Evidence of Prognosis

https://pixabay.com/illustrations/prognosis-icon-patient-chart-2803190/

Objectives

* This presentation aims to increase the participants' knowledge to appraise scientific evidence on prognosis.
* At the end of this session, the participants are expected to;
  * Discuss the appraisal of the validity of a prognostic evidence
  * Discuss the importance of a valid evidence about prognosis for clinical practice
  * Discuss the application possibility of a valid and important evidence into clinical practice

Critical Appraisal

* Validity
  * Bias in the study?
  * Fatal flaw or weakness?
* Results
  * Clinical significance?
  * Statistical significance?
* Applicability
* Basic study types
  * Therapy
  * Harm
  * Diagnosis
  * Prognosis
* Advanced study types
  * Systematic review
  * Practice guideline
  * Disease prevalence
  * Economic analysis
  * Decision analysis

Essential Questions in Medicine

* What is going on? Describe the problem/diagnosis.
* Which treatment/management should be applied?
* What is expected to happen? Prognosis.

* What's going to happen to my memory?”
* Will I regain function of my arm?
* What is the prognosis in this patient with metastatic lung cancer?
* What is the risk of stroke in a patient with nonvalvular atrial fibrillation?

Why do we want to know the prognosis?

* Improve Diagnosis
* Improve Treatment
* Relieve discomfort
* Prepare for death or disability
* Avoid unwarranted treatment
* Compare outcomes of systems of care

Sources of reports

* The best evidence would come from systematic reviews of prognosis studies.
* Cohort studies are good to answer prognosis questions.
* Framingham cardiac risk calculation: http://chd.bestsciencemedicine.com/calc2.html

Clinical Scenario

* Many more men with prostate cancer will have indolent, asymptomatic disease, which will progress to a life-threatening condition.
* Though treatment of prostate cancer is effective, it carries a significant morbidity and mortality.
* Deciding which patients with prostate cancer should be exposed to treatment with curative intent is complex.

Clinical Question

* *P* In patients with newly diagnosed prostate cancer
* *I* Are molecular markers of cell cycle regulation
* *C* Compared to conventional risk factors
* *O* Associated with an increased risk of mortality?

Article: Molecular markers and death from prostate cancer

Annals of Internal Medicine | ARTICLE

Molecular Markers and Death From Prostate Cancer

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Background: Current methods to assess the prognosis of prostate cancer at the time of diagnosis are limited.

Objective: To determine whether molecular markers of cell cycle regulation (bcl-2 and p53) and angiogenesis (β-3 integrin, vascular endothelial growth factor, and microvessel density) are associated with increased long-term risk for death among men with prostate cancer.

Design: Observational cohort study from 1991 to 2006.

Setting: The Veterans Affairs Healthcare System in New England.

Patients: Among 64 545 veterans at least 50 years of age, 1313 patients who had incident prostate cancer from 1991 to 1995 were identified. Clinical data were available for 1270 men and complete for 1172 men.

were moderately differentiated. During an 11- to 16-year follow-up, 71.8% (842 of 1172) of men died, with 21.5% (181 of 842) of deaths attributable to prostate cancer. Among 1007 men with results for all pertinent markers and after adjustment for age and clinical characteristics, bcl-2 (adjusted hazard ratio [HR] for positive vs. negative staining, 1.61 [95% CI, 1.01 to 2.57]; $P = 0.045$), p53 (adjusted HR for positive vs. negative staining, 1.48 [CI, 1.06 to 2.08]; $P = 0.022$), and microvessel density (adjusted HR for highest vs. lowest quartile, 3.20 [CI, 1.77 to 5.78]; $P < 0.001$) were associated with death from prostate cancer.

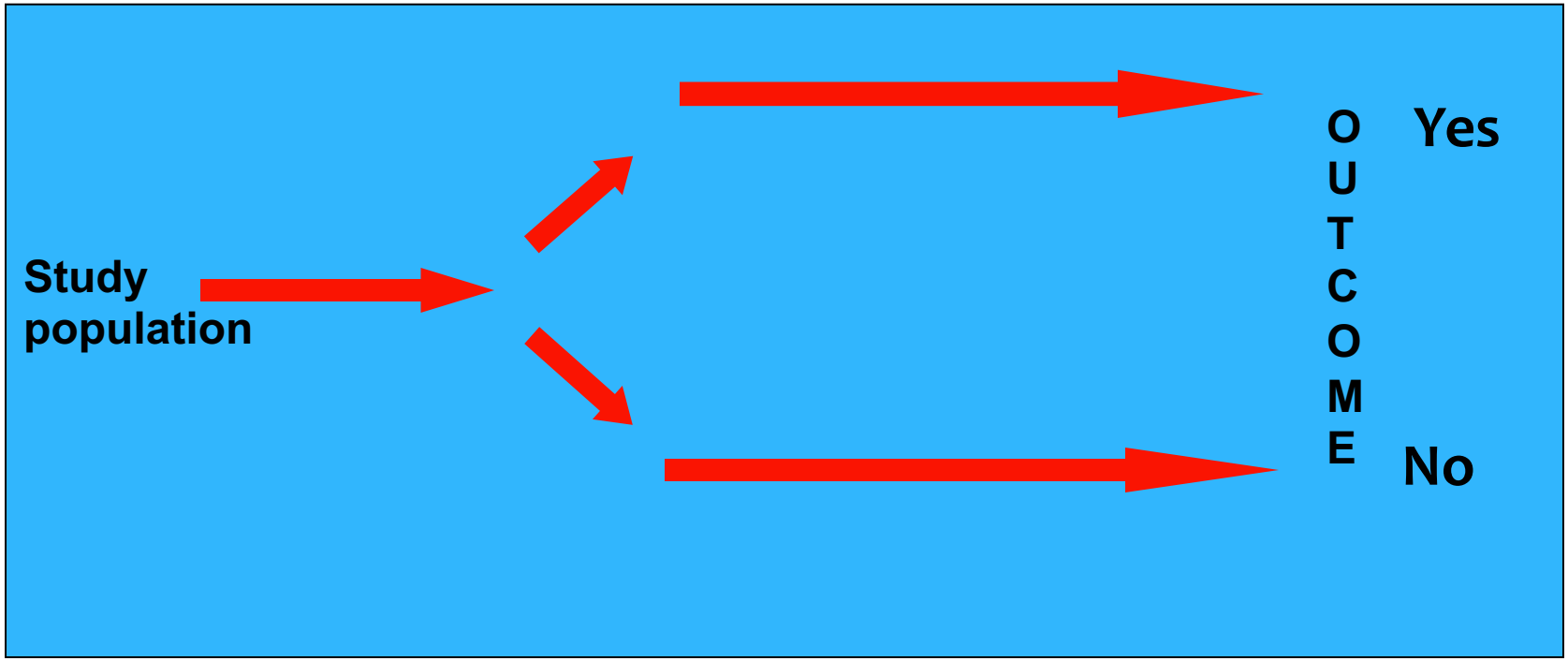
Limitations: Results may be affected by residual confounding. Some patients were not included in complete case analyses because information was not available from clinical care records (7.5%) or tissue staining (12.6%).

https://www.acpjournals.org/doi/10.7326/0003-4819-150-9-200905050-00005?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed

1. Is the evidence valid?

* 1. Was a defined, representative sample of patients assembled at a common point in the course of their disease?
* 2. Was follow-up of study patients sufficiently long and complete?
* 3. Were objective outcome criteria applied in a “blind” fashion?
  4. If subgroups with different prognoses are identified:
* • Was there adjustment for important prognostic factors?
  • Was there validation in an independent group of “test-set” patients?

Critical Appraisal of Prognosis Articles
VALIDITY



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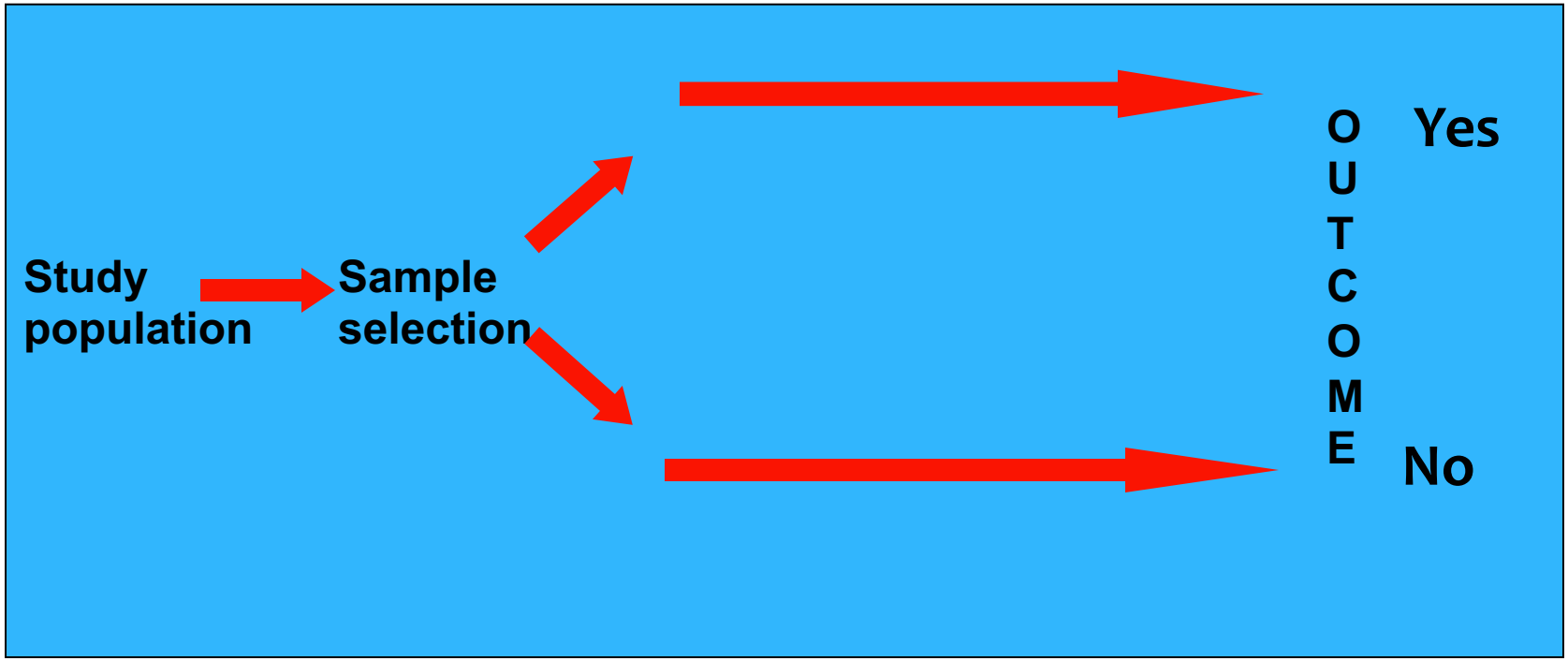

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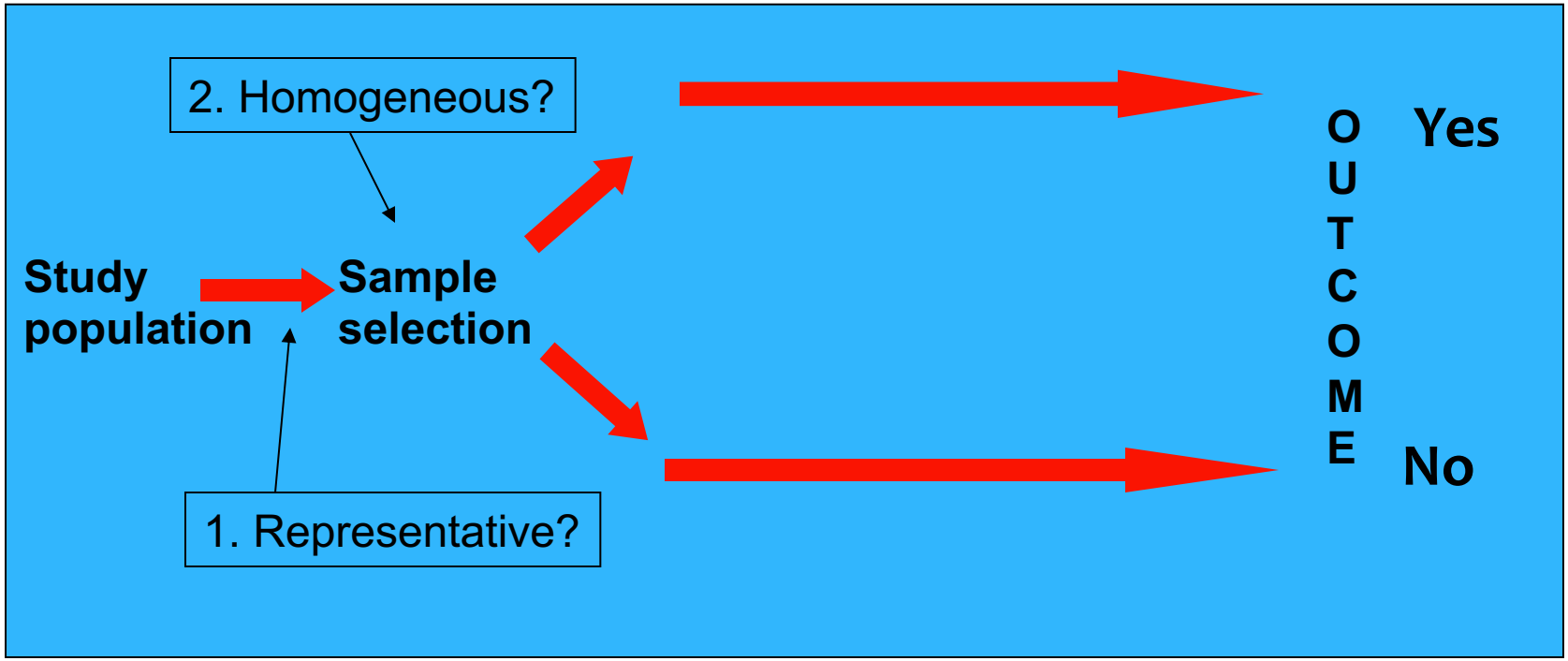

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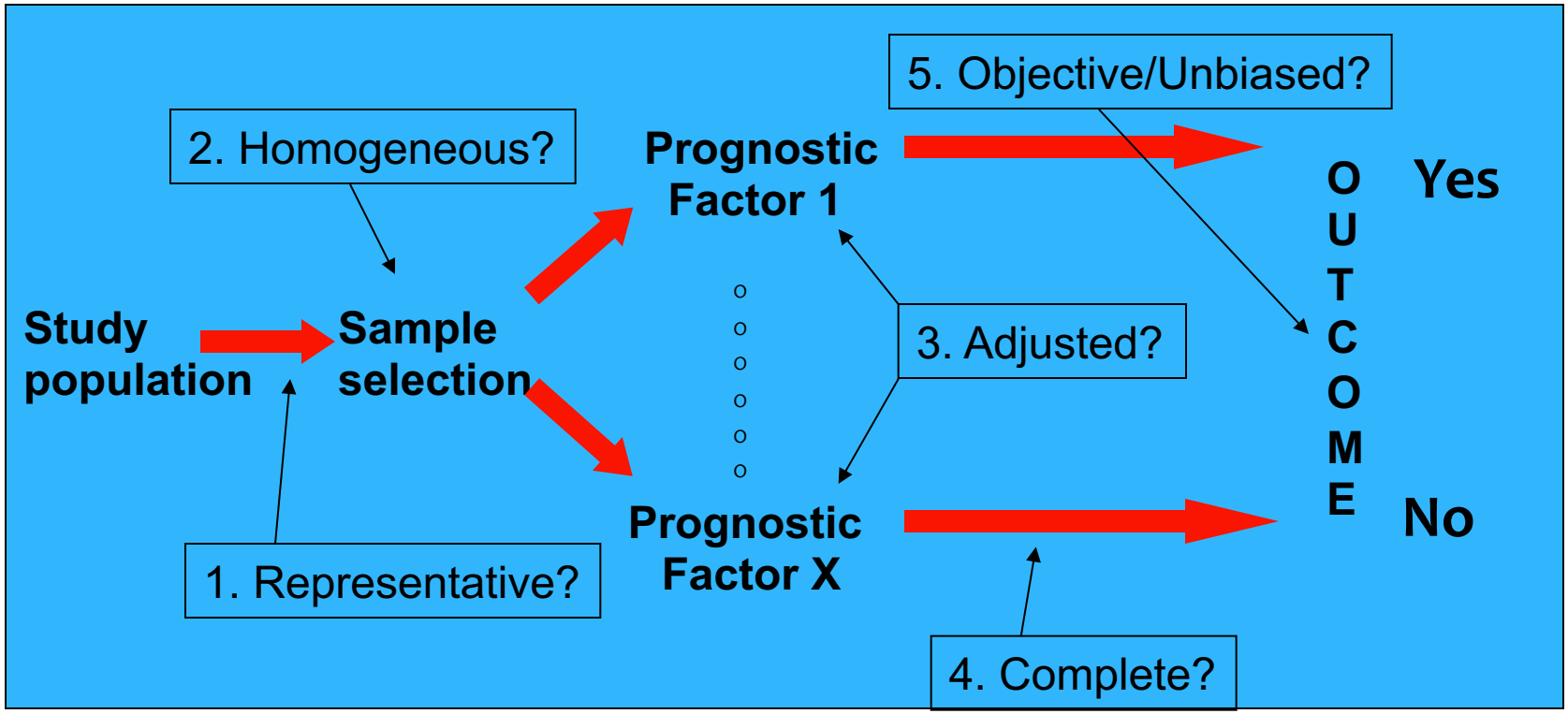
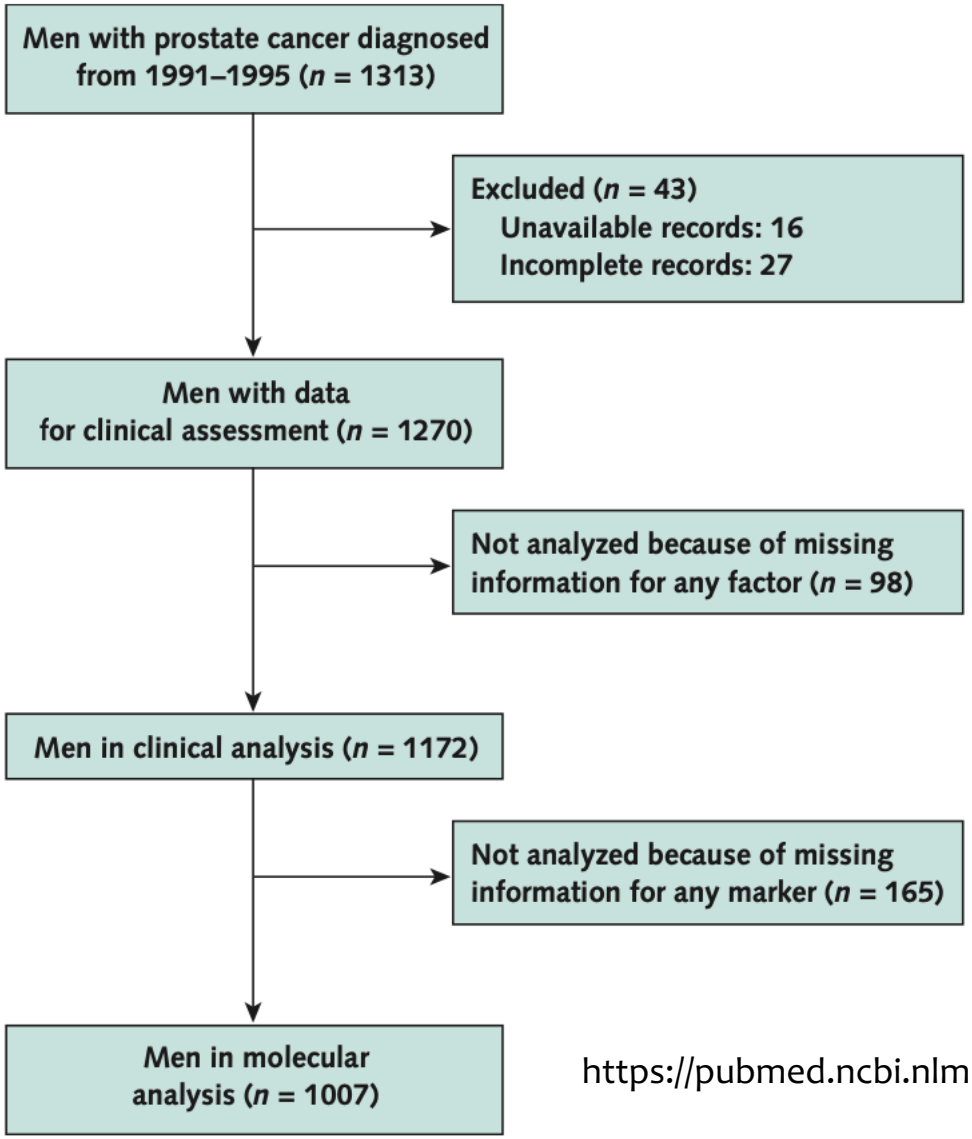


Critical Appraisal of Prognosis Articles VALIDITY

* **Was the sample of patients representative?**
* Were the patients sufficiently homogeneous with respect to prognostic risk?
* Was follow-up sufficiently complete?
* Were objective and unbiased outcome criteria used?

Figure 1. **Study flow diagram.**



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Critical Appraisal of Prognosis Articles VALIDITY

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Table 2. **Effect of Traditional Factors on Death From Prostate Cancer (n = 1172)**

Prognostic Factor	Adjusted Hazard Ratio (95% CI)*	*P* Value
Age (per year)	1.03 (1.01–1.06)	0.032
Race (nonwhite)	0.73 (0.45–1.18)	0.198
Comorbid conditions		
None	Reference	–
1	1.03 (0.69–1.56)	0.87
2	1.31 (0.85–2.03)	0.23
≥3	1.74 (1.14–2.67)	0.011
Anatomical stage		
Localized	Reference	–
Regional	2.14 (1.29–3.55)	0.003
Metastatic	6.52 (4.24–10.01)	<0.001
Differentiation (Gleason score)		
Good (2–4)	Reference	–
Moderate (5–7)	2.58 (1.40–4.74)	0.002
Poor (8–10)	3.98 (2.07–7.65)	<0.001
Prostate-specific antigen		
0–3.9 μg/L	Reference	–
4.0–9.9 μg/L	0.94 (0.45–1.96)	0.86
10.0–19.9 μg/L	1.81 (0.88–3.69)	0.106
≥20.0 μg/L	3.71 (1.87–7.37)	<0.001
Symptoms		
None	Reference	–
Local only	1.14 (0.68–1.93)	0.62
Metastatic	1.49 (0.85–2.60)	0.161
Systemic	1.68 (0.82–3.48)	0.158

* Results are adjusted for all other prognostic factors listed in this table.

Critical Appraisal of Prognosis Articles VALIDITY

* Was the sample of patients representative?
* Were the patients sufficiently homogeneous with respect to prognostic risk?
* **Was follow-up sufficiently complete?**
* **Were objective and unbiased outcome criteria used?**

METHODS

Study Sample

The source sample included all 64 545 male veterans who were receiving ambulatory care linked to 9 Veterans Affairs (VA) medical centers in New England as of 1 January 1991. The institutional review board at each institution approved the research protocol with a waiver of informed consent. Pathology registries identified 1313 men with incident prostate cancer diagnosed from 1991 to 1995 (**Figure 1**). Medical records were unavailable (after at least 3 requests) for 16 (1.2%) men and were inadequate for 27 (2.1%) men (for example, missing entire sections). We collected data on candidate prognostic variables among the remaining 1270 men by using strategies for prognostic studies (7).

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Data Collection

We analyzed 3 sources of data: paper and electronic medical records, immunohistochemical staining of prostatic tissue from which the initial diagnosis of cancer was made, and determination of vital status according to national databases. We first obtained clinical data before primary treatment (designated as "zero-time" [7]) through a comprehensive medical record review by using a standardized extraction form adapted from a previous study (8). We recorded each man's age (years), race (black or other), and comorbid condition (Charlson comorbidity index [9]). We recorded the anatomical extent (clinical stage) and histologic grade (Gleason score) of cancer on the basis of classification systems in use at the time. We also documented PSA levels and cancer-related symptoms (8). We always found certain factors, such as age, in the medical record. Other factors, such as at least 2 PSA tests before diagnosis (to calculate PSA velocity), were sometimes not available. Although our study was not designed to assess the effect of therapy, we coded initial treatment as surgery (prostatectomy), radiation therapy (nonadjuvant), hormone ablation, watchful waiting, or none.

We also requested diagnostic tissue blocks and slides for the men: 1149 (90.5%) from needle biopsies, 114 (9.0%) from transurethral resections of the prostate, 6 (0.5%) from prostatectomies for presumed benign disease, and 1 (0.1%) from a metastatic lesion. After confirming the presence of a tumor, our institutional pathology laboratory did immunohistochemical staining by using indirect immunoperoxidase methods with antibodies against selected factors and by blocking nonspecific staining (10). We evaluated the tissue for bcl-2 (11), an apoptosis-related molecule (dilution, 1:160; Dako, Carpinteria, California); p53 (12), a tumor-suppressor oncogene (dilution, 1:3000; Dako); β-3 integrin (13) (measured as CD-61), an adhesion molecule implicated in tumor invasion and angiogenesis (dilution, 1:40; Vector Laboratories, Burlingame, California); and soluble vascular endothelial growth factor (14), an angiogenic cytokine (dilution, 1:1; BioGenex, San Ramon, California). We recorded intensities of staining in areas of carcinoma on a scale from 0 to 3. In addition, we evaluated microvessel density (15) as a manifestation of tumor angiogenesis by using antibodies to factor VIII (dilution, 1:4000; Dako) in a more labor-intensive process of counting the number of antigen-stained blood vessel cross-sections seen on high-powered magnification (original magnification, ×400). A pathologist blinded to patient outcome did all of the readings.

We assessed the vital status of each patient by using the VA Patient Treatment File, the VA Beneficiary Identifier Locator System (16), and the National Death Index (17). Death from prostate cancer was determined while investigators were blinded to marker status through post-treatment medical record review and consensus decision (8). A censoring date of 31 December 2006 provided an 11- to 16-year range of potential follow-up after zero-time for each patient.

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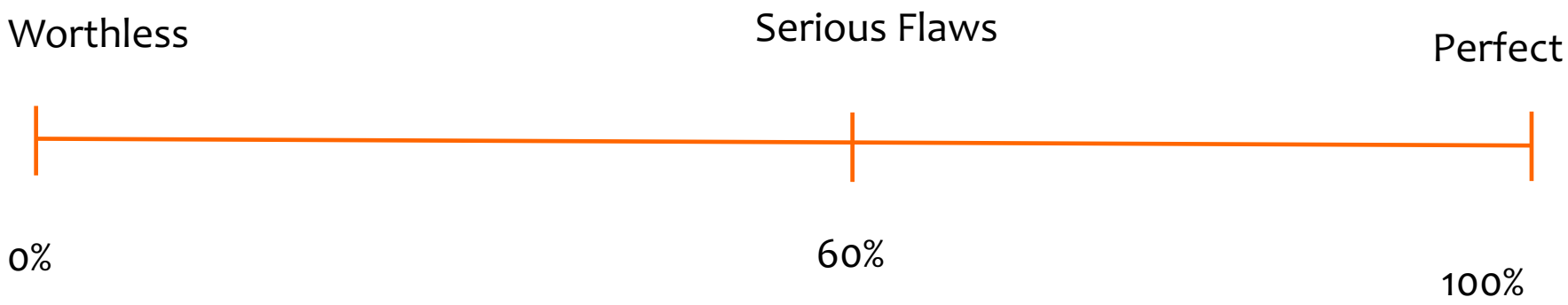
* Validity should be seen as an array from 0 to 100%



2. Is the valid evidence important?

* How likely are the outcomes over time?
* How precise are the estimates of likelihood?

Table 3. **Effect of Molecular Markers on Death From Prostate Cancer***

Candidate Prognostic Factor	Unadjusted Hazard Ratio (95% CI)	*P* Value	Adjusted Hazard Ratio (95% CI)*	*P* Value
bcl-2				
Negative	Reference	–	Reference	–
Positive	2.71 (1.73–4.25)	<0.001	1.61 (1.01–2.57)	0.045
Tumor too small	0.37 (0.19–0.72)	0.004	3.43 (0.50–23.8)	0.21
p53				
Negative	Reference	–	Reference	–
Positive	1.66 (1.20–2.30)	0.002	1.48 (1.06–2.08)	0.022
Tumor too small	0.35 (0.17–0.72)	0.004	0.42 (0.05–3.72)	0.44
Microvessel density				
<19 vessels/hpf	Reference	–	Reference	–
20–28 vessels/hpf	2.43 (1.35–4.37)	0.003	2.79 (1.51–5.16)	0.001
29–39 vessels/hpf	2.47 (1.37–4.42)	0.003	2.43 (1.32–4.47)	0.004
≥40 vessels/hpf	3.71 (2.10–6.55)	<0.001	3.20 (1.77–5.78)	<0.001
Tumor too small	0.78 (0.35–1.74)	0.54	1.36 (0.36–5.12)	0.65

hpf = high-power field.
* Sample size for this analysis was 1007 men. Hazard ratios are adjusted for statistically significant factors from **Table 2**.

3. Is the evidence applicable?

* Were the study patients and their management similar to those in my practice?
* Was follow-up sufficiently long?
* Can I use the results in the management of my patients in my practice?

Summary

* How do we appraise the validity of a prognostic evidence?
* How do we decide if a valid evidence about prognosis is important for clinical practice?
* How do we decide if a valid and important evidence about prognosis is applicable into our clinical practice?