are weighted by odds ratio [OR] based on an external meta-analysis of each SNP). A Prompt PGS score of 1.0 indicates an average lifetime risk in the general population, whereas a score of <0.6 indicates below average risk and a score >1.3 indicates above average PCa risk (Figure 2).

Prompt PGS was initially developed in a cohort of 1654 men from the placebo arm of the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial. In this unique study, Prompt PGS outperformed all other biomarkers of PCa risk, including PSA and FH, and had a negative predictive value (NPV) of 97% for high-grade PCa (Gleason score ≥7).[8] It has subsequently been validated in more than 100,000 men from some of the most important PCa trials of our generation, including PCPT (Prostate Cancer Prevention Trial) and PLCO (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) studies.[9,10]

Case Reports

The following case reports provide examples of the early clinical experience and potential value of Prompt PGS testing.

Case 1: Brothers With Family History of PCa, Personalized Screening Using Prompt PGS

Targeted PCa screening based on FH is a well-established approach that has been endorsed by many current guidelines. Unfortunately, FH is subject to recall bias and changes with time as the number and age of male family members changes, which limits its performance. Furthermore, just because a man has an affected family member does not necessarily make him high risk. Prompt PGS is a stable objective measure of a man's lifetime risk of PCa that is independent of FH and can thus help to develop a personalized screening approach in all men including those with a FH.

Figure 3 depicts the PSA and biopsy results of two brothers with a weak FH of PCa (paternal uncle). Their father died at age 54 years of cardiac disease. Although FH in a second-degree relative does not substantially increase risk, the patients' father may not have lived long enough to be diagnosed with PCa. Brother A began screening at age 50 years with a PSA of 1.2 ng/mL and a normal digital rectal examination (DRE). Over the next 4 years, his PSA progressively increased. The patient underwent a prostate biopsy when his PSA increased to 3.3 ng/mL and subtle changes were noted on DRE. His biopsy demonstrated Gleason 3+3 PCa in 5/15 cores. A radical prostatectomy was performed revealing

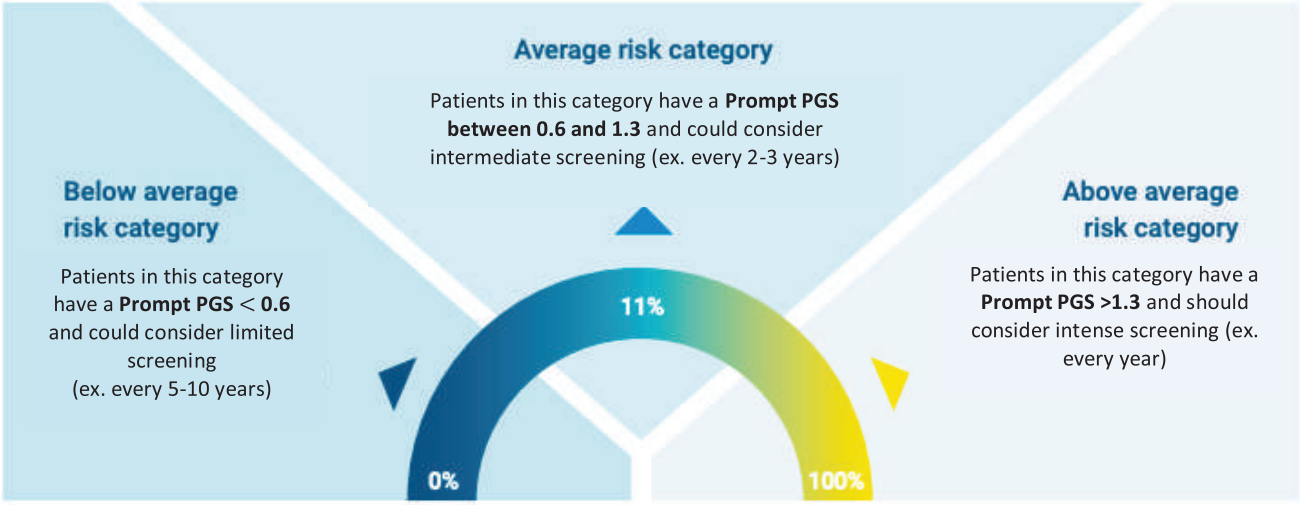

Figure 2. Prompt Prostate Genetic Score™ (PGS; Stratify Genomics, San Diego, CA) risk categories.

Gleason 3+3, organ-confined disease with negative margins. Ten years later, the patient continues to have undetectable PSA and good urinary and sexual function.

Brother A became aware of Prompt PGS and, despite already having PCa, underwent testing. His result was markedly elevated at 2.26 (upper limit of average risk, 1.3). In retrospect, had this genetic information been available during the screening phase, it is likely that the patient would have undergone a biopsy earlier when his PSA kinetics demonstrated a steadily rising PSA.

The younger brother, Brother B, began PCa screening at age 50 years with an initial PSA of 7.2 ng/mL and normal DRE. At age 52, he underwent a prostate biopsy that was negative for cancer. His PSA increased to 8.6 ng/mL. This, together with his brother's recent diagnosis of PCa, prompted a repeat biopsy at age 54 years that again was negative for malignancy. Over the past 10 years, his PSA levels have continued to fluctuate. In 2019, the patient underwent Prompt PGS testing based on his older brother's recommendation. His Prompt PGS score was 0.38, demonstrating below average risk of PCa (lower limit of average risk, 0.6). Based on his below average risk, which has an NPV of 97%, of developing clinically significant PCa (Gleason Score ≥7), he elected not to pursue any further biopsies and has moderated the intensity of PSA-based screening with testing every 5 to 7 years.

Case 2: Family History of PCa With Normal PSA Level, Elevated Prompt PGS, Biopsy Demonstrating PCa

Despite early onset of screening, there is no clear PSA threshold with which men can be reassured they are cancer free. In the placebo arm of the large randomized PCPT, 15% of men with PSA values of lower than 4.0 ng/mL harbored PCa, reiterating that there is no PSA cut point at which men can safely forego screening without risk.[11]

A 60-year-old man with a FH of PCa (father diagnosed in his 90s, and father's identical twin brother, who has identical genetic risk, diagnosed in his 60s) began intermittent PCa screening at age 45 years with a PSA of 3.5 ng/mL. Approximately 10 years later, the patient's PSA remained stable (3.8 ng/mL) with a normal DRE. After a PSA screening hiatus of 5 years, in 2018 the patient elected to undergo a Prompt PGS test that revealed a markedly elevated score of 3.6. Based on this result, a repeat PSA was ordered and found to be increased (5.5 ng/mL). A multi-parametric-MRI (mpMRI) was performed demonstrating a Prostate Imaging Reporting & Data System (PI-RADS) 4 lesion. DRE revealed a cT2a nodule and biopsy confirmed the presence of clinically significant PCa (Gleason 3+4). The patient underwent a radical prostatectomy (pT3a with negative margins) with a good functional outcome and an undetectable PSA.

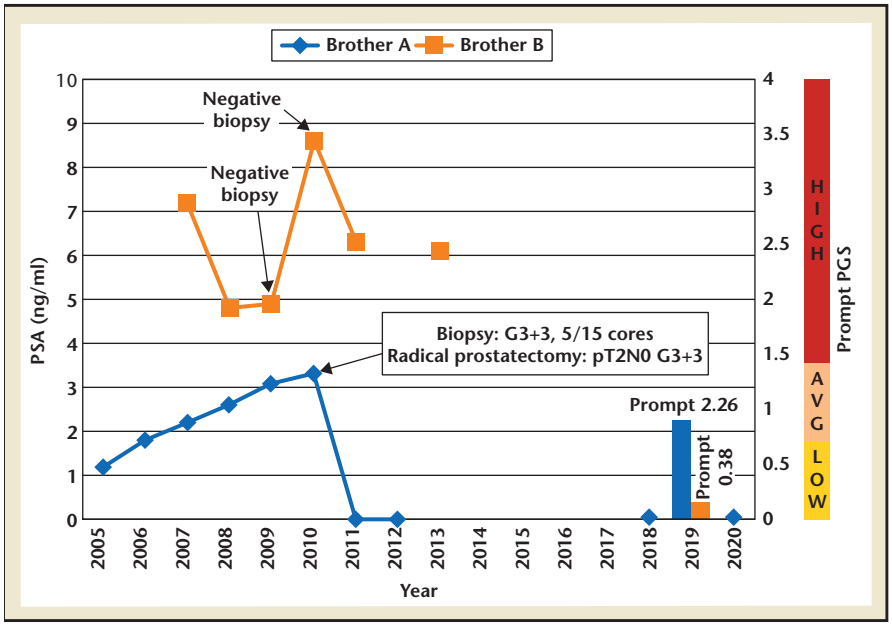

Figure 3. Prostate cancer (PCa) screening in two brothers with family history of PCa.

Case 3: Elevated PSA, Negative mpMRI, High-volume Clinically Significant PCa on Biopsy

The introduction of mpMRI has improved the detection of clinically significant prostate cancer and helped to reduce the over-diagnosis of indolent disease. Despite this improvement, there is a subset of patients in whom mpMRI fails to identify high-risk disease. A recent meta-analysis of 526 patients demonstrated a pooled sensitivity of 74% for PCa detection—a false-negative rate of 26%—highlighting the importance of continued evaluation of men with clinical concern for PCa.[12]

Figure 4 displays the PSA values in a 63-year-old man with no FH of PCa who presented with a first PSA of 11.2 ng/mL and prostatitis symptoms. Repeat PSA following a course of antibiotics dropped substantially to 7.2 ng/mL less than 1 month later. He was hesitant to undergo prostate biopsy and ancillary testing was ordered. Prompt PGS was markedly elevated at 2.52, however, mpMRI was negative for

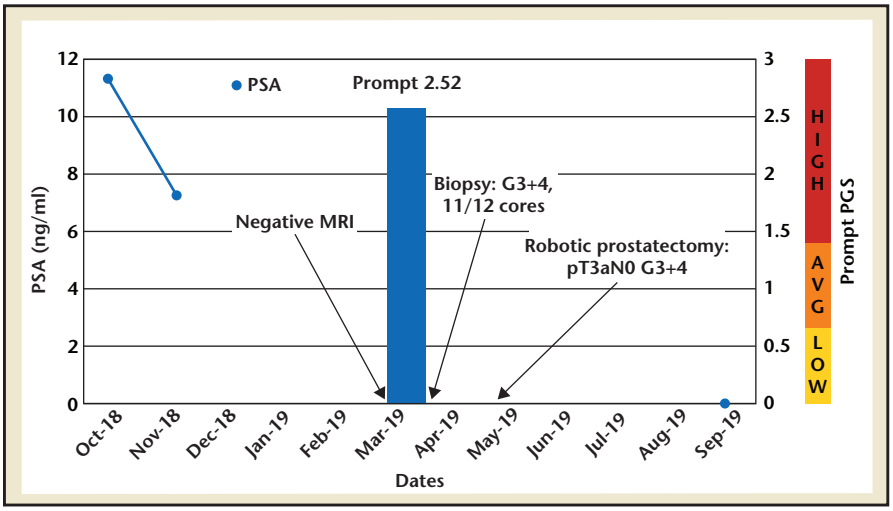

Figure 4. Prostate-specific antigen (PSA) values in a 63-year-old man with no family history of prostate cancer who presented with a first PSA of 11.2 ng/mL and prostatitis symptoms.

any lesions. Based upon the elevated Prompt PGS score the patient agreed to a prostate biopsy that demonstrated high-volume Gleason 3+4 prostate cancer with perineural invasion (11/12 cores positive for malignancy). The patient subsequently underwent robotic prostatectomy for pT3aN0R0 G3+4 PCa. His PSA remains undetectable.

Many men are fearful of prostate biopsy and although mpMRI has proven helpful in detecting high-grade malignancy, it is not without false-negative results and care should be taken in reassuring men they can forego further testing based on this test alone. Prompt PGS provides a helpful adjunct test to provide personalized risk assessment that can then be used in conjunction with mpMRI.

Case 4: Large Prostate With Urinary Retention, Elevated PSA, and Equivocal MRI

Elevated PSA in a man with significant prostatic enlargement and lower urinary tract symptoms (LUTS) with or without urinary retention poses a significant dilemma to both the patient and provider. Prior studies have demonstrated that 28% of men with histologically proven BPH have a PSA level above 4.0 ng/mL.[13] It is also well established that there is a strong correlation between PSA levels and prostate volume, however, an elevated PSA in a patient with prostatomegaly does not exclude the possibility of concomitant PCa as the two can coexist. PSA density and velocity can assist in determining risk, as can imaging such as mpMRI—but all such tests are not without flaws. When mpMRI is obtained, up to one third of men will be diagnosed with indeterminate lesions, assigned as PI-RADS 3. Current data suggests that up to 21% of men with PI-RADS 3 lesions harbor clinically significant PCa. Although considerably less than PI-RADS 4 and PI-RADS 5 lesions, this further complicates clinical decision making and again emphasizes the need for improved personalized markers of PCa risk.[14]

A 69-year-old man presented to clinic with an elevated PSA and urinary retention. He had a longstanding history of elevated PSA levels for which he had previously undergone negative biopsy in 2014. He presented to clinic with a Foley catheter in place and a PSA of 18.4 ng/mL (increased from 11 ng/mL 6 years prior). His DRE was notable for a large prostate but no nodules. Prostate mpMRI was performed demonstrating a PIRADS 3 lesion in the right transition zone, a 295-cc gland, and a few conspicuous and enlarged perivesical lymph nodes. Prompt PGS was 0.44, indicating below-average risk of PCa. Based on this low Prompt PGS score, the patient's urologist offered, and the patient elected to undergo simple prostatectomy rather than repeat biopsy and/or radical prostatectomy. Pathology from the simple prostatectomy specimen demonstrated BPH, the previously noted enlarged perivesical nodes were negative for malignancy.

Case 5: Elevated PSA, Multiple Prior Negative Biopsies in Patient Awaiting Renal Transplant

Given the increased risk of malignancy amongst transplant recipients, patients are routinely screened for occult malignancies prior to transplantation. PCa screening in the general population is controversial, and there is even further debate in the transplant community about how best to evaluate men awaiting transplantation for PCa. In many institutions, PSA-based screening has been used, however, recent data suggest that PSA screening significantly delays time to listing and transplantation without any improvement in survival.[15] Utilization of other markers of malignancy risk would be helpful in assessing which patients truly require delay in transplantation with biopsy and possible treatment.

Figure 5 shows the PSA and PCa screening history of a 69-year-old man with end-stage renal disease awaiting renal transplantation who presented with elevated PSA. The patient had a longstanding history of elevated PSA levels with three prior negative biopsies, however,

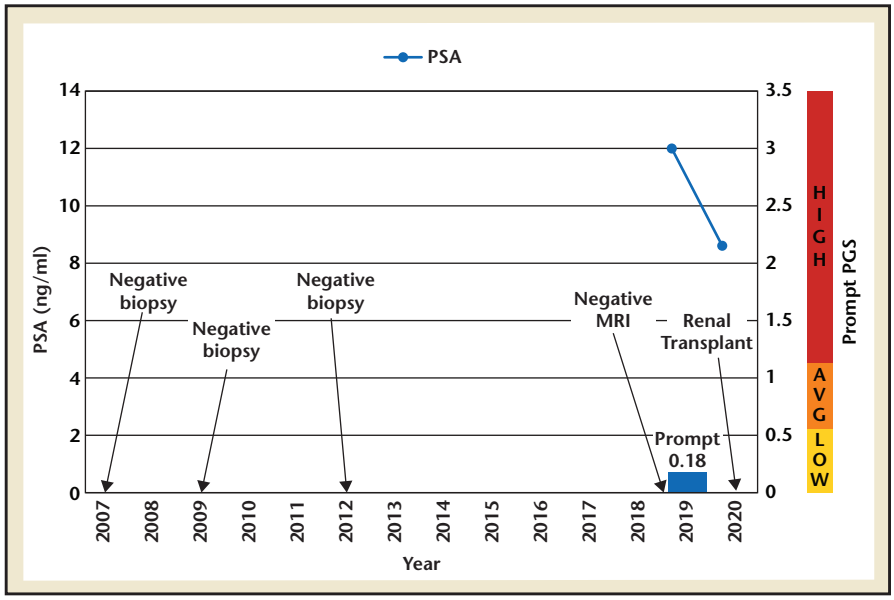

Figure 5. Prostate-specific antigen (PSA) and prostate-cancer screening history of a 69-year-old man with end-stage renal disease awaiting renal transplantation who presented with elevated PSA.

given a recent PSA of 11.8 ng/mL, he was referred to urology by his transplant team for potential biopsy. Prostate mpMRI was obtained that was unremarkable, however, the transplant team continued to have reservations about proceeding with renal transplantation. Prompt PGS testing was then performed demonstrating a value of 0.18, indicating below-average risk of PCa. Based upon this germline genetic testing, the transplant team was reassured that the patient was unlikely to harbor clinically significant PCa and agreed to proceed with transplantation without a fourth biopsy.

Discussion

Broad-based PSA screening has saved lives but at a substantial human and financial cost. One way of mitigating this harm, while maintaining and possibly improving the benefit, is by focusing screening efforts on men at higher risk. This strategy was investigated in a large screening study that demonstrated the benefit of screening men at higher risk based on FH.[16,17] PCa is thought to be the most hereditary cancer,[18] with both the number of relatives and the age at diagnosis impacting the relative risk (RR) of a man developing PCa.[19,20] Unfortunately, FH has many limitations. Furthermore, it is only meaningful if positive, as a lack of a positive FH is not protective. Therefore, with age, race, and FH as the only risk factors, many men lack any reliable data to inform their PCa screening decisions.

As highlighted in the cases described, complexities including history of previous negative biopsies, interpretation of negative and/or equivocal mpMRI findings, and patient comorbidities further compound the already complicated decisions surrounding PCa screening and early detection. These cases provide real-world examples of how Prompt PGS can provide patients and providers with personalized

MAIN POINTS

- Broad-based prostate-specific antigen screening has saved lives but at a substantial human and financial cost. One way of mitigating this harm, while maintaining and possibly improving the benefit, is by focusing screening efforts on men at higher risk.
- With age, race, and family history as the only risk factors, many men lack any reliable data to inform their PCa screening decisions.
- Complexities including history of previous negative biopsies, interpretation of negative and/or equivocal mpMRI findings, and patient comorbidities further compound the already complicated decisions surrounding PCa screening and early detection.
- Prompt Prostate Genetic Score™ (PGS; Stratify Genomics, San Diego, CA) is a SNP-based test that provides an objective assessment of a man's lifetime risk of developing PCa. It is a simple buccal swab test that can be performed in a clinic or at home.
- Prompt PGS has been validated for use in White, Japanese, and Hispanic men with studies underway for validation in Black men.

PCa risk assessments and allow for development of improved risk stratified screening regimens. Additionally, with the ongoing coronavirus disease 2019 (COVID-19) pandemic and its resultant impact on cancer screening, Prompt PGS provides an opportunity for patients to be tested in their homes and confer by telemedicine with their physicians as to the intensity of PCa screening that may be necessary.

Prompt PGS is currently available (promptpgs.com) and has been validated for use in White, Japanese, and Hispanic men with studies underway for validation in Black men. ■

Drs. Franklin Gaylis, Christopher Kane, and Gerald Andriole are Stockholders in and Scientific Advisory Board Members at Stratify Genomics. Drs. Kelly Bree and Paul Dato are Stockholders in Stratify Genomics. Dr. A Karim Kader is a Founder, Stockholder, Board Member of Stratify Genomics and Patent Holder for SNP-based Prostate Cancer Risk Stratification.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7–30.
2. Moyer VA; US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157:120–134.
3. Gaylis FD, Choi JE, Hamilton Z, et al. Change in prostate cancer presentation coinciding with USPSTF screening recommendations at a community-based urology practice. *Urol Oncol*. 2017;35:663.e1–663.e7.
4. Carroll PR, Parsons KJ, Andriole G, et al. Prostate cancer early detection, version 2.2016: Featured updates to the NCCN guidelines. *J Natl Compr Canc Netw*. 2016;14:509–519.
5. Brawley O, Gansler T. Introducing the 2010 American Cancer Society Prostate Cancer Screening Guideline. Ca *Cancer J Clin*. 2010;60:68–69.
6. Carter BH, Albertsen PC, Barry MJ, et al. Early Detection of Prostate Cancer: AUA Guideline. *J Urol*. 2013;190:419–426.
7. Goh C, Schumacher F, Easton D, et al. Genetic variants associated with predisposition to prostate cancer and potential clinical implications. *J Intern Med*. 2012;271:353–365.
8. Kader AK, Sun J, Reck BH, et al. Potential impact of adding genetic markers to clinical parameters in predicting prostate biopsy outcomes in men following an initial negative biopsy: findings from the REDUCE trial. *Eur Urol*. 2012;62:953–961.
9. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate cancer screening trial. *N Engl J Med*. 2009;360:1310–1319.
10. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349:215–224.
11. Thompson IM, Ankerst DP, Chi C, et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/mL or lower. *JAMA*. 2005;294:66–70.
12. deRooij M, Hamoen EHJ, Futterer JJ, et al. Accuracy of multiparametric MRI for prostate cancer detection: a meta-analysis. *AJR Am J Roentgenol*. 2014;202:343–351.
13. Lepor H. Evaluating men with benign prostatic hyperplasia. *Rev Urol*. 2004;6(suppl 1):S8–S15.
14. Schoots IG. MRI in early prostate cancer detection: how to manage indeterminate or equivocal PI-RADS 3 lesions? *Transl Androl Urol*. 2018;7:70–82.
15. Vitiello GA, Sayed BA, Wardenburg M, et al. Utility of prostate cancer screening in kidney transplant candidates. *J Am Soc Nephrol*. 2016;27:2157–2163.
16. Chen H, Liu X, Brendler CB. Adding genetic risk score to family history identifies twice as many high-risk men for prostate cancer: results from the prostate cancer prevention trial. *Prostate* 2016;76:1120–1129.
17. Liss MA, Xu J, Chen H, Kader AK. Prostate Genetic Score (PGS-33) is independently associated with risk of prostate cancer in the PLCO trial. *Prostate*. 2015;75:1322–1328.
18. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA*. 2016;315:68–76.
19. Powell IJ. The precise role of ethnicity and family history on aggressive prostate cancer: a review analysis. *Arch Esp Urol*. 2011;64:711–719.
20. Meikle AW, Smith JA Jr. Epidemiology of prostate cancer. *Urol Clin North Am*. 1990;17:709–718.