

# Techniques and Predictive Models to Improve Prostate Cancer Detection\*

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The use of prostate-specific antigen (PSA) as a screening test remains controversial. There have been several attempts to refine PSA measurements to improve its predictive value. These modifications, including PSA density, PSA kinetics, and the measurement of PSA isoforms, have met with limited success. Therefore, complex statistical and computational models have been created to assess an individual's risk of prostate cancer more accurately. In this review, the authors examined the methods used to modify PSA as well as various predictive models used in prostate cancer detection. They described the mathematical underpinnings of these techniques along with their intrinsic strengths and weaknesses, and they assessed the accuracy of these methods, which have been shown to be better than physicians' judgment at predicting a man's risk of cancer. Without understanding the design and limitations of these methods, they can be applied inappropriately, leading to incorrect conclusions. These models are important components in counseling patients on their risk of prostate cancer and also help in the design of clinical trials by stratifying patients into different risk categories. Thus, it is incumbent on both clinicians and researchers to become familiar with these tools. **Cancer 2009;115(13 suppl):3085-99. © 2009 American Cancer Society.**

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**Despite** intensive work over the last several decades, prostate cancer continues to be the most common cancer in men and their second leading cause of cancer death. In 2008, it is estimated that 186,320 men received a new diagnosis of this disease, and nearly 29,000 died from it.<sup>1</sup> However, there is no universal agreement on screening for prostate cancer. The American Urological Association and the American Cancer Society both recommend using a combination of digital rectal examination (DRE) and serum prostate-specific antigen (PSA) level to screen low-risk white men starting at age 50 years and to screen high-risk populations (including African Americans) starting at age 40 years.<sup>1,2</sup> Some respected prostate cancer researchers believe that PSA screening should begin in all men starting in their 40s.<sup>3</sup> Conversely, the US Preventive Services Task Force does not fully endorse prostate cancer screening and recently stated that men aged  $\geq 75$  years should not be screened.<sup>4</sup> Therefore, it is understandable that confusion and controversy regarding prostate cancer screening persists in both professional and lay communities.

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Much of the dilemma has to do with limitations of the PSA test itself, which has poor sensitivity and specificity. Various attempts to improve the predictive capacity of PSA likewise have met with only partial success. Because of these deficiencies, statistical and computational models have been created to more accurately predict a patient's risk of prostate cancer at biopsy. This, in turn, helps patients make a more informed decision concerning the choice to proceed with biopsy, a decision that should not be made lightly given the costs involved, the possibility of complications, and the chance of diagnosing clinically insignificant cancer. In this review, we provide a brief summary of PSA and its permutations and examine the methods that generate the predictive models as well as their inherent strengths and weaknesses.

### **Overview of PSA and PSA-specific antigen modifications**

Catalona et al initially explored the use of PSA as a screening tool. In 2 large studies of healthy men aged  $\geq 50$  years, a higher screening PSA level was correlated with a greater likelihood of cancer.<sup>5,6</sup> Furthermore, the addition of PSA to DRE improved the sensitivity of cancer detection. On the basis of these findings, PSA received US Food and Drug Administration (FDA) approval for use as a screening tool in 1994. Consequently, as testing became widespread in the United States, prostate cancer incidence increased significantly in the early 1990s.<sup>1</sup>

Nonetheless, problems with PSA as a screening test quickly became apparent. Inherent limitations in its specificity led to the unnecessary biopsy of many patients. Furthermore, it was known from its inception that men with cancer could have a PSA below the traditional threshold of 4 ng/mL.<sup>5</sup> This was made particularly apparent in 2003 with the publication of the Prostate Cancer Prevention Trial.<sup>7</sup> In that prospective trial of over 18,000 men, 15.2% of patients who never had a PSA  $>4$  ng/mL harbored prostate cancer.<sup>8</sup> Even more striking, 14.9% of those men had a Gleason sum of at least 7, indicating potentially aggressive cancers.

In addition, the widespread use of PSA combined with changing biopsy practices caused a marked change in PSA performance characteristics. A retrospective study examined all prostate biopsies at a single institution between 1993 and 2005.<sup>9</sup> Temporal trends were exam-

ined over 3 separate periods: 1993 to 1997, 1998 to 2001, and 2002 to 2005. In the initial time cohort, there was a significant correlation between PSA and positive biopsy rate. This correlation had disappeared by the most recent time period. The authors also reported that, on multivariate analysis with a normal DRE, PSA did not correlate with the positive biopsy rate. Those results and other studies have led to doubt regarding the value of PSA as a screening tool.<sup>10,11</sup>

### **PSA density**

Even before PSA was approved by the FDA as a screening test, Benson et al attempted to improve its specificity by deriving PSA density (PSAD) (PSA divided by prostate volume as measured on transrectal ultrasound [TRUS]).<sup>12</sup> A PSAD  $\geq 0.15$  eventually was proposed as a threshold for biopsy in men who had PSA levels between 4 ng/mL and 10 ng/mL.<sup>13</sup> However, it appeared that this cutoff level could miss approximately 40% of prostate cancers.<sup>14</sup> Although there have been attempts to improve the performance characteristics of PSAD by adjusting for transition zone volume,<sup>15</sup> 1 of the most significant barriers to its widespread acceptance is the unwillingness of patients and physicians to perform an invasive TRUS without committing to a biopsy.

### **PSA velocity**

Measuring the rate of change of PSA over time has become known as PSA velocity (PSAV), and numerous methods are used to calculate this value.<sup>16</sup> To date, there have been conflicting results on using PSAV for prostate cancer detection.<sup>17,18</sup> Furthermore, PSAV should be considered carefully before proceeding with biopsy. Eastham et al demonstrated that an elevated PSA should be confirmed before making decisions about biopsy and that an isolated elevation does not accurately reflect true PSAV.<sup>19</sup> In addition, many of the studies that explored PSAV suffered from verification and attribution biases.<sup>16,20</sup> Verification bias comes from the finding that it was not a high PSAV per se that triggered a biopsy in most of those studies but, rather, some other predefined endpoint (eg, total PSA cutoff or abnormal DRE). The true sensitivity and specificity of PSAV cannot be determined under these circumstances. In addition, the actual method of calculating PSAV can change the value significantly.<sup>16</sup>

### Free PSA and percentage free PSA

PSA circulates in the serum in several different isoforms that can be categorized into either “free” or “complexed” PSA.<sup>21</sup> In 1998, a prospective, multicenter clinical trial was published in which serum was obtained from 773 men between ages 50 years and 75 years who had a PSA level between 4 ng/mL and 10 ng/mL, a negative DRE, and who had undergone a transrectal biopsy.<sup>22</sup> A percentage free PSA (%fPSA) cutoff of 25% produced a sensitivity of 95% but a specificity of only 20%. Reducing the %fPSA cutoff to 22% increased the specificity to 29% but only decreased the sensitivity to 90%. The area under the receiver operating characteristic (ROC) curve (AUC) for %fPSA was 0.72 compared with 0.53 for the total PSA level, a statistically significant improvement. Similarly, in another large cohort using the Physician’s Health Study, it was reported that the AUC for the %fPSA was 0.75 compared with 0.52 for total PSA in men who had a PSA between 4 ng/mL and 10 ng/mL. It is important to note that the sera from which those results were obtained were collected in the early 1980s, and it is unclear whether the results still would be applicable.

A recent study explored what percentage of men ages 40 years to 79 years would require a biopsy in a contemporary screening cohort based on %fPSA levels.<sup>23</sup> Those investigators examined PSA and fPSA levels in 2323 men undergoing routine screening. They observed that 50.4% of men had a %fPSA <25%, suggesting that, if this threshold were applied, then half of all men would require a biopsy. That study was limited significantly by the finding that none of the men actually underwent a biopsy, so the incidence of cancer in the group could not be assessed. Thus, the performance characteristics of %fPSA could not be determined.

### Pro-PSA

Pro-PSA is a zymogen precursor of PSA that makes up a portion of the free component of PSA.<sup>24,25</sup> It can exist in both native and truncated forms and has been correlated more strongly with malignant tissue compared with benign tissue.<sup>26,27</sup> An initial study examined serum from 119 men who underwent prostate biopsy with a PSA between 2.5 ng/mL and 4 ng/mL. Pro-PSA was defined as the sum of the various forms of precursor enzyme, and the percentage pro-PSA was defined as pro-PSA/fPSA. The percentage pro-PSA demonstrated a significantly

improved specificity of 59% compared with a specificity of 33% for %fPSA at a fixed sensitivity of 75%.<sup>28</sup> Furthermore, the AUC was significantly greater for the percentage pro-PSA than for the %fPSA. In a study of 1091 men who underwent prostate cancer screening, the percentage pro-PSA was increased significantly in men who had a Gleason score  $\geq 7$ .<sup>29</sup> One form of pro-PSA, (-2) pro-PSA, had greater specificity for detecting prostate cancer compared with %fPSA and complexed PSA, particularly among men who had a total PSA between 2 ng/mL and 4 ng/mL.

A recent multicenter clinical trial cast some doubt regarding the utility of pro-PSA in clinical decision making.<sup>30</sup> In that trial, 2055 white men from 4 European centers underwent screening using PSA, %fPSA, and percentage pro-PSA. ROC curves were constructed for total PSA, %fPSA, percentage pro-PSA, and pro-PSA/fPSA. The AUC of total PSA did not improve significantly with the addition of pro-PSA. One important caveat is that the study did not assess the most promising isoform of pro-PSA, (-2) pro-PSA. Further studies will be needed before any definitive conclusions can be made on the usefulness of pro-PSA.

The limitations of these diagnostic tests in isolation for detecting prostate cancer encouraged the development of more complicated predictive models. These models seek to gauge more accurately who is at risk for prostate cancer. This, in turn, could reduce the number of unnecessary biopsies and avoid some of the controversy surrounding prostate cancer screening.

## Predictive Models in Prostate Cancer Detection

### Background of predictive modeling

PSA and its various derivatives are useful for determining who is at risk for prostate cancer on a population level; however, these tools are less useful for counseling individual patients. Stephenson and Kattan pointed out that patients are not interested in the percentage of prostate cancer in a population given a particular PSA (or equivalent) value: they want to know their personal risk.<sup>31</sup> To this end, clinicians have created a variety of predictive models that take into account a patient’s specific risk factors and that calculate the probability of that individual having prostate cancer. In addition to creating more

specific physician-patient discussions, several studies have demonstrated that predictive models are more accurate than physician judgment, which often is affected disproportionately by past experience and other biases.<sup>32-35</sup>

Although they are more accurate than physician judgment in certain situations, predictive models cannot be applied appropriately without knowledge of their various strengths and weaknesses. The first step in assessing a predictive model is it to examine its accuracy or its overall ability to discriminate the endpoint of interest. There are 2 main ways of describing accuracy: the concordance index and the AUC. The concordance index is used for models that are based on censored data, whereas the AUC describes the accuracy of models studying binary outcomes that do not depend on censored observations. Therefore, the AUC is the most frequent measure of accuracy for predictive models in diagnosing prostate cancer.

Calibration is another statistical feature that needs careful examination. Although accuracy assesses a model's overall ability to predict various probabilities, it may not apply equally to all subpopulations. In other words, a model's overall accuracy can be quite good although its accuracy for a particular subpopulation is not. Calibration curves adjust for this by demonstrating more explicitly the accuracy of a model within various subpopulations, and such curves can be created from either internally or externally validated data.

A model's validity describes its ability to translate its accuracy to novel data. Ideally, a model's validity is demonstrated with data external to that from which the model was created. Practically, however, this often is not possible, so a method called bootstrapping frequently is used for internal validation. This method is the best way to internally validate a model and is done by testing the model on multiple samples drawn from the original group. When this is not possible, other methods of internal validation include cross-validation and split-sample validation. An interesting alternative involves sequential analysis of a series of patients. This may reduce the number needed to validate the model while simultaneously making it more specific for a particular clinic's population.<sup>36</sup>

Even if a model is valid across different datasets, it is important to note the characteristics and outcomes that were measured in the original sample and to apply the model only to those patients who have similar characteris-

tics. For example, a PSA of 6 ng/mL may be very different in a patient who is screened for prostate cancer versus a patient who presents with lower urinary tract symptoms. It should not be assumed automatically that PSA plays the same predictive role in both of these patients, and the same model should not be applied to both without first demonstrating similar results and performance characteristics. An ideal model should be generalizable, which means that predictions in 1 cohort are comparable to those in other cohorts. If a model is not generalizable, then it should be applied only to men who have the same characteristics as the men on whom the model originally was based.

Finally, to be clinically useful, a model must be simple to use. Data points should be based on information that is relatively common or easy to access, and the number of variables should be limited. An automated model is clearly the easiest to use from a physician's perspective, but patients sometimes find it more understandable if they know how much each risk factor contributes to their overall risk. Recent innovations include graphic interfaces or online risk calculators that allow patients to calculate their own risk.<sup>37-39</sup> The extent to which patients can interpret these tools remains to be established.

### Nomograms

Most likely, the predictive model most familiar to physicians is the nomogram. This is used a graphic representation of a statistical formula that sums predictor variables to provide the probability of a particular outcome. The actual statistical formula most typically used is based on Cox proportional hazards analysis or multivariate logistic regression. There are several mathematical methods to allow for nonlinear effects of predictor variables, a function that is not normally a part of regression models.<sup>40</sup>

Nomograms have multiple advantages for the physician. Predictor variables can be either continuous or categorical, and the ability of nomograms to graphically signify complex mathematical relations leads to improved communication between physicians and patients. Nomograms also have the advantage of using statistical techniques that are familiar to most physicians. This allows for the reporting of hazard ratios as well as tests of significance, which, in turn, help generate additional hypotheses. The graphic nature of nomograms makes them user friendly and facilitates their acceptance into clinical

practice. Several nomograms have been adapted to personal computers or personal digital assistants, and many more are freely available for downloading (available at: <http://www.nomograms.org> accessed on April 29, 2009). Similar to when using other predictive models, care must be taken to ensure appropriate validity, calibration, and generalizability.<sup>31</sup>

Nomograms have been used for multiple aspects of prostate cancer decision making from prediction of cancer at initial biopsy, to prediction of pathologic stage, to biochemical recurrence, etc. A detailed analysis of these various nomograms is beyond the scope of this report but is available in recent reviews.<sup>31,41</sup> At least 16 nomograms have been developed to predict the diagnosis of prostate cancer.<sup>42-57</sup> Their predictor variables, sample sizes, methods of validation, and study populations are summarized in Table 1.

To our knowledge, Eastham et al were the first to use a nomogram to predict the risk of prostate cancer.<sup>50</sup> They were able to achieve 75% accuracy using just race, age, and PSA level as predictor variables. It is worth noting that much of their study was conducted during the early phases of the PSA era, and primarily sextant biopsy patterns were performed, potentially limiting the current applicability of this nomogram. Finne et al were the first to look at the likelihood of cancer in a cohort of men undergoing screening.<sup>54</sup> By using a PSA cutoff of 4 ng/mL, those authors observed that total PSA, %fPSA, prostate volume, and DRE were significant predictors of disease. There were several significant limitations to their study. They did not report the model's validation measures, accuracy, sensitivity, or specificity. Also, they did not convert their multivariate risk equation into the standard graphic format, thus limiting its clinical applicability.

Lopez-Corona et al used a history of high-grade prostate intraepithelial neoplasia as well as atypical small acinar proliferation in their nomogram predicting the risk of cancer on repeat biopsy.<sup>47</sup> Several recent studies also supported a correlation between these pathologic findings and a risk for cancer, although the correlation remains somewhat controversial.<sup>58-60</sup> Yanke et al examined the role of race in predicting prostate cancer and indicated that Caucasians had a hazard ratio of 0.74 compared with African Americans.<sup>43</sup> The only other nomogram that takes into account racial differences was the 1 published by Eastham et al mentioned above. The study by Yanke

et al also was significant because it had the largest study population ( $n = 9473$ ) of any of the models.

It is important that predictive models remain current with changing practice patterns. There is evidence that 6 biopsy cores may not be adequate to detect prostate cancer.<sup>61</sup> Thus, there has been a trend toward performing extended biopsy patterns.<sup>9</sup> Several nomograms have examined the risk of prostate cancer using only extended prostate biopsies.<sup>44,51,52,55,56</sup> It is interesting to note that the predictive models generated during the sextant biopsy era are not as accurate when applied to men undergoing extended biopsy.<sup>51</sup> This reinforces the importance of ensuring appropriate validation and generalizability before applying predictive tools to new populations.

### Artificial neural networks

Artificial neural networks (ANNs) originally were developed in the 1950s as a type of predictive modeling meant to mimic human learning. Although there are various types of ANNs, the most common type in the medical field is known as the multilayer perceptron. In this system, there are at least 3 layers of computation: the input layer, the hidden layer, and the output layer. The creation of ANNs occurs in 3 phases. First is the design phase, during which the model is given the independent variables and the outcome being studied. Second comes the training phase, during which the system creates and refines interconnections between the independent variables, generating the hidden layer of multifactorial analysis. By using highly computational techniques, software coding identifies connection strengths between data points. The ANN places various weights on these data points or nodes, as they are referred to in this context. Then, these weights are adjusted as the ANN goes through the training phase. Finally, in the validation stage, the ANN tests its accuracy on data that were not included in the training phase.

The relations and the weights that the ANN creates between the different layers are difficult to discern. Because ANNs do not provide hazard ratios or tests of significance for particular input characteristics, ANNs are thought of as "black boxes," and their clinical interpretation becomes difficult. This is the primary drawback of this type of modeling, because it is difficult to generate and test hypotheses regarding the association between input variables and the outcome of interest. Another disadvantage to ANNs is that their results are not

**Table 1.** Summary of Nomograms Predicting the Risk of Prostate Cancer

Study	Patient Characteristics	Sample Size	Dates of Analysis	Predictor Variables	Type of Biopsy	Accuracy, %	Validation
Eastham 1999 <sup>50</sup>	Abnormal DRE and PSA 0-4 ng/mL	700	1990-1997	Race, age, PSA	Sextant	75	Internal
O'Dowd 2000 <sup>46</sup>	Negative biopsy within past y	813	1994-1998	Age, initial biopsy diagnosis, total PSA, free/total PSA	Not available	70	Not performed
Finne 2002 <sup>54</sup>	Finnish men with PSA 4-20 µg/L undergoing screening	758	1996-1997	PSA, %fPSA, prostate volume, DRE	Sextant	Not reported	Not performed
Lopez-Corona 2003 <sup>47</sup>	Previous negative biopsy	343	1999-2001	Age, DRE, prior no. of negative cores, history of HGPIN, history of ASAP, PSA, PSA slope, family history	Mixed sextant and extended	70	Not performed
Garzotto 2003 <sup>49</sup>	Referred for prostate biopsy with PSA <10 ng/mL and TRUS	976	1993-2000	Age, DRE, TRUS, PSAD	Sextant	73	Internal
Yanke 2005 <sup>42</sup>	Validation of Guzzo 2008 <sup>58</sup>	230	1993-2003	As above	Mixed sextant and extended	71	Internal
Karakiewicz 2005 <sup>48</sup>	Referred for abnormal PSA, free PSA, or DRE	6469	1992-2000	Age, DRE, PSA, %fPSA	Sextant	77	Internal and external
Suzuki 2006 <sup>45</sup>	Japanese men on initial biopsy	834	2000-2003	Age, PSA, %fPSA, prostate volume, DRE	Sextant	81.8	Internal
Yanke 2006 <sup>43</sup>	White or African-American men on initial biopsy	9473	1990-2003	Age, race, PSA, DRE, total cores	Mixed	75	Internal
Walz 2006 <sup>44</sup>	Men undergoing saturation biopsy after prior negative biopsy	115	2001-2004	Age, PSA, %fPSA, prostate volume, BPH volume, no. of prior biopsies, transition zone density	Saturation (at least 18 cores)	72	Internal
Chun 2007 <sup>51</sup>	Men undergoing extended biopsy with abnormal DRE or PSA	1162	Not reported	Age, DRE, PSA, %fPSA, sampling density	Extended (at least 10 cores)	77	External
Chun 2007 <sup>52</sup>	Prior biopsy and abnormal DRE, PSA, %fPSA, HGPIN, or ASAP	721	Not reported	Age, DRE, PSA, %fPSA, prostate volume, no. of prior biopsies, sampling density	Extended (at least 10 cores)	76	Internal and external
Benecchi 2006 <sup>53</sup>	Prior biopsy and data on PSA kinetics	419	2001-2007	DRE, %fPSA, PSA density, PSA slope, HGPIN	Extended (at least 12 cores)	86	Internal
Kawakami 2008 <sup>55</sup>	Japanese men, PSA 2.5-10 ng/mL, or abnormal DRE	1767	2000-2007	Age, PSA, DRE, family history, prior malignancy	Extended (at least 12 cores)	66	Internal and external
Kawakami 2008 <sup>56</sup>	Japanese men, PSA 2.5-20 ng/mL, or abnormal DRE	1509	2000-2007	Age, DRE, PSA, fPSA, TRUS, prostate volume	Extended (at least 12 cores)	79	Internal and external
Nam 2007 <sup>57</sup>	Abnormal DRE or PSA >4 ng/mL	3108	1999-2005	Age, race, family history, symptom score, PSA, %fPSA, DRE	6-15 Cores	74	Internal

DRE indicates digital rectal examination; PSA, prostate-specific antigen; %fPSA, percentage free PSA; HGPIN, high-grade prostatic intraepithelial neoplasia; ASAP, atypical small acinar proliferation; TRUS, transrectal ultrasound; BPH, benign prostatic hyperplasia.

consistently reproducible, even within the same dataset. Each time a new training phase is performed, the computational model may yield different results because of random sampling. This contrasts with standard statistical analyses, in which only 1 outcome will be derived as long as the same test is performed on a particular dataset.

Another disadvantage to ANNs is their tendency to overfit data, which means that the computational software “learns” the training data too well, creating such tight associations between the various layers of that particular dataset that it is no longer generalizable to other datasets. Although there are ways to program an ANN to limit overfitting, this also contributes to its black-box quality and can make validation difficult.

Despite these drawbacks, ANNs do have some advantages over standard statistical analyses. They allow complex nonlinear relations between dependent and independent variables as well as between dependent variables, achieving a level of complexity that is problematic with most regression techniques. Also, they do not require assumption regarding normal distribution, potentially making them more useful for real-world application. And, although, their black-box qualities make them somewhat difficult for researchers to generate and test hypotheses, those qualities do not automatically make ANNs less useful as a predictive model per se. So long as the statistical parameters of accuracy, validity, and generalizability are fulfilled, there is no reason to discount ANNs just because their inner workings are not transparent.

Table 2 is a summary of ANNs in prostate cancer detection.<sup>56,62-82</sup> In 1994, Snow et al were the first investigators to use ANNs.<sup>73</sup> In a cohort of 1787 men who underwent screening with a PSA >4 ng/mL, they were able to achieve 87% accuracy by incorporating PSA kinetics. Subsequently, an ANN termed the proStAsure Index became commercially available.<sup>62,63</sup> This ANN used various isoforms of creatine kinase and prostatic acid phosphatase as its input variables, and their initial reported accuracy of 95% was extremely high. These results should be viewed with uncertainty, because the test cohort was designed retrospectively and included some men with known prostate cancer as controls. Indeed, a modification of this ANN did not perform as well when it was tested prospectively.<sup>62</sup>

Several subsequent trials were performed in screening populations with various results.<sup>65,67,81</sup> In a study of

only 212 men, Virtanen et al derived an ANN that performed less well than a logistic regression analysis developed from the same test cohort. Conversely, Horninger et al reported that their ANN provided from 150% to 200% increased specificity compared with established cutoff values for PSA and %fPSA. Each of those predictive models was limited, because their overall accuracy was not reported.

The first ANN that was used to predict prostate cancer after a negative biopsy was performed in 890 patients between 1997 and 2001. In that study, octant biopsies were performed in both the original biopsies and in repeat biopsies.<sup>72</sup> There was an overall accuracy of 83% with significantly improved specificity compared with a multivariate logistic regression analysis. Lee et al were the first to examine ANNs using only an extended biopsy pattern.<sup>68</sup> By using a cohort of 684 consecutive men who were undergoing biopsy for an abnormal DRE, PSA, or TRUS, those authors examined whether an ANN would perform better with or without ultrasound data and observed that TRUS information in fact did improve the accuracy of ANNs. Of course, the ideal predictive model would not require any input variable from invasive testing.

ANNs also have been used in a variety of studies investigating new markers in prostate cancer.<sup>76,78,82,83</sup> Stephan et al reported in a series of articles that the addition of human kallikrein-11, kallikrein-2, and pro-PSA can add to the predictive power of ANNs. It is important to note that those authors also observed that ANNs developed for 1 particular PSA assay do not fare as well when they are used for a different PSA assay.<sup>79,84</sup> Not only does this point out that ANNs suffer from the same problem of generalizability as all predictive models, but it also indicates that the black-box nature of ANNs makes it difficult to precisely determine why this is true.

### **The Cancer of Prostate Risk Index test, look-up tables, Bayesian modeling, and other predictive models**

Although nomograms and ANNs are the best known predictive models in the literature, a variety of others have shown promise as well and are summarized in Table 3. In 1997, Optenberg et al published a decision-making tool called the Cancer of Prostate Risk Index (CAPRI) test.<sup>85</sup> By using a model population of 633 white or black patients, they created a map of risk

**Table 2.** Summary of Artificial Neural Networks Predicting the Risk of Prostate Cancer

Reference	Training Cohort	Sample Size	Dates of Study	Input Variables	Type of Biopsy	Accuracy, %	Validation
Snow 1994 <sup>73</sup>	Screening population, PSA >4 ng/mL	1787	1989-1992	Age, max PSA, average PSA, DRE, TRUS, PSA kinetics	Not reported	87	Internal
Babaian 2000 <sup>62</sup>	PSA <4 ng/mL, with or without BPH, or patients with known diagnosis	225	1996	Age, PSA, prostatic acid phosphatase, CK-MM, CK-MB, CK-BB	Not reported	95	Internal
Virtanen 1999 <sup>81</sup>	Screening population ages 55-66 y, PSA >3 µg/L	212	Not reported	Age, total PSA, %fPSA, DRE, TRUS, family history	Not reported	Not reported	Internal
Finne 2000 <sup>65</sup>	Screening population ages 55-67 y, PSA 4-10 ng/mL	656	1996-1997	PSA, %fPSA, prostate volume, DRE	Sextant	Not reported	Internal
Babaian 1998 <sup>63</sup>	Screening population, PSA 2.5-4 ng/mL	151	1998-1999	Age, PSA, prostatic acid phosphatase, CK, free PSA	11 Cores	74	Internal
Horninger 2001 <sup>67</sup>	Screening population, PSA >4ng/mL	3474	1993-1997	Age, PSA, %fPSA, DRE, prostate volume, PSAD, TZ volume, TZ PSAD	Not reported	Not reported	Internal
Porter 2002 <sup>71</sup>	Patients undergoing biopsy	319	1999-2001	Age, PSA, prostate volume, TRUS, DRE, prior negative biopsy, race	Mixed sextant and extended	77	Internal
Stephan 2002 <sup>75</sup>	Abnormal DRE, PSA, or urologic symptoms	1188	1996-2001	Age, PSA, %fPSA, prostate volume, DRE	Sextant or octant	80-82	Internal
Djavan 2002 <sup>64</sup>	Screening population	1246	1997-2000	PSA, %fPSA, PSA velocity, PSAD, PSA-TZ, TZ volume	Sextant or octant	87-91	Internal
Remzi 2003 <sup>72</sup>	PSA 4-10 ng/mL, prior negative biopsy	890	1997-2001	PSA, %fPSA, prostate volume, TZ volume, PSAD, PSA-TZ	Octant	83	Not reported
Matsui 2004 <sup>69</sup>	Japanese screening population or urologic symptoms, PSA 2-10 ng/mL	228	2000-2002	Age, PSA, %fPSA, prostate volume, TZ volume, PSAD, PSA-TZ, DRE, LUTS	10 Cores or 12 cores	79	Internal
Finne 2004 <sup>66</sup>	Screening population ages 55-67 y, PSA 4-10 µg/L	1775	1991-1999	PSA, %fPSA, prostate volume, DRE, age	Sextant	76	Internal
Stephan 2005 <sup>76</sup>	Abnormal DRE, PSA, or urologic symptoms	475	Not reported	PSA, %fPSA, hK2, hK2/fPSA, hK2/%fPSA	Sextant or octant	Not reported	Internal
Porter 2005 <sup>70</sup>	Screening population	3814	1993-2001	Age, PSA, prostate volume, PSAD, DRE, TRUS	Sextant	77	Internal and external
Stephan 2006 <sup>83</sup>	Abnormal DRE, PSA, or urologic symptoms	288	1998-2002	Age, PSA, %fPSA, prostate volume, MIC-1, hK11, MIF	Sextant or octant	91	Internal
Lee 2006 <sup>68</sup>	Abnormal DRE, PSA, or TRUS	684	2003-2005	Age, DRE, PSA, PSAD, TZ volume, PSA-TZ, TRUS	Extended (at least 12 cores)	80-89	Internal
Stephan 2006 <sup>77</sup>	Abnormal DRE, PSA, or urologic symptoms	357	1998-2002	Age, PSA, %fPSA, hK11	Sextant or octant	85	Not reported
Stephan 2006 <sup>78</sup>	Mixed screened and nonscreened population, PSA1-10 µg/L	898	1999-2004	Age, PSA, %fPSA, prostate volume, DRE, proPSA, profPSA	Mixed sextant or extended	86	Internal
Stephan 2007 <sup>79</sup>	Mixed screened and nonscreened, PSA 2-10 ng/mL	4480	Not reported	Age, PSA, %fPSA, prostate volume, DRE	Mixed sextant or extended	65-93	Internal

(Continued)

Table 2. (Continued)

Reference	Training Cohort	Sample Size	Dates of Study	Input Variables	Type of Biopsy	Accuracy, %	Validation
Stephan 2007 <sup>80</sup>	Mixed screened and nonscreened, PSA 4-10 ng/mL	1262	1996-2001	Age, PSA, %fPSA, prostate volume, DRE	Sextant or octant	75-85	Internal and external
Stephan 2008 <sup>84</sup>	Mixed screened and nonscreened,	780	2001-2004	Age, PSA, %fPSA, prostate volume, DRE	Sextant or octant	88-91	Internal
Kawakami 2008 <sup>86</sup>	Japanese men, PSA 2.5-20 ng/mL, or abnormal DRE	1509	2000-2007	Age, DRE, PSA, fPSA, TRUS, prostate volume	Extended (at least 12 cores)	75	Internal and external
Stephan 2008 <sup>74</sup>	Patients undergoing biopsy	199	1996-2006	Age, PSA, PSAV, fPSA, DRE, prostate volume, ANNV	Sextant or octant	56	Internal
Stephan 2009 <sup>82</sup>	Patients undergoing biopsy or BPH surgery	586	2002-2006	Age, PSA, %fPSA, %p2PSA	8-12 Cores	85	Internal

PSA indicates prostate-specific antigen; DRE, digital rectal examination; TRUS, transrectal ultrasound; BPH, benign prostatic hyperplasia; CK, creatine kinase; CK-MM, creatine kinase isoenzyme with 2 muscle subunits; CK-MB, creatine kinase isoenzyme with 1 muscle subunit and 1 brain subunit; CK-BB, creatine kinase isoenzyme with 2 brain subunits; %fPSA, percentage free PSA; PSA, PSA density; TZ, transition zone; LUTS, lower urinary tract symptoms; hK2, human glandular kallikrein 2; MIC-1, macrophage inhibitory cytokine 1; hK11, human kallikrein 11; MIF, macrophage migration inhibitory factor; proPSA, the "pro-cancer" form of PSA; fPSA, free PSA; proPSA, zymogen precursor of PSA; ANNV, artificial neural network velocity; %p2PSA, percentage [-2]proPSA.

contours with the patient's age on the x-axis and his PSA level on the y-axis. The validity of the model was tested on a completely different set of 766 white or black patients at a separate institution in a different geographic location. The AUC was 0.81 in the model population and 0.76 in the validating population, which was an interesting finding because that there were several statistical differences between the 2 groups, including ethnic make-up, PSA level, and age. Although a software package that included the CAPRI test was made available to physicians, to our knowledge, there are no additional studies reported in the literature, and this model should be considered investigational.

In addition to the ANNs described above, several other advanced computational models have been used to predict the likelihood of prostate cancer. Kalra et al developed a neurocomputational model that achieved 82.5% accuracy.<sup>86</sup> A separate study used a combination of ANNs and a separate type of computational modeling termed fuzzy logic.<sup>87</sup> Although the population studied was not a screening population, the "neuro-fuzzy" system still was able to perform with an accuracy of 80%, and it had the highest specificity of any of the tests, including PSA and %fPSA.

Other statistical models also are possible.<sup>88</sup> Look-up tables have been well known in the urologic literature since the publication of the so-called Partin tables in 1997, which helped predict pathologic staging.<sup>89</sup> The same group created a look-up table using age, PSA, and %fPSA.<sup>90</sup> Risk tables have the downside of categorizing a heterogeneous group of men into potentially oversimplified groups and are not able to predict an individual's risk of a particular outcome.<sup>91,92</sup> Conversely, they are relatively easy to use and incorporate into clinical practice. A variation of a look-up table was published in 2006 using data from the Prostate Cancer Prevention Trial.<sup>93</sup> Instead of a table, the investigators used line graphs. They also used their risk formula to create an online risk calculator, which subsequently was validated externally.<sup>39,94,95</sup> The addition of PCA3, a novel biomarker, improved the diagnostic accuracy of this model from 65% to 69%.<sup>96</sup>

Bayesian modeling represents an alternative form of statistics that uses pretest probabilities to inform post-test decisions. One advantage of this technique is that it does not require assumptions concerning normal distribution. Although this method has not yet been applied to prostate

**Table 3.** Summary of Other Predictive Models in Prostate Cancer Detection

Study	Study Cohort	Sample Size	Dates of Study	Type of Predictive Model	Input Variables	Type of Biopsy	Accuracy, %	Validation
Optenberg 1997 <sup>85</sup>	Suspicion for prostate cancer	633	1991-1995	Multiple logistic regression	PSA, PSA <sup>2</sup> , DRE, race, age at biopsy	Not reported	81	External
Kalra 2003 <sup>86</sup>	PSA >4 ng/mL or abnormal DRE	218	Not reported	Neural computational	Age, race, family history, urologic symptoms, DRE, PSA, complexed PSA	Mixed (at least 6 cores)	83	Internal
Beneccchi 2006 <sup>87</sup>	Urologic symptoms, abnormal PSA or DRE	1030	2002-2005	Neurofuzzy inference system model	Age, PSA, %fPSA	Mixed sextant or extended	80	Internal
Thompson 2006 <sup>93</sup>	Age ≥55 y, initially normal DRE, PSA <3 ng/mL	5519	1994-2003	Logistic regression	Age, family history, DRE, PSA	At least 6 cores	70	Internal
Parekh 2006 <sup>94</sup>	External validation of [39]	446	2000-2008	Logistic regression	Age, family history, DRE, PSA	Not specified	65	Internal
Hernandez 2008 <sup>95</sup>	Men undergoing biopsy	1108	1995-2001	External validation of [39], logistic regression	Age, family history, DRE, PSA	At least 6 cores	67	Internal
Ankerst 2008 <sup>96</sup>	Men undergoing biopsy	521	Not specified	Logistic regression	Age, family history, DRE, PSA, PCA3	At least 6 cores	70	Internal and external
Carlson 1998 <sup>90</sup>	PSA 4-20 ng/mL	3773	1995-1996	Logistic regression	Age, PSA, %fPSA	Sextant	Not reported	

PSA indicates prostate-specific antigen; PSA<sup>2</sup>, prostate-specific antigen squared; DRE, digital rectal examination; %fPSA, percentage free PSA; PCA3, prostate cancer gene 3.

cancer detection, it has shown promise in other areas of research, including risk assessment in pancreatic cancer.<sup>97,98</sup> There still are other predictive models that have been described, including continuous-time state transition methods, stochastic microsimulation, classification and regression trees, and group methods of data handling, among others.<sup>88,98-100</sup> Although these remain promising predictive tools, they have not yet been applied to prostate cancer detection. The same performance characteristics, including accuracy, calibration, and validation, should be considered when assessing each of these models.

### Future Directions

Since its inception, PSA has been problematic as a test to detect prostate cancer. Its inherent lack of specificity has led to many unnecessary biopsies and to the possible over treatment of indolent cancers.<sup>101</sup> Nonetheless, its use in the United States clearly led to a significant rise in prostate cancer incidence in the early 1990s, and it continues to be the main driver of decisions to proceed with biopsy. Whether or not this has decreased disease-specific mortality has not been determined, and the results of 2 trials examining the utility of screening are eagerly awaited.<sup>102-104</sup> In the meantime, attempts to refine PSA by using PSAD, PSAV, or PSA isoforms have met with limited success and have not been evaluated in prospective trials.

Predictive modeling using statistical and computational methods attempts to compensate for these shortcomings. Each technique comes with inherent strengths and weaknesses, and increasing accuracy often comes at the cost of increasing complexity and difficulty of use, limiting their clinical utility. It is not known how often these models actually are incorporated into practice, although at least some online tools appear to be well used.<sup>105</sup> The widespread acceptance of PSA screening in the United States has led to a distinct change in the population characteristics of the men who undergo testing. This mandates a frequent re-examination of the various predictive models to ensure their continued accuracy.

An intriguing development in prostate cancer detection is the advent of several novel biomarkers.<sup>106-108</sup> Although they were outside the scope of this review, these new tests may be more specific for prostate cancer than PSA.<sup>109,110</sup> Thus, even if they are not able to act as screening tests in isolation, their addition to current predictive

models could prove very useful. Whether or not all prostate cancer requires immediate therapy is another important question. It is not known whether the treatment of "indolent" cancers can be delayed.<sup>111-113</sup> If these tumors truly are not clinically meaningful, then new predictive models should attempt to diagnose only those cancers that will affect a patient's life.

At this point, it is not clear which is the best predictive model or even which methodology is better. Direct comparisons of nomograms and ANNs have produced conflicting results.<sup>56,114,115</sup> Also, the abundance of predictive models without significant improvement in predictive accuracy limits their overall usefulness. Future work in this area should focus on prospectively evaluating the clinical utility of these models in real-world situations in terms of both cancer detection and improvements in patient understanding and decision making.

In the interim, predictive models for prostate cancer detection are critical components in the clinical repertoire of urologists and other physicians involved in men's health. It is vital for physicians to understand the principles as well as the strengths and weaknesses that underlie these models. By using them, physicians can better advise men about their risk of prostate cancer and the important decision regarding whether or not to proceed with a biopsy. Risk stratification using predictive models also can be useful for clinical trial design and enrollment. We believe that the ideal predictive technique should achieve the following goals: Detect all cancers in young men, clinically significant cancers in all men, and aggressive cancer in older men while limiting unnecessary biopsies and over detection of insignificant cancers. Until these goals are met, patients should be fully advised regarding their options before proceeding with biopsy.

### Conflict of Interest Disclosures

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