The IMPACT study: Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in men at higher genetic risk and controls

Prostate-Specific Antigen Velocity as a Predictive Biomarker in a Prospective Prostate Cancer Screening Study of Men with Genetic Predisposition

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Background

• BRCA mutation carriers are at a higher risk of Prostate Cancer (PrCa) [1] and BRCA2 carrier status is associated with an aggressive phenotype and worse clinical outcomes [2]. Early diagnosis may be fundamental to improve outcome in BRCA1/2 mutation carriers but the most accurate method for PrCa screening has not yet been established
• The rate of prostate-specific antigen (PSA) change over time has been described as PSA velocity (PSA V) and could assist in differentiating between men with cancer and those with benign disease [3,4]. A PSA V cut-off of 0.75ng/ml/year is a well established strategy with high specificity and reasonable sensitivity [5]
• Results from the European Randomised Study of Screening for Prostate Cancer (ERSPC) however suggest that PSA V is no better than an isolated PSA reading [6]
• Review of PSA V identified that, despite being a promising strategy, there is high co-linearity between PSA and PSA V resulting in no added value of PSA V to solitary PSA readings [7]
• PSA V above 2ng/ml/year the year prior to PrCa diagnosis predicted for a 10 fold increase in prostate cancer specific mortality for men receiving radiotherapy treatment [8]
• The National Comprehensive Cancer Network (NCCN) has provided guidelines that for men with a PSA<4ng/ml a PSA V >0.35ng/ml should raise the suspicion of an underlying PrCa and biopsy is indicated [9]

Objectives

•To retrospectively:
• Assess whether PSA V can identify PrCa in men with higher genetic risk
• Determine if PSA V can predict aggressive versus low-risk PrCa
• Assess PSA V as a predictive biomarker in men with genetic predisposition to PrCa (BRCA1 or BRCA2 mutation carriers)

Methods

IMPACT study design (Figure 1)
• Prospective, international, multi-centre study [10]
• Inclusion criteria:
• Men 40-69 years old
• Tested positive (carriers) or negative (controls) for a familial BRCA1/2 mutation
• Target population: 500 BRCA1, 500 BRCA2, 500 BRCA1 controls, 350 BRCA2 controls

PSA V calculation:
• Linear Regression [11] (PSA V= (slope*years) + intercept) of men with ≥3 PSA readings over more than 18 months

Statistical Analysis:
IBM SPSS statistical software version 22 was utilised
Fisher's Exact Tests, t-tests, ROC curves and AUC calculations were performed, as well as sensitivity/specificity/NPV/PPV determination

Figure 1: IMPACT Study algorithm

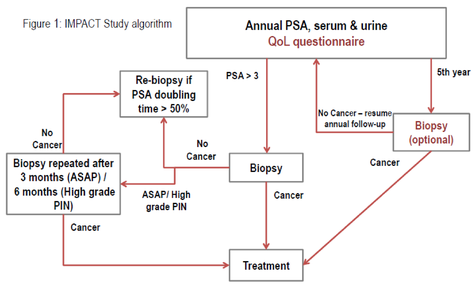

Table 1: Genetic status of men who underwent a prostatic biopsy within the IMPACT study

Genetic Status	Number
BRCA2 carriers (mutation positive)	65
BRCA1 carriers (mutation positive)	55
Controls (negative predictive test for familial *BRCA1/2* mutation)	54

Results

• PSA V data were available in 1654 men, with 174 diagnostic prostate biopsies performed
• 49 PrCas were diagnosed
• The mean age of PrCa diagnosis was 62.5 years with a median age of 63 years
• We analysed PSA V in men diagnosed with PrCa compared with those with a benign biopsy

Table 2: Indication and results of the 174 biopsies performed

Biopsy Indication	Result	n	%
PSA >3ng/ml	Benign	66	57.8
	Cancer	38	33.3
	HG PIN/ASAP	10	8.8
Clinical indication (PSA ≤ 3ng/ml)	Benign	1	33.3
	Cancer	2	66.7
	HG PIN/ASAP	0	0
End-of-study biopsy (all PSAs ≤ 3ng/ml)	Benign	44	77.2
	Cancer	9	15.8
	HG PIN/ASAP	4	7.0
Total		174	

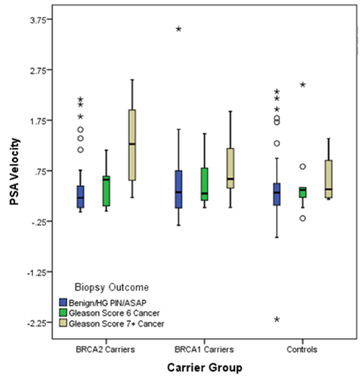

Figure 3: Boxplot of PSA V separated by genetic status and biopsy outcome

PSA V as a predictive biomarker

•PSA V was consistently predictive of cancer in the group of BRCA2 carriers (Figure 3; Table 3)
•While there were no significant relationships between cancer and PSA V in the groups of BRCA1 carriers and controls, the BRCA1 carrier group tended to trend more towards significance than the control group.
• BRCA2 carriers with PSA V > 0.35ng/ml/year were 6.5 times more likely to have PrCa (p=0.003) and 20.2 times more like to have Gleason Score (GS) 7+ cancer (p=0.001

Table 3: Odd ratios and mean differences using PSA V with defined cut-offs and as a continuous variable respectively, divided by genetic subgroup. *p<0.02

PSA V		*BRCA2* carriers	*BRCA1* carriers	Controls
0.75ng/ml/year	OR of cancer(95% CI)	4.6* (1.4-14.5)	1.4 (0.4-5.6)	1.2 (0.3-5.6)
	OR of GS 7+ cancer (95% CI)	8.4* (2.3-31.1)	1.5 (0.3-9.5)	1.3 (0.2-14.2)
0.35ng/ml/year	OR of cancer (95% CI)	6.5* (2.0-21.0)	1.9 (0.5-6.9)	1.5 (0.4-5.2)
	OR of GS 7+ cancer (95% CI)	20.2* (2.4-166.2)	6.1 (0.7-56.5)	1.2 (0.2-9.0)
Continuous	Mean PSA V difference for cancer vs other	0.55*	0.19	0.12
	Mean PSA V difference for >GS7 vs other	0.88*	0.32	0.14

PSA V as a prognostic biomarker

• PSA V was predictive of significant cancer in the BRCA2 cohort of men (Figure 4)
• PSA V did not predict for tumour aggressiveness for controls or BRCA1 carriers (Table 3)
• AUCs for PSA V in the BRCA2 cohort were:
• PSA V as a continuous variable: 0.86 (p<0.001)
• 0.35ng/ml/year: 0.77 (p=0.002)
• 0.75ng/ml/year: 0.73 (p=0.008)

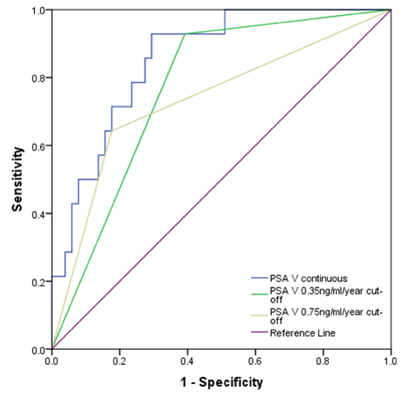

Figure 4: ROC curve for PSA V predicting GS7+ cancer as a continuous variable, with a cut-off of 0.35ng/ml/year and of 0.75ng/ml/year in the BRCA2+ biopsied cohort of men

Sensitivity/Sensitivity/PPV/NPV

• High negative predictive value (84%) and high sensitivity (78%) seen with PSA V >0.35ng/ml/year in BRCA2 carriers
• In BRCA1 carriers PSA V had a lower sensitivity and specificity

Table 4 : Sensitivity and specificity of PSA V for BRCA1, BRCA2 carriers and controls for predicting PrCa

	>0.75ng/ml/year cut-off			>0.35ng/ml/year cut-off		
Genetic Status	*BRCA2*	*BRCA1*	Controls	*BRCA2*	*BRCA1*	Controls
Sensitivity	48%	31%	23%	78%	62%	54%
Specificity	83%	76%	81%	64%	55%	56%
PPV	61%	29%	27%	55%	30%	28%
NPV	75%	78%	77%	84%	82%	79%

Conclusions

• PSA V may be useful within a longitudinal screening protocol to inform biopsy decisions, particularly in men at higher genetic risk of prostate cancer
• In men with a known BRCA2 germline mutation, PSAV may be used as a predictive and prognostic biomarker to identify those men with aggressive cancers who need immediate treatment
• PSA V >0.35ng/ml/year was associated with a sensitivity of 78% for detecting cancer in BRCA2 carriers but it was associated with a lower sensitivity for BRCA1 carriers and controls. NPV was high in all genetic groups ad specificity was moderate

Future Directions

• The target population has been reached for the IMPACT study. Follow up will continue until 2018 and all men enrolled will have a minimum of 5 years follow-up.
• To use PSA V as a surrogate marker for biopsy decisions especially in BRCA2 carriers
• Application of the IMPACT study protocol and algorithm to men with Lynch syndrome
• To investigate PSA V as a surrogate marker in a prospective study of men with family history of PrCa (PROFILE study)

An application created by Tokhir Dadaev to assist with PSA V calculation is available at:
https://zx8754.shinyapps.io/PSA_Velocity/

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