Research Communication

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The diagnostic impact of UK regional variations in age-specific prostate-specific antigen guidelines

The ideal prostate cancer diagnostic pathway would maximize detection of clinically significant prostate cancer (csPCa) while avoiding unnecessary biopsies and other investigations. The introduction of pre-biopsy MRI has done much to aid this goal. However, referrals into the image-based diagnostic pathway still depend on PSA testing performed in primary care and interpreted using referral guidelines. In the UK, the National Institute for Health and Care Excellence (NICE) only provides guidance on PSA thresholds for men aged 50–69 years (PSA ≥3.0 ng/mL) [1]. For other age groups, PSA thresholds are set by regional cancer networks without any unified consensus. In the present study, we explored if different regional guidelines impacted csPCa detection in modern image-based pathways.

We assembled a large English cohort of men investigated between 2013 and 2020 using image-based diagnostics from three geographically separate tertiary units. Through correspondence we obtained current PSA referral guidelines from 16 cancer networks in England and Wales. These represented 10 discrete referral models, ranging from a single PSA threshold to five-strata age-reference models. We applied these models to our cohort to evaluate detection of Grade Group 2 disease or higher (≥GG2). We calculated rates of men avoiding referral, rates of missed diagnoses, and negative predictive value (NPV). Men not meeting referral criteria were assumed to have avoided further investigation. Analyses were performed for the whole cohort and then stratified by age ranges: <50 years; 50–59 years; 60–69 years; 70–79 years; and ≥80 years.

A total of 2760 men were included, with a median age of 67 years and a median referral PSA level of 7.47 ng/mL. ≥GG2 cancers were detected in 38.7% of men, and no cancer in 38.8%. Table 1 shows the referral criteria for the 10 models, plus our overall and age-stratified results. The 10 models varied considerably in avoided referrals when applied to this cohort (6.5–14.6%). There was also considerable variation in missed ≥GG2 diagnoses (2.6–11.5%) and NPV (69.4–84.4%). On stratifying by age range, all models performed better in younger men (≤59 years). For the age range 50–59 years, this was attributable to all models using the NICE-recommended PSA threshold of ≥3.0 ng/mL, or >3.0 ng/mL. The rate of missed diagnoses in this age range was 0–0.9%, and the NPV was 97.5–100%. For the age range 60–69 years, the 10 models performed reasonably well, with low rates of missed diagnoses (2.5–4.8%), and high NPV (82.2–85.1%). The greatest discrepancies were observed in older men, reflecting greater heterogeneity in guidelines. For the age range 70–79 years, rates of avoided referrals were as high as 21.6% (range 6.1–21.6%), with rates of missed diagnoses as high as 14.2% (range 3.1–14.2%). NPV in this group was modest and variable (60.8–71.4%). For the age group ≥80 years, there was even greater variation in avoided referrals (4.7–71.9%), missed diagnoses (2.3–68.2%) and NPV (34.8–75.0%).

These results suggest that different PSA age-reference thresholds in current use may produce large geographical variations in referral rates, missed diagnoses and NPV across England and Wales. This is particularly evident in older men where there is a conspicuous lack of national guidance. The main limitation of this study is the use of a cohort comprising men already referred to tertiary care, rather than an unfiltered primary care cohort. Furthermore, these men would have been subject to local PSA referral thresholds themselves, although we have tried to mitigate this by combining data from three regions. Nevertheless, these results do suggest a geographical difference in how men are assessed. Crucially, where an individual lives may determine whether they are referred and investigated. It is certainly interesting to speculate how a lack of central age-referenced PSA guidance could offset the diagnostic advantages of pre-biopsy MRI. Specifically, the notion that MRI enhances csPCa detection rates, balanced against the notion that geographically different PSA models may reduce the number of men referred for an MRI in the first place.

Current PSA age-reference ranges are based on historical, cross-sectional measurements with limited implications for modern diagnostics [2]. An analysis of men in the UK aged 50–69 years from the ProtecT trial identified that a single PSA ≥3.0 ng/mL threshold (current NICE guidance) missed 0.1% of high-risk disease [3]. NICE guidance at the time of their article writing (age 50–59 years: PSA ≥3.0 ng/mL; age 60–70 years: PSA ≥4.0 ng/mL; age ≥70 years: PSA ≥5.0 ng/mL), and age-specific ranges from the Krimpen study resulted in fewer biopsies, but unacceptable rates of missed high-risk disease [4]. Notably, these men were investigated prior to 2009 using transrectal biopsy without pre-biopsy MRI. This study aside, there is little novel research in this area. Further work incorporating modern MRI-based diagnostic pathways would be timely for informing contemporary PSA age-reference ranges.

The optimal balance between maximizing diagnoses and minimizing referrals is most unclear in older men, where

Table 1 Comparative model performance for all ages and further stratified by age range.

Model	Referral criteria	Age range, years	Avoids referral, %	Missed ≥GG2 cancer, %	NPV for ≥GG2 cancer, %
1	Age <50 years: PSA >3.0 ng/mL	All	9.5	4.6	81.4
	Age 50–59 years: PSA >3.0 ng/mL	<50	23.2	0.0	100.0
	Age 60–69 years: PSA >4.0 ng/mL	50–59	8.5	0.9	97.5
	Age ≥70 years: PSA >5.0 ng/mL	60–69	8.7	4.8	82.4
		70–79	10.5	5.5	71.4
		≥80	6.3	2.3	75.0
2	Age 50–59 years: PSA >3.0 ng/mL	All	11.1	5.5	80.4
	Age 60–69 years: PSA >4.0 ng/mL	<50	100.0	100.0	82.1
	Age ≥70 years: PSA >5.0 ng/mL	50–59	8.5	0.9	97.5
		60–69	8.7	4.8	82.4
		70–79	10.5	5.5	71.4
		≥80	6.3	2.3	75.0
3	Age 40–49: PSA ≥2.5 ng/mL	All	7.8	3.7	81.2
	Age 50–69 years: PSA ≥3.0 ng/mL	<50	12.5	0.0	100.0
	Age ≥70 years: PSA ≥5.0 ng/mL	50–59	8.5	0.9	97.5
		60–69	5.3	2.5	84.8
		70–79	10.4	5.5	71.1
		≥80	6.3	2.3	75.0
4	Age 40–49 years: PSA ≥2.5 ng/mL	All	9.9	7.8	81.3
	Age 50–69 years: PSA ≥3.0 ng/mL	<50	12.5	0.0	100.0
	Age 70–79 years: PSA ≥5.0 ng/mL	50–59	8.5	0.9	97.5
		60–69	5.3	2.5	84.8
		70–79	10.4	5.5	71.1
		≥80	10.4	100.0	31.3
5	Age 50–69 years: PSA ≥3.0 ng/mL	All	9.5	4.7	80.7
	Age ≥70 years: PSA ≥5.0 ng/mL	<50	100.0	100.0	82.1
		50–59	8.5	0.9	97.5
		60–69	5.4	2.5	84.8
		70–79	10.4	5.5	71.1
		≥80	6.3	2.3	75.0
6	Age <50 years: PSA >2.5 ng/mL	All	8.4	4.8	77.9
	Age 50–69 years: PSA >3.0 ng/mL	<50	12.5	0.0	100.0
	Age 70–79 years: PSA >5.0 ng/mL	50–59	8.5	0.9	97.5
	Age ≥80 years: PSA >10.0 ng/mL	60–69	8.5	2.5	85.1
		70–79	10.5	5.5	71.4
		≥80	29.7	27.3	36.8
7	Age 40–49 years: PSA ≥2.5 ng/mL	All	7.5	4.3	77.6
	Age 50–69 years: PSA ≥3.0 ng/mL	<50	12.5	0.0	100.0
	Age 70–75 years: PSA ≥4.0 ng/mL	50–59	8.5	0.9	97.5
	Age 76–79 years: PSA ≥5.0 ng/mL	60–69	8.5	2.5	84.8
	Age ≥80 years: PSA ≥10.0 ng/mL	70–79	7.9	4.5	68.9
		≥80	29.7	27.3	36.8
8	Any age: PSA >3.0 ng/mL	All	6.5	2.6	84.4
		<50	23.2	0.0	100.0
		50–59	8.5	0.9	97.5
		60–69	5.4	2.5	85.1
		70–79	6.1	3.1	71.9
		≥80	4.7	2.3	66.7
9	Age <50 years: PSA ≥2.0 ng/mL	All	13.3	11.3	73.4
	Age 50–59 years: PSA ≥3.0 ng/mL	<50	5.4	0.0	100.0
	Age 60–69 years: PSA ≥4.0 ng/mL	50–59	8.5	0.9	97.5
	Age 70–74 years: PSA ≥5.0 ng/mL	60–69	8.6	4.8	82.2
	Age 75–80 years: PSA ≥7.5 ng/mL	70–79	17.8	12.7	60.8
		≥80	17.8	81.8	28.0
10	Age <50 years: PSA >2.5 ng/mL	All	14.6	11.5	69.4
	Age 50–59 years: PSA >3.0 ng/mL	<50	12.5	0.0	100.0
	Age 60–69 years: PSA >4.0	50–59	8.5	0.9	97.5
	Age 70–79 years: PSA >6.5 ng/mL	60–69	8.7	4.8	82.4
	Age ≥80 years: PSA >20.0 ng/mL	70–79	21.6	14.2	63.7
		≥80	71.9	68.2	34.8

GG, Grade Group; NPV, negative predictive value.

treatment decisions are more complex. To derive benefit from curative treatment, men with localized disease should have ≥10 years life expectancy, and be fit enough for the treatments themselves [5]. Accordingly, high PSA thresholds investigate fewer men and may miss more csPCa, on the probable assumption that these men will be poor candidates

for curative treatment. By extension, it is also unreasonable to subject these men to potentially harmful biopsies. However, older men who do meet these high thresholds are more likely to harbour locally advanced or metastatic disease that could benefit from therapy irrespective of life expectancy or comorbidity [5].

Developing new PSA thresholds will be challenging as this needs to balance the risk of missed cancers versus over-investigation, including unnecessary MRI and biopsies. Higher thresholds miss more csPCa, but investigate fewer men, whilst lower thresholds identify more csPCa through investigating more men. For example, a single ≥3.0 ng/mL threshold in the present study (model 8) led to the fewest men avoiding referral (6.5%), but also the fewest missed diagnoses (2.6%). In contrast, the five-strata model 10 led to the most men avoiding referral (14.6%), but also the most missed diagnoses (11.5%). A further consideration is whether it is time to abandon age-reference PSA models and move to alternative screening tests such as PSA density (PSA corrected for prostate volume), novel biomarkers such as Prostate Health Index (PHI) and 4K, or indeed primary MRI [6–8].

We have demonstrated that the use of different age-reference PSA threshold guidelines across England and Wales may produce geographical variation in referrals and csPCa diagnostics. This argues for a single, national PSA referral model to unify practice until new detection strategies are adopted.

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Disclosure of Interest

None declared.

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Abbreviations: csPCa, clinically significant prostate cancer; GG, Grade Group; NICE, National Institute for Health and Care Excellence; NPV, negative predictive value.