

Predictive Models for Newly Diagnosed Prostate Cancer Patients

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Accurate risk assessment is of paramount importance to newly diagnosed prostate cancer patients and their physicians. Risk prediction models help identify those at high (or low) risk of disease progression and guide discussions about prognosis and treatment. Widely used, well-validated prediction tools are based on standard, readily available clinical and pathologic parameters, but do not include biomarkers, some of which may have an important role in predicting prognosis or determining therapeutic options. A new approach, known as systems pathology, may improve the accuracy of traditional prediction methods and provide patients with a more personalized risk assessment of clinically relevant outcomes. The ultimate goal of prediction models is to improve medical decision making.

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Prostate cancer remains the most common solid organ malignancy in American men, with over 186,000 new cases diagnosed in 2008 and an estimated 28,000 deaths.¹ With the widespread use of prostate-specific antigen (PSA) screening in the 1990s, there has been a dramatic stage migration for prostate cancer, with more patients diagnosed at earlier clinical stages and lower serum PSA values. Because of enhanced screening, the number of clinically insignificant prostate cancers diagnosed has increased, and, as a result, there is rising concern over treatment of such cancers.

The recent European and American prostate cancer screening trials reported in the *New England Journal of Medicine* provide new insights into cancer screening and the associated overdiagnosis and overtreatment of clinically insignificant tumors.^{2,3} According to data from the European Randomized Study of Screening for Prostate Cancer, 48 cases of prostate

Currently there is a host of prostate cancer prediction tools to gauge the risk of specified oncologic outcomes available for use in clinical practice. Multiple prediction methods were developed for use in the posttreatment setting to estimate the risk of PSA recurrence or disease progression after definitive treatment (radical prostatectomy or radiation therapy).

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cancer need to be treated to prevent a single death from prostate cancer within 10 to 12 years.³ Clearly, we are in need of better tools for risk assessment of newly diagnosed prostate cancer patients, enabling physicians to focus treatment efforts on those most likely to benefit from aggressive therapy.

Risk estimation from such posttreatment prediction tools typically relies heavily on PSA, pathologic Gleason score, and detailed pathologic stage information available after radical prostatectomy (eg, surgical margin status, presence of extracapsular extension, and seminal vesicle or lymph node involvement). Other prediction

tools are available for use in the pre-treatment setting, allowing for risk assessment in newly diagnosed prostate cancer patients contemplating treatment options. These prediction tools also primarily rely on PSA, Gleason score, and clinical stage to estimate risk, but lack the detailed pathologic variables accounted for in most posttreatment models. Risk categorization, probability tables, risk scores, and nomograms are some examples of widely used risk analysis methods (Table 1). These risk estimators use clinical and pathologic features and do not account for novel molecular biomarkers or genomic variants that may contribute to improved predictive accuracy.

This article reviews the value of select traditional predictive tools for guiding treatment decisions and prognosis discussions in patients with clinically localized prostate cancer, and discusses the role of novel predictive

Table 1
Tools for Risk Estimation in Newly Diagnosed Prostate Cancer Patients

Tool	Description	Example
Risk categories	Uses categorized clinical and pathologic variables to separate patients into broad risk groups	D'Amico risk groups ⁴⁻⁶ (low, intermediate, or high risk of BCR)
Probability tables	Shares some features of risk categories and nomograms; uses categorized clinical and pathologic predictor variables to calculate the probability of specified outcomes	Partin tables ¹¹⁻¹³ (probability of organ-confined cancer, extracapsular extension, seminal vesicle, or lymph node involvement)
Risk score	Similar to risk categories, but also incorporates % of positive biopsy cores and age; more personalized risk assessment compared with risk groups	UCSF-CAPRA score ^{14,15} (risk score 1-10, denoting different probabilities of recurrence)
Nomograms	Most widely used risk prediction tools; calculate probability of event based on continuous and categorical input; most individualized risk assessment compared with risk groups, scores, or probability tables	Kattan nomograms ^{20-22,30,31} (probability of 5- and 10-year freedom from BCR; indolent cancer or pathologic stage)
Systems pathology	Combines common clinical and pathologic parameters with quantitative tissue morphology and biomarkers obtained through advance imaging analysis	Prostate Px [®] ³⁴ (probability of clinical failure or favorable pathology/indolent disease)

BCR, biochemical recurrence; UCSF-CAPRA, University of California, San Francisco-Cancer of the Prostate Risk Assessment. Prostate Px[®], Aureon Laboratories, Yonkers, NY.

tools utilizing systems pathology and genomic analyses.

Risk Categories

A straightforward and logical way for clinicians to estimate risk of disease recurrence after treatment is to stratify patients into distinct risk categories. In the pretreatment setting, this approach is attractive for many physicians, as they can easily categorize patients based on a few ubiquitous clinical parameters. The most widely used risk grouping system was developed by D'Amico and colleagues,⁴⁻⁶ where men with localized prostate cancer are grouped into categories according to whether their risk of biochemical recurrence (BCR) after definitive treatment was low, intermediate, or high. Patients are primarily stratified according to their biopsy Gleason score, serum PSA level, and clinical stage, and defined as: (1) *low risk*, clinical stage T1c and T2a, PSA level ≤ 10 ng/mL, and biopsy Gleason score ≤ 6 ; (2) *intermediate risk*, clinical stage T2b or biopsy Gleason score of 7 or PSA level > 10 and ≤ 20 ng/mL; (3) *high risk*, clinical stage \geq T2c or PSA level > 20 ng/mL or biopsy Gleason score ≥ 8 . Note that a patient must meet all 3 criteria to be included in the low-risk group, but any 1 criterion can move him to a higher risk group. The American Urological Association (AUA) has incorporated D'Amico's risk groups into their most recent prostate cancer clinical guidelines.⁷

Another example of pretreatment risk categorization is described by Zelefsky and colleagues. Patients are divided into favorable, intermediate, and unfavorable prognostic groups based on whether PSA is ≤ 10 ng/mL, clinical stage \leq T2, and Gleason sum ≤ 6 .⁸ If all 3 conditions are met, the patient is considered to have a favorable prognosis. If 1 of the conditions

is not met, then the patient falls into the intermediate group, and if 2 or 3 are unmet, then an unfavorable prognosis is assigned. The National Comprehensive Cancer Network (NCCN) adopted a modified version of Zelefsky's and D'Amico's risk grouping systems for their prostate cancer clinical practice guidelines.⁹ The NCCN guidelines panel recommends risk stratification incorporating "available predictive features included in the guidelines, risk tables, and nomograms when discussing options for the treatment of clinically localized prostate cancer."⁹

The enthusiasm for risk groupings is primarily a result of their ease of application, but this enthusiasm

advising newly diagnosed prostate cancer patients.

Probability Tables

Created in 1997 and updated in 2001 and 2007, the Partin¹¹⁻¹³ tables are the most well-known and widely used probability tables in urology. Using PSA value, Gleason score, and clinical stage, these probability tables separately predict the likelihood of organ-confined disease, extracapsular extension, seminal vesicle, or lymph node involvement. The Partin tables were originally based on the pathologic findings of over 4000 patients who underwent radical prostatectomy at 1 of 3 different academic institutions from 1982 through 1996.

The enthusiasm for risk groupings is primarily a result of their ease of application, but this enthusiasm should be tempered by the loss of predictive power associated with collapsing variables into broad categories.

should be tempered by the loss of predictive power associated with collapsing variables into broad categories. For example, when 2 newly diagnosed prostate cancer patients are classified as intermediate risk according to D'Amico's grouping strategy, one assumes they are at equal risk of disease recurrence after treatment. In fact, patients within each of the 3 risk groups are a heterogeneous group and the individual risk may vary widely.¹⁰ Additionally, the clinical variables used to assign risk groups are weighted equally in their potential to result in a given outcome, when 1 variable (eg, grade) may have a much greater effect on prognosis than another (eg, stage). Inappropriate weighting results in a mixture of patients with very different individualized risks of recurrence all lumped into a broad category. Despite their limitations, many clinicians continue to rely on these methods of risk characterization when

Like risk grouping, probability tables are relatively easy to understand and use, and they have been widely validated. However, their ease of use does not come without a cost. By collapsing data such as PSA and Gleason score into broad categories, the Partin tables lose some of their predictive accuracy for the 4 pathologic outcomes described above. Therefore, risk estimates are not as personalized as they could be, and instead are more akin to the low-, intermediate-, and high-risk categories discussed earlier. Additional drawbacks to the use of probability tables include the fact that they only predict pathologic stage and not prognosis. The pathologic outcome predictions are mutually exclusive; the Partin table-predicted probability of extracapsular extension is too low because those with seminal vesicle or lymph node involvement and extracapsular extension are excluded. Lastly, the tables do not use quantitative biopsy results, and there

is no way to estimate location of extracapsular extension, which would be helpful in surgical planning.

Risk Score

Investigators from the University of California, San Francisco (UCSF) developed a novel risk assessment tool that provided more detailed risk prediction than the previous 3-level risk categories.¹⁴ Known as the UCSF-Cancer of the Prostate Risk Assessment (CAPRA) score, it predicts cancer recurrence after radical prostatectomy based on PSA, biopsy Gleason score, clinical T stage, percentage of positive biopsy cores, and age. The UCSF-CAPRA prediction index was derived from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) data and validated in an independent cohort that showed accurate preoperative prediction of cancer recurrence.¹⁵ All input variables are categorized and weighted according to their predictive power. As with risk categories, some of the predictive ability of the input variables is lost after collapsing them into categories, but the effect is less with this scoring system compared with D'Amico's groupings because more categories are allowed (eg, D'Amico's system incorporates 3 PSA categories vs 5 PSA categories used by the UCSF-CAPRA score). The UCSF-CAPRA score ranges from 0 through 10, and the risk of recurrence roughly doubles per 2-point increase (Table 2).

Nomograms

Using traditional statistical methods, nomograms are graphical devices that allow for the approximate calculation of a given function. In medicine, that function tends to be the probability of a certain endpoint based on specified predictor variables. The number of available prostate cancer prediction nomograms can be overwhelming for the practicing physician. There seems

to be a nomogram for every possible clinical setting and endpoint. For example, there are multiple tools for predicting cancer prevalence at the time of prostate biopsy.¹⁶⁻¹⁸ Other tools allow risk assessment after diagnosis, but prior to treatment; they predict outcomes like pathologic stage, pathologic Gleason sum, BCR, or prostate cancer-specific-mortality after various treatment options.¹⁹⁻²⁶ Additionally, there are prediction models for the

posttreatment setting, providing risk information about important clinical endpoints (eg, BCR, metastasis, or survival).²⁷⁻²⁹ Useful prediction models, regardless of the clinical setting and outcome of interest, must be accurate, easy to use, generalizable, and have strong performance characteristics. For the purposes of this review, we focus primarily on nomograms predicting prostate cancer outcomes in the pretreatment setting.

Table 2
Scoring System for the UCSF-CAPRA Risk Score Prediction Tool
With Corresponding 5-Year Recurrence-Free Survival
Estimates According to Score

<u>I. PSA</u>		<u>II. Gleason Score</u>	
2.1-6.0 = 0		1-3/1-3 = 0	
6.1-10 = 1		1-3/4-5 = 1	
10.1-20 = 2		4-5/1-5 = 3	
20.1-30 = 3			
>30 = 4			
<u>III. Clinical T Stage</u>			
T1/T2 = 0			
T3a = 1			
<u>IV. % Positive Biopsies</u>		<u>V. Age</u>	
<34% = 0		<50 years = 0	
≥34% = 1		≥50 years = 1	
UCSF-CAPRA Score		5-Year Recurrence-Free Survival Estimate (95% CI)	
0-1 points		85% (73-92)	
2 points		81% (69-89)	
3 points		66% (54-76)	
4 points		59% (40-74)	
5 points		60% (37-77)	
6 points		34% (12-57)	
≥ 7 points		8% (0-28)	

PSA, prostate specific antigen; UCSF-CAPRA, University of California, San Francisco-Cancer of the Prostate Risk Assessment.

A point value from each of the 5 categories is summed to calculate the CAPRA score. Scores range from 0-10.

Recurrence defined as PSA ≥ 0.2 ng/mL on 2 consecutive postprostatectomy measurements or a 2nd cancer treatment > 6 months after prostatectomy.

Adapted with permission from *The Journal of Urology*, Vol 173, Cooperberg MR et al., "The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy," pp. 1938-1942, Copyright 2005, with permission from the American Urological Association.¹⁴

Unlike probability tables, risk scores, or risk groupings where predictor variables must be collapsed into categories, predictors can be incorporated into nomograms as continuous variables. The full original value of the predictor variable is preserved, leading to improved risk estimation. The different weight given to each variable can be adjusted to fit the data. As a result, nomograms provide individualized risk prediction for newly diagnosed prostate cancer patients.

A preoperative prostate cancer risk assessment nomogram developed by Kattan and colleagues in 1998 and last updated in 2009 now estimates the 10-year freedom from BCR.^{20,22} Figure 1 demonstrates the updated nomogram where surgeon experience is factored along with PSA, clinical stage, and Gleason score. Points are summed for each of the parameters and then equated to a PSA recur-

rence-free probability. The graphical nature of nomograms facilitates their clinical use and interpretation. Kattan and colleagues also developed nomograms predicting the probability of newly diagnosed prostate cancer patients harboring clinically insignificant disease, as well as those to predict pathologic stage.^{21,30,31} Useful websites are available where multiple predictor values can be entered and precise risk calculations made based on easy-to-use, freely available computerized versions of these nomograms (Table 3).

Comparing Risk Prediction Methods

With so many decision aids available for use, how do clinicians choose? Prediction tools should be judged on their accuracy in a given patient population, usability, and generalizability. *Usability* refers to how user-friendly a prediction tool is in the

clinic. Accuracy can be measured using a concordance index (CI) or area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and the hazard ratio. These are similar statistically derived values used to describe the discriminatory ability (accuracy) of a test or model. Simply stated, the CI represents the probability of concordance between predicted and observed events. Likewise, the AUC measures the ability of a test to correctly differentiate between those with or without a condition. Whether prediction models are assessed using CI or AUC is dependent on the outcome predicted by the model. Models predicting time-to-event outcomes are evaluated via a CI, whereas models predicting a binary outcome use AUC. The range of values for both CI and AUC is from 0.5 to 1, with 1 being perfect discrimination and 0.5 being equal to a coin flip or random chance. These values can be used to directly compare the performance of different prediction models on a common dataset; the more accurate prediction tool in terms of discrimination will have the higher CI or AUC.

Systems Pathology

Unfortunately, none of the above prediction methods for a prostate cancer-related endpoint is perfect, largely because the input variables are not sufficiently informative and/or reproducible. For example, Gleason score, which is a heavily weighted predictor factored into most risk assessment models, is determined by the subjective interpretation of the microscopic morphology of prostate glands by a single pathologist. This amount of subjectivity naturally results in significant variability in outcome predictions.

Systems pathology is a novel multidisciplinary methodology created to eliminate the subjectivity inherent in

Figure 1. Preoperative nomogram predicting 10-year freedom from biochemical recurrence for use in patients who have chosen radical prostatectomy. Reprinted with permission from Kattan MW et al.²²

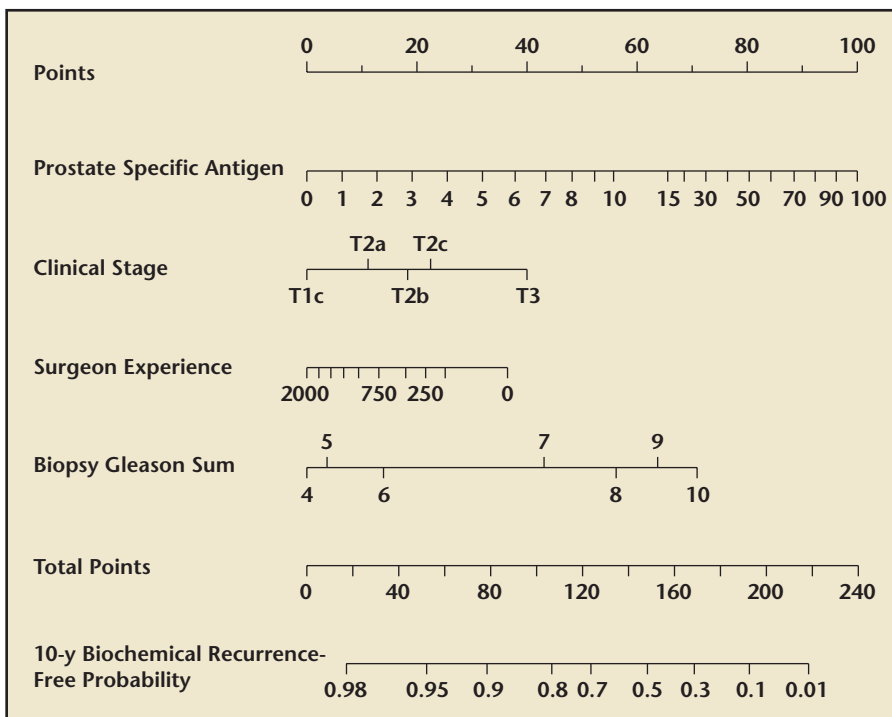


Table 3
Web-Based Resources for Pretreatment Personalized
Prostate Cancer Risk Estimation

Probability Tables
http://urology.jhu.edu/prostate/partintables.php
Nomograms
http://www.mskcc.org/applications/nomograms/prostate/
Prostate Px⊕
http://www.aureon.com/prognostic-tests-prostate-px.htm
Prostate Px [®] ⊕, Aureon Laboratories, Yonkers, NY.

how pathologists currently evaluate the morphologic and molecular characteristics of tumor specimens.^{32,33} Systems pathology strives to replace subjective analyses with quantitative ones to increase the accuracy of

Pretreatment Setting
Using a systems pathology platform similar to that developed for post-prostatectomy outcome predictions, Aureon Laboratories developed Prostate Px[®]⊕, a test focusing on risk

Systems pathology strives to replace subjective analyses with quantitative ones to increase the accuracy of current prediction tools used in prostate cancer and other diseases.

current prediction tools used in prostate cancer and other diseases. Through machine learning (specifically support vector regression for censored data), the systems pathology approach was used to create several new prostate cancer prediction models by Aureon Laboratories (Yonkers, NY). The new prediction tools involve the use of standard clinical and pathologic features combined with advanced image analysis techniques that allow for the quantitation of biomarkers using immunofluorescence or immunohistochemistry and quantitation of specific microanatomic cellular characteristics. This new prediction approach fuses clinicopathologic features with state-of-the-art molecular and cellular markers utilizing advanced image analysis and artificial intelligence (Figure 2).

assessment in the newly diagnosed prostate cancer patient (prior to treatment). By combining clinical parameters with comprehensive

molecular and microanatomical image analyses of prostate core biopsy tissue, Prostate Px⊕ provides physicians and patients with personalized outcome predictions to aid in treatment decision making. The goal of this technology is to increase the predictive accuracy of the typical pretreatment risk assessment methods currently in use that may be limited by only factoring in clinicopathologic variables.

Under the direction of Aureon Laboratories, a multi-institutional group developed and validated this pretreatment prediction model.³⁴ The model used 3 clinicopathologic variables, 1 biomarker variable, and 2 advanced imaging features from the biopsy tissue. It predicted clinical failure (as defined earlier) within 8 years of radical prostatectomy. Table 4 specifies the variables included in the pretreatment model predicting clinical failure. The model was validated on an independent cohort of patients and yielded a concordance index of 0.73. Within their validation cohort, Donovan and colleagues compared the performance of their systems pathology-based model with the Kattan 5- and 10-year BCR nomograms and found, in addition to a slightly higher concordance

Figure 2. Overview of the systems pathology approach to risk prediction.

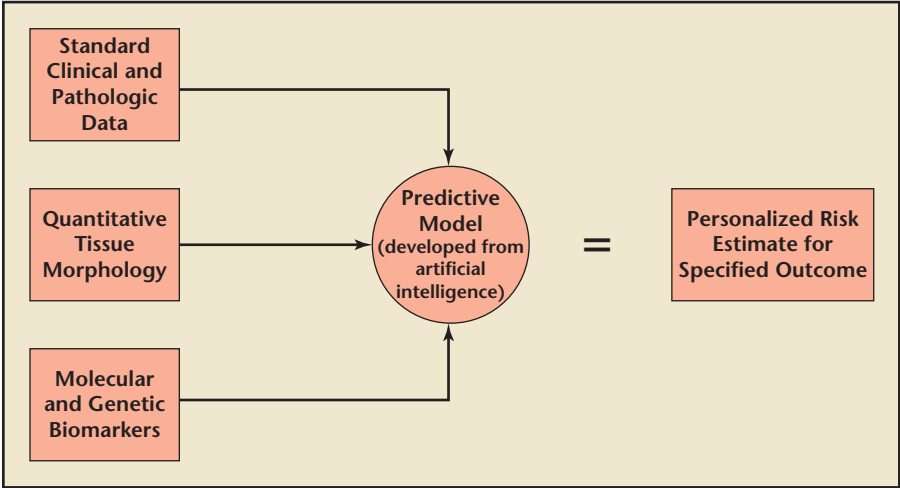


Table 4
Variables Included in Pretreatment Prediction Model for Clinical Failure Based on Systems Pathology Platform (in Order of Weighted Significance)

Clinical/Pathologic Variables

Preoperative PSA

Dominant Gleason grade

Biopsy Gleason score

Biomarker Variable

Combined androgen receptor dynamic range at dominant Gleason grade ≤ 3 , total Ki-67 at dominant Gleason grade > 3

Advanced Imaging Variables

Combined mean distance between epithelial tumor cells at dominant Gleason grade ≤ 3 , actual grade at dominant Gleason grade > 3

Area of isolated (non-lumen associated) tumor epithelial cells relative to total tumor area

PSA, prostate-specific antigen.

Data from Donovan et al.³⁴

Table 5
Variables Included in Pretreatment Prediction Model for Favorable Pathology Based on Systems Pathology Platform (in Order of Weighted Significance)

Clinical/Pathologic Variables

Preoperative PSA

Biopsy Gleason score

Advanced Imaging Variables

Area of isolated (non-lumen associated) tumor epithelial nuclei relative to total tumor area

Area of epithelial nuclei with differential distance from gland lumens relative to total tumor area

Biomarker Variable

Combined androgen receptor dynamic range at dominant Gleason grade ≤ 3 , total Ki-67 at dominant Gleason grade > 3

PSA, prostate-specific antigen.

Data from Donovan et al.³⁴

index for the systems pathology model (0.73 vs 0.69), the systems approach was twice as sensitive as the Kattan nomogram in identifying patients initially designated by the AUA classification as intermediate risk who were actually high risk, that is, who developed clinical recurrence within 8 years.³³

Also included in the Prostate Px \oplus test is another pretreatment model developed by the same authors and recently reported in the *Journal of Urology*.³⁴ This model predicts indolent disease, defined by favorable pathology at the time of radical prostatectomy. They specified favorable pathology to include: (1) pathologic T stage ≤ 2 ; (2) pathologic Gleason score ≤ 6 (no Gleason 4 or 5 pattern); (3) an undetectable PSA (≤ 0.2 ng/mL). This model uses 5 predictors, 4 of which overlap with the clinical failure model described above. The differing variable is associated with tumor differentiation and is measured using specialized hematoxylin and eosin-stained image analysis, specifically measuring tumor epithelial nuclei area within a certain distance from gland lumens. Table 5 outlines the variables analyzed in the favorable pathology model. Validation studies showed this prediction tool to be accurate, with an AUC of 0.74.

The combining of the 2 pretreatment prostate cancer prediction models developed through the systems pathology approach provides a new risk assessment method that can be used when counseling newly diagnosed prostate cancer patients. It is hoped that with the discovery of more informative biomarkers, all patients and physicians will benefit from improved risk prediction accuracy.

Genomic Advances

Genomic and proteomic studies are likely to yield exciting new biomarkers to help distinguish clinically significant prostate cancers from

Table 6
Top 10 Most Frequently Selected Genes in
Leave-One-Out-Cross-Validation of Combined Modeling Approach

Gene Symbol	Gene Title	Models*	Mean Expression in Recurrent Tumors
<i>EI24</i>	Etoposide-induced 2.4 mRNA	79	Overexpressed
<i>EPB49</i>	Erythrocyte membrane protein band 4.9	78	Underexpressed
<i>MAP4K4</i>	Mitogen-activated protein kinase kinase kinase 4	78	Overexpressed
<i>GMCL</i>	Germ cell-loss homolog (<i>Drosophila</i>)	50	Overexpressed
<i>HNRPC</i>	Heterogeneous nuclear ribonucleoprotein C (C1/C2)	22	Overexpressed
<i>PCOLN3</i>	Procollagen (type III) N-endopeptidase	22	Underexpressed
<i>SIL</i>	TAL1 (SCL) interrupting locus	21	Overexpressed
<i>APP</i>	Amyloid beta (A4) precursor protein	20	Overexpressed
<i>SSRI</i>	Signal sequence receptor, alpha	13	Overexpressed
<i>BTF</i>	Bcl-2-associated transcription factor	9	Overexpressed

*Number of models in which variable was selected.

Reprinted with permission from Stephenson AJ et al.⁴⁰

those that pose little threat to their host. A systems pathology platform allows the integration of such markers into clinical risk assessment tools. Recently, expression array analyses have identified common somatic mutations in prostate cancer that may have prognostic value. The most common example is the fusion of the androgen responsive transmembrane protease serine 2 (TMPRSS2) gene with the erythroblast-transformation specific (ETS) gene (eg, ERG, ETV1, or ETV4) discovered by Tomlins and colleagues.³⁵ In some studies the TMPRSS2:ERG fusion has been associated with more aggressive prostate cancer and poor prognosis,³⁶ whereas other reports question its clinical prognostic capabilities.³⁷ More research is needed to better define its role in clinical practice, but the TMPRSS2:ERG fusion certainly represents an exciting new genetic marker.

In an attempt to provide prognostic information to prostate cancer patients beyond what is available from well-established clinical and patho-

logic variables, prediction models based on multiple gene signatures have been created. For example, Cheville and colleagues developed a multivariable model for the post-prostatectomy setting to distinguish men who develop systemic progression from those who do not by accounting for gene expression of topoisomerase-2a, cadherin-10, predicted TMPRSS2 (ERG, ETV1, or ETV4) fusion status, and aneuploidy.³⁸ In validation studies, this model yielded an AUC of 0.79. Likewise, Glinksy and colleagues were able to accurately predict biochemical recurrence in the posttreatment setting using a predictive algorithm of gene signatures.³⁹ Combining gene expression signatures with traditional clinical and pathologic variables may create even more accurate prostate cancer recurrence prediction models. Stephenson and coworkers used such a combined modeling approach, integrating multiple prognostic gene markers with Kattan's postoperative nomogram to correctly classify recurrence status in

89% of prostate cancer specimens (concordance index, 0.89).⁴⁰ Table 6 shows the 10 most frequently used genes in the combined modeling approach, and Figure 3 depicts the probability of BCR for men classified as nonrecurrent versus recurrent by this combined model.⁴⁰ Based on certain gene expression patterns, Febbo and Sellers were also able to separate patients into recurrent and nonrecurrent groups.⁴¹

Currently available prostate cancer risk prediction tools incorporating novel genetic markers are only available for the posttreatment setting. Their translation into the pretreatment arena has been slow and will continue to be difficult because of the limited tumor tissue provided by a transrectal biopsy for advanced genetic or proteomic analyses. Nonetheless, the future of risk prediction methods in prostate cancer will most likely involve the thoughtful combination of well-established clinical and pathologic features with novel cellular, molecular, and genetic biomarkers.

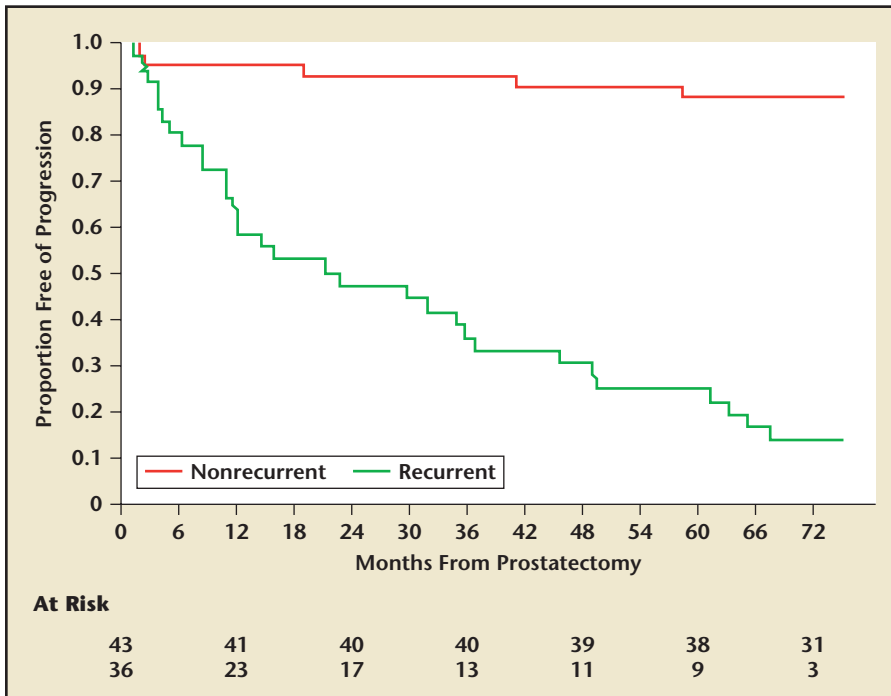


Figure 3. Kaplan-Meier estimates of the probability of disease recurrence for patients classified as nonrecurrent and recurrent by model combining gene expression signatures and clinical variables. Reprinted with permission from Stephenson AJ et al.⁴⁰

Conclusion

The accurate assessment of risk for disease progression or treatment failure in a newly diagnosed prostate cancer patient is of critical importance

and should guide all treatment discussions and recommendations. Traditionally, risk categorization, probability tables, and nomograms—all based on established clinical and pathologic

features—have guided risk assessment for prostate cancer patients. Prostate Px⁺, a risk prediction tool based on a systems pathology approach, demonstrates good potential for improving the way risk is assessed in these patients. Methods of risk prediction will continue to evolve as more biomarkers are discovered and the understanding of genetic variations and prostate cancer progresses. ■

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Main Points

- Risk assessment methods currently used for newly diagnosed prostate cancer patients are not perfect, primarily because input variables are not sufficiently informative.
- Widely used risk prediction tools in the pretreatment setting include D'Amico risk categories, Partin probability tables, University of California, San Francisco-Cancer of the Prostate Risk Assessment risk score, and Kattan nomograms; all rely heavily on traditional clinical variables (eg, serum prostate-specific antigen level, Gleason score, and clinical stage) to estimate risk of various outcomes.
- In general, nomograms maximize the predictive ability of each input variable, allowing for a more individualized characterization of risk compared with risk categories or probability tables.
- The systems pathology approach is a new prediction method that fuses clinicopathologic features with state-of-the-art molecular and cellular markers utilizing advanced image analysis and artificial intelligence. With the goal of improving the accuracy of current risk prediction methods, this approach decreases subjectivity inherent in traditional pathologic tumor specimen processing and incorporates novel biomarkers into the prediction process.
- Including new gene expression signatures in risk assessment models can also improve prediction accuracy.
- Future risk prediction methods in prostate cancer will likely involve the thoughtful combination of clinical and pathologic features with novel molecular and genetic biomarkers in either a systems pathology-based approach or via a traditional nomogram.

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