

Counter Arguments to This Letter	Response to Counter Argument
<p>1. A Cochrane Library’s systematic review of evidence regarding the effect of prostate specific antigen screening (PSA) on mortality found “...there is not enough high quality evidence to inform whether or not screening for prostate cancer, via either a DRE [digital rectal examination], PSA [prostate specific antigen] or TRUS [transrectal ultrasound guided biopsy], is more effective than no screening in reducing the number of deaths attributable to prostate cancer.” (Ilic, O’Connor, Green &amp; Wilt, 2006, p. 1) “Two randomized controlled trials with a total of 55,512 participants were included: however, both trials had methodological weaknesses. Re-analysis using intention-to-screen and meta-analysis of results from the two randomized controlled trials, indicated no statistically significant difference in prostate cancer mortality between men randomized for prostate cancer screening and controls (RR [relative risk] 1.01, 95% CI [confidence interval]L 0.80-1.29).” (Ilic, O’Connor, Green &amp; Wilt, 2006, p. 1)</p>	<p>“Recommendations cannot be made until data from the ERSPC [European Randomized study of Screening for Prostate Cancer] and PLCO [Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial] trials are made available to provide the highest level of evidence for practice. <b>In the absence of evidence health professionals, rather than routinely conducting prostate cancer screening, should adopt a shared approach to decision making for men who express an interest in prostate cancer screening and discuss both the potential benefits and harms associated with prostate cancer screening.</b> Furthermore, because of the lack of evidence for benefit and the risk of harms associated with testing and treatment, men who have a life expectancy less than approximately 10-15 years (either due to age or co-morbid conditions) should be informed that testing and treatment is unlikely to be beneficial.” (Ilic, O’Connor, Green &amp; Wilt, 2006, p. 8)</p> <p>My letter advocates making probabilities explicit using nomograms and family history. These can be discussed with one’s doctor to decide what to do regarding prostate cancer screening.</p> <p>One way to make risk explicit would be to calculate life years that might</p>

	<p>be saved due to screening by multiplying a patient's life expectancy by the probability of prostate cancer (based on a nomogram). For example, a sixty year-old white male has a life expectancy of about 20 years. The probability of a sixty year old man with a PSA of 1.9 and a family history of prostate cancer, negative DRE, no positive biopsy history, based on the Prostate Cancer Prevention Trial's nomogram (most applicable to men tested annually and managed very carefully) <a href="http://www.compass.fhcrc.org/edrnci/bin/calculator/main.asp">http://www.compass.fhcrc.org/edrnci/bin/calculator/main.asp</a>) is .27; so (assuming effective treatment) benefit may be very approximately <math>20 \times .27 = 5.4</math> years. For an eighty year old man with the same history with a life expectancy of 7 years the potential benefit is <math>7 \times .27 = 2</math> years. Methodolgical issues regarding the nomogram above have been discussed in this source: (Thompson, Ankerst, Chi, Goodman, Tangen, Lucia, Feng, Parnes &amp; Coltman, 2006).</p> <p>It appears that radical prostatectomy does reduce mortality from prostate cancer mortality over watchful waiting (Bill-Axelson, 2005).</p>
<p>2. Most doctors and fewer patients know how to sift through the Internet to find the best evidence, weigh its quality, and understand its clinical significance.</p>	<p>Such deficiency is my reason for writing this letter. Those learning how to consult the Internet may benefit. A September-October 2001 survey of 800 (748 responded) sent to Web-using physicians (UK</p>

	<p>members of Medix) reported that 1-2% of their patients consulted the Internet regarding their care in the past month. (Potts &amp; Wyatt, 2005) Their survey showed that twice as many doctors reported benefits to the patient (85%) than problems (44%).</p> <p>Additionally, the second most common request for information from the Internet concerns health care, the first being e-mail (Pew Internet and American Life Project, July 2003). If people are going to search, they need to know how, thus our letter about the evidence-based practice process.</p>
<p>3. You have fallen into the trap of hindsight bias to construct an argument that you could have known about your cancer and would have treated it effectively.</p>	<p>Hind sight bias is surely a problem in my letter, as stated up front in the first draft of my letter. Consequently, I have toned an earlier version of this letter down, making my inferences more tentative. The thinking in my letter underlies the spirit of a morbidity conference—determine how an unfortunate event took place without blame to do better in the future. Only through such thinking can we progress. Scientific reasoning does not seek to blame anyone, but rather to understand and to better the human condition.</p>
<p>4. You could not have located such an aggressive prostate cancer. The PSA test is not very good at locating aggressive prostate cancer. See Thompson et al. (2005). This article references confusion over where to set the cut off value of PSA to decide on biopsy.</p>	<p>This article concerns absolute PSA value, not PSA velocity.</p> <p>This Prostate Cancer Prevention Trial was done prospectively between 1993 and 2003 following 18,882 healthy men, aged 55 or older, with PSA levels less than or</p>

equal to 3.0 mg/mL. to test the relationship between PSA levels and biopsy results. Receiver Operating Curves summarize sensitivity, specificity and 1-specificity (false positive rate) for PSA detecting cancer/no cancer for all patients, those with Gleason scores of greater than or equal to 8 and greater than 7 but less than 8. The authors cite evidence stating that the frequently used 4.0 mg/mL PSA is common. They cite literature to describe confusion and controversy over where to place the PSA cut off to decide on biopsy.

In Table 3 the authors provide data regarding sensitivity and specificity for PSA values by age and by Gleason Score (index of aggressiveness of the tumor) for all patients in the study. The authors conclude that the commonly used 4.0 will miss high Gleason (aggressive cancers) particularly among younger men, that doctors need to recognize that there is a continuum of risk with no clear cut off, and that “It will be the patient in concert with his health professional, who will ultimately have to weigh the sensitivity-specificity tradeoffs in combination with the uncertain natural history of the disease to determine whether further evaluation with a prostate biopsy is appropriate.”

Doctors might use Table 3 on Page 69 and the Figure on page 68 to

	<p>explain these tradeoffs based on sensitivity and specificity values to help each patient to decide whether to do biopsy, in conjunction with individual characteristics of each patient including age, general health, family history (unless a better study and table can be located).</p> <p>This article addresses why early screening with PSA of 4.0 may not have affected survival rates—because aggressive cancers are missed that might be detected with lower PSA values, thus the utility of the tables for lower PSA patients.</p> <p>This article did not include a separate analysis regarding patients with a family history of cancer such as myself (half of my blood relatives died of cancer or have it).</p>
<p>5. PSA velocity is not robust enough as a predictor of prostate cancer.</p>	<p>If this is so, then the National Guideline Clearinghouse for the American Urological Association Education and Research should stop publishing the guideline of an absolute value of 4.0 mg/ml or .75 PSA velocity for one year as a criterion for biopsy (please see <a href="http://www.guideline.gov/">http://www.guideline.gov/</a>). To check the evidentiary basis for the .75 PSA velocity guideline as a criterion for biopsy, I entered into Medline via EBSCO these terms: (PSA velocity OR prostate specific antigen) AND (sensitivity OR specificity OR positive predictive value OR negative predictive value) finding 59 documents. I read the</p>

	<p>abstracts of these and selected fourteen documents whose abstracts included the term “PSA velocity”. These documents are summarized in Table 1 below. The table demonstrates that PSAV has sufficient Positive Predictive Value and Negative Predictive Value to guide clinical decision making; that PSAV had the highest predictive values when compared with other indices; that norms for PSAV are available with smaller average PSAV changes typical in younger men, and that studies were consistent with each other and in the expected direction (i.e. studies with higher base rates had higher PPV and higher NPV.</p>
<p>6. You might not have been able to use PSA velocity, because the literature regarding PSA velocity might not have been out in Spring of 2004, the time to make the decision for your biopsy.</p>	<p>The National Guideline Clearinghouse for the American Urological Association Education and Research at the URL above are dated 2000. The copyright dates for the articles described in the box immediately above are: 2001, 2002, 1998, 1997, 2005, 2004, 2003, 2003, 2002, 2000, 1998, 1998, 1995, 1993. Three are in Japanese or Spanish.</p>
<p>7. Using PSA absolute values or PSA velocity is generally not economically feasible because of the overwhelming number of false positives when such tests are applied to the general population.</p>	<p>I am not representative of the general population in the sense that half of my closest blood relatives died of cancer or have it (grandfather with prostate cancer, mother with breast cancer, father with esophageal cancer, sister living with breast cancer). Such a history might warrant closer observation.</p>

**Table 1: Articles Regarding PSA Velocity**

Source	Number of Subjects/Number With Cancer	Base Rate	Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Fang, Metter, Landis & Carter, 2002	68/21	.31	PSAV (.1 mg/mL/year)	.81	.50	.42	.85
Roobol, Kranse, Koning & Schroder, 2004	774/149	.19	PSAV greater than or equal to .1	.852	.18	.20	.85
	774/149	.19	PSAV greater than .1 or equal to .2	.644	.41	.20	.83
	774/149	.19	PSAV greater than .2	.389	.67	.21	.82
Ukimura, Durrani & Babaian, 1997	193/33	.17	PSA	.88	.29	.20	.92
	193/33	.17	PSAD	.79	.48	.24	.92
	193/33	.17	Age-R-PSA	.76	.37	.20	.88
	193/33	.17	PSAV (difference between first test and second divided by interval in days)	.50	.84	.39	.89
	193/33	.17	Vol-R-PSA	.85	.21	.18	.87
	193/33	.17	DRE	.39	.63	.13	.70
	193/33	.17	TRUS	.91	.39	.24	.95
<b>Other Types of Studies Not Giving Sufficient Data to Use Bayes' Theorem to Calculate PPV and NPV (using calculator available at <a href="http://www.sgim.org/bayes_calc.cfm">http://www.sgim.org/bayes_calc.cfm</a>)</b>							
Ciatto, Bonardi, Lombardi, Zappa, Gervasi & Cappelli, 2002	The average PSAV in one year among 1,666 healthy subjects (no cancer at biopsy) was 0.0 ng/mL/year (range -2.18+5.99, 95% confidence interval 0.05-0.09). For the cancer subjects the average change was 1.16 ng/mL (range 0.10-5.6, 95% confidence interval was 0.56-1.7). This difference was statistically significant at .01 level.						
DeAntoni, 1995	This article is a review dated 1995. It gives norms for PSA change by age group (just a group of men checked over one year who may or may not have cancer), second hand table from Prostate Cancer Education Council.						

	Age Cohort	% Change PSA (95% CI)	Mean Change PSA(ng/mL) (95% CI)
	40-49 (n=867)	29 (2, 54)	0.13 (0.02, 0.25)
	50-59 (n=2795)	32 (18,47)	0.22 (0.15, 0.28)
	60-69 (n=3656)	28 (16,41)	0.26 (0.20, 0.31)
	70-79 (n=1995)	42 (24, 59)	0.32 (0.25, 0.40)
	Total (n=9273)		
Lynn, Collins & O'Reilly, 2000	Among 97 patients referred for TRUS (sonogram) and biopsy, 158 not having cancer and 3 (24%) had cancer of the prostate. Mean interval between PSA measurements in both groups was 2.24 months (95% confidence interval 2.2-2.4 months. Mean PSAV per month for non-cancer group was -0.5 (range -8.6 to 7.1) ng/mL/month, for cancer group it was 0.14 (range 5.7 to 6.8)		
Manseck, Pilarky, Froschermaier, Menschikowski & Wirth, 1998	A study of 85 men with PSA values between 3 and 8 ng/mL using the Abbot IMx and Jybritech Tandem-E assays found differences from one assay to the next for the former was 0.02 to 2.74 ng/mL SD .35 and for the latter 0.05 to 4.05 ng/mL, SD 1.15 ng/mL . The authors conclude that test variance may be greater than PSA increase per year.		

### PSA Velocity as an Indicator of Prostate Cancer

Unpublished research based on 26,000 patients by Catalona [http://www.drcatalona.com/quest/Spring05/quest\\_spring05\\_2.asp](http://www.drcatalona.com/quest/Spring05/quest_spring05_2.asp) suggests that .50 would be a more effective PSAV cut off value to decide on biopsy.

Here are data from an abstract of this article (Antenor, Roehl, Misop & Catalona, 2005).

PSAV Cutoffs and Cancer Detection Rate			
PSA Velocity Cutoffs	No. of Men	% Men with Cancer	P-value
>0.5	1274	45	<.0001
>0.75	1030	46	<.0001
>1.0	842	46	<.0001
>2.0	386	46	<.0001

## References

Antenor, J. A. V., Roehl, K. A., Han, M., & Catalona, W. J. (May 22, 2005) PSA Velocity Cutoff for Recommending Biopsy: Positive Predictive Values. Abstract in *The Journal of Urology Supplement*, 173(4), p. 146.

American Urological Association. (February 2000). [\*Prostate specific antigen \(PSA\): best practice policy\*](#). American Urological Association Education and Research, Inc. - Medical Specialty Society. [www.guideline.gov](http://www.guideline.gov), retrieved 4 November, 2005. 11 pages. NGC:001407

Bill-Axelson, A. et al. (2005). Radical prostatectomy versus watchful waiting in early prostate cancer. *New England Journal of Medicine*. 352(19), 1977-1984.

Colombet, I., Dart, T., Leneveut, L., Zunino, S., Menard, J. & Chatellier, G. (November 27, 2003). A computer decision aid for medical intervention: A pilot qualitative study of the Personalized Estimate of Risks (EsPeR). *BMC Medical Informatics and Decision Making*. Retrieved November 2<sup>nd</sup>, 2005, <http://www.biomedcentral.com/1472-6947/3/13>.

Ebell, M. H. (September 15, 2005). Predicting the risk of prostate cancer on biopsy. *American Family Physician*. <http://www.aafp.org/afp/20050915/poc.html> .

Ilic D, Green S, O'Connor D, Wilt T. Screening for prostatic cancer. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD004720. DOI: 10.1002/14651858.CD004720.pub2.

Ilic D, Green S, O'Connor D, Wilt T. Screening for prostatic cancer. (Protocol) *The Cochrane Database of Systematic Reviews* 2004, Issue 2. Art. No.: CD004720. DOI: 10.1002/14651858.CD004720.

Lee, R., & Skinner, J. (1999). Will aging baby boomers bust the federal budget? *Journal of Economic Perspectives*, 13(1), 117-140.

Thompson, I. M., Ankerst, D. P., Che, C., Goodman, P. J., Tangen, C. M., Lucia, M. S., Feng, Z. Parnes, H. L, & Coltman, C. A. (2006) Assessing

prostate cancer risk: Results from the Prostate Cancer Prevention Trial. *Journal of the National Cancer Institute*. 98(8), 529-534.

Thompson, I. M., Ankerst, D. P., Chi, C., Lucia, M. S., Goodman, P. J., Crowley, J. J., Parnes, H. I., & Coltman, C. A. (2005). Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 mg/mL or lower. *JAMA*. 294(1), 66-70.

Wilt, T., Nair, B., MacDonald, R., & Rutks, I. (2001). Early versus deferred androgen suppression in the treatment of advanced prostate cancer. *The Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No CD003506 DOI: 10.1002/14651858.CD00356.

#### References for Table 1

Ciatto, S., Bonardi, R., Lombardi, C., Zappa, M., Gervasi, G., & Cappelli, G. (2002). Analysis of PSA velocity in 1666 healthy subjects undergoing total PSA determination at two consecutive screening rounds. *The International Journal of Biological Markers*, 17(2), 79-83.

DeAntoni, E. P. (1995). Screening strategies: A clinical perspective. *Cancer Surveys*, 23, 99-115.

Fang, J., Metter, J., Landis, P., Carter, H. B. (2002). PSA velocity for assessing prostate cancer risk in men with PSA levels between 2.0 and 4.0 ng/mL. *Urology*, 59(6), 889-894.

Lynn, N.N. K., Collins, G. N., & O'Rielly, P. H. (2000). The short-term prostate specific antigen velocity before biopsy can be used to predict prostatic histology. *BJU International*, 85,847-850.

Manseck, A., Plarsky, C., Frosehermaier, S., Mwnschikowski, M., Wirth, M. P. (1998). *Urologia Internationalis*, 60, 25-27.

Roobol, M. J., Kranse, H. J., De Konig, H. J., & Schroder, F. H. (2004). Prostate specific antigen velocity at low prostate-specific antigen levees as screening tool for prostate cancer: Results of second screening round of ERSPC (Rotterdam). *Urology*, 63(2), 309-313.

Ukimura, O., Durrani, O, & Babain, R. J. (1997). Role of PSA and its indices in determining the need for repeat prostate biopsies. *Urology*, 50(1), 66-72.

In summary, specific to detecting aggressive prostate cancer, I think it wise to consider family history of prostate cancer, breast cancer, PSA velocity, age, and race when estimating risk and deciding on more conservative tests (biopsy). Data already point to greater sensitivity and specificity for PSA value for younger men for aggressive prostate cancer (Thompson et al., 2005 tables).

I recommend, based on this quick and superficial review, that this policy be adopted to screen for aggressive prostate cancer:

- In cases where men have blood relatives with breast or prostate cancer, screen more conservatively.
- Do PSA annually, not biannually, so PSA velocity can be computed and trends noted early.
- At the very least, follow clinical guidelines published by the National Guideline Clearinghouse for the American Urological Association Education and Research that states 4.0 mg/mL or a PSA velocity of .75 mg/mL over one year as criterion for more conservative testing. Catalino's data indicate .5 mg/mL would be a better
- \ but particularly PSA velocity ([http://www.urologychannel.com/HealthProfiler/healthpro\\_psa\\_Vel.shtml](http://www.urologychannel.com/HealthProfiler/healthpro_psa_Vel.shtml)), to detect aggressive prostate cancer.

Speaking generally, since many consult the Internet for health-related evidence, my intent here is not to find fault with anyone, but rather to help others to follow a process that may help them to work as a team with their helping professional, possibly improving decision making.

Because general use of PSA test results may not have reduced prostate cancer death, which is primarily due to the 4.7% that are aggressive (i.e. high Gleason Scores), we need to develop a way to screen specifically for these aggressive cancers. I am working on a proposal to do a study that will develop a statistical algorithm to test whether predictor variables can increase positive predictive value for aggressive prostate cancer. I will present these ideas to Dr. Eugene Kwon of the Mayo Clinic in mid October.

Here is a review that will come out in the Cochrane Library soon:

[Protocol]

## Screening for prostatic cancer

D Ilic, S Green, D O'Connor, T Wilt

*The Cochrane Database of Systematic Reviews* 2006 Issue 1

Copyright © 2006 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DOI: 10.1002/14651858.CD004720 This version first published online: 19 April 2004 in Issue 2, 2004

Date of Most Recent Substantive Amendment: 18 February 2004

This record should be cited as: Ilic D, Green S, O'Connor D, Wilt T. Screening for prostatic cancer. (Protocol) *The Cochrane Database of Systematic Reviews* 2004, Issue 2. Art. No.: CD004720. DOI: 10.1002/14651858.CD004720.

### References

Pew Internet and American Life Project. Internet Health Resources, Retrieved August 11<sup>th</sup> 2005 from [Pewinternet.org/pdfs/PIP\\_Health\\_Report\\_July\\_2003.pdf](http://Pewinternet.org/pdfs/PIP_Health_Report_July_2003.pdf) .

Potts, H. W. W., & Wyatt, J. C. (2002). Survey of doctors' experience of patients using the Internet. *Journal of Medical Internet Research*. 4(1):e5, retrieved on August 2005 from <http://www.jmir.org/2002/1/e5/>> or <http://www.jmir.org/2005/> .

Thompson, I. M., Ankerst, D. P, Chi, C., Lucia, M. S., Goodmkan, P. J., Crowley, J. J., Parners, H. I., & Coltman, C. A. (2005). Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 or lower. *JAMA*, 294(1), 66-70.