Recent advances in understanding of the natural history of benign prostatic hyperplasia (BPH) and the development of new treatment options are enabling a shift in approach to treatment from palliative to preventive strategies. Studies of the natural history of BPH reveal that it is a progressive condition with a predictable course. Furthermore, with the introduction of 5α-reductase inhibitor pharmacotherapy, it may be possible to prevent progression of BPH and to reduce the risk of serious sequelae. Symptomatic BPH does not progress in all patients; therefore, progression-modifying intervention is not always warranted. To tailor therapeutic and/or preventive approaches appropriately, it is valuable to differentiate patients at high risk of progression from those at low risk of progression. A considerable body of evidence shows that serum prostate-specific antigen (PSA), a commonly used screening test for prostate cancer, can also be useful in predicting disease progression in BPH when considered in conjunction with other clinical indicators. Specifically, patients with PSA of at least 1.5 ng/mL, in the presence of an enlarged prostate and lower urinary tract symptoms, are at increased risk of disease progression. These patients may benefit from close monitoring and may be good candidates for pharmacotherapy to arrest the disease process. On the other hand, patients with a small prostate gland, low serum PSA, and bothersome lower urinary tract symptoms might benefit most from symptomatic treatment but should be periodically monitored to assess changes in clinical status. The strong predictive utility of PSA—combined with the fact that it, unlike other clinical markers of BPH status, can be accurately and easily measured—renders it an important tool for the clinician seeking to optimize outcomes for patients with BPH.
years) or asthma (which affects ~6% of the US population at large). The prevalence of BPH increases with age. By the time men are 80 years old, 90% have histologically verifiable BPH. As life expectancy continues to increase and the US population continues to age, BPH will affect a growing proportion of the population. BPH is a chronic condition characterized by gradually increasing prostate volume, decreasing urinary flow rate, and worsening of lower urinary tract symptoms (LUTS) such as urgency, frequency, and nocturia. The effects of BPH symptoms on the patient range from mild discomfort and embarrassment to significant impairment in activity and quality of life. Serious sequelae of BPH include acute urinary retention—a painful event necessitating emergency care and catheterization—and ultimately surgery. These sequelae, which are costly from both humanistic and economic perspectives, are not uncommon. For a 60-year-old man, for example, the 10-year cumulative incidence of acute urinary retention (14%) exceeds that of myocardial infarction (5%), a new diagnosis of diabetes (5%), or stroke (7%). Because of its high prevalence and its potential functional and economic impacts, BPH is a significant men’s health concern.

Medical and surgical intervention for BPH has historically focused on relieving symptoms. However, recent advances in understanding of the natural history of BPH and the development of new treatment options enable a more proactive, comprehensive approach to BPH management. Studies of the natural history of BPH reveal that it is a progressive condition with a predictable course. Furthermore, with the introduction of 5α-reductase inhibitor pharmacotherapy, it may be possible to prevent progression of BPH and to reduce the risks of acute urinary retention and prostate surgery. These developments are facilitating a shift from palliative to preventive strategies for managing BPH.

BPH does not progress in all patients, and progression-modifying intervention is not always warranted. The treatment of a patient with mild bothersome LUTS who is unlikely to have progressive disease differs from the treatment for a patient with moderate to severe LUTS who is at high risk of disease progression and BPH-associated sequelae. To optimize patient care, it is valuable to differentiate patients at high risk of progression from those at low risk of progression so that treatment can be customized appropriately. A considerable body of evidence shows that serum prostate-specific antigen (PSA), a commonly used screening test for prostate cancer, is also useful in predicting disease progression in BPH when considered in conjunction with other clinical indicators. Specifically, data suggest that patients with PSA of at least 1.5 ng/mL, in the presence of an enlarged prostate and LUTS, may be at increased risk of disease progression. These patients may benefit from close monitoring and may be good candidates for pharmacotherapy to arrest the disease process (Figure 1). This monograph discusses the evidence regarding serum PSA as a biomarker for disease progression in BPH and considers how serum PSA can be used to facilitate therapeutic decision making.

**Figure 1.** The therapeutic strategy for preventive management of BPH depends on whether or not the patient is at high risk of disease progression.

<table>
<thead>
<tr>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA ≥ 1.5 ng/mL</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Prostate volume ≥ 30 cc</td>
</tr>
<tr>
<td>Increased Risk of Progression</td>
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<tr>
<td>Pharmacotherapy to Arrest Disease Progress</td>
</tr>
<tr>
<td>PSA &lt; 1.5 ng/mL</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Prostate volume &lt; 30 cc</td>
</tr>
<tr>
<td>Disease Not Likely to Progress</td>
</tr>
<tr>
<td>Symptomatic Treatment</td>
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</tbody>
</table>

On the basis of the literature reviewed in this paper, patients with PSA of at least 1.5 ng/mL and prostate volume of at least 30 cc may be at increased risk of disease progression. These patients may benefit from close monitoring and may be good candidates for pharmacotherapy to arrest the disease process. Patients with serum PSA below 1.5 ng/mL and smaller prostates are unlikely to have progressive disease. If experiencing bothersome symptoms, patients meeting the latter criteria may benefit from symptomatic treatment.
community-based studies as well as among men treated with placebo in long-term clinical trials. These studies show that, while the course of BPH varies from patient to patient, in many men it is a progressive condition characterized by:

- Increasing prostate volume;
- Worsening lower urinary tract symptoms;
- Decreased urinary flow rate; and
- Increased risk of acute urinary retention and BPH-associated surgery.1

**Prostate Volume**

Prostate volume increases over time and is directly related to age in patients with BPH.7,9,10 For example, in the community-based Olmsted County (Minnesota) study, which followed approximately 2100 randomly selected men, prostate volume was measured by transrectal ultrasound up to 4 times over a 7-year follow-up period in a subset of 631 white men ages 40 to 79 years who had not previously undergone prostate surgery or had prostate cancer.9 The results show that, although prostate growth rates were variable between patients, prostate volume increased with age across the population. Across all age groups, the average annual change in prostate volume (estimated by a mixed-effects regression model) was 1.6% (Figure 2).9 The mean overall annual growth was 0.6 cc and ranged from 0.4 cc in men ages 40 to 59 years to 1.2 cc in men ages 60 to 79 years. Higher baseline prostate volumes were associated with higher rates of prostate growth over the follow-up period. A similar pattern of results was observed among 164 placebo-treated patients in the PLESS (Proscar Long-Term Efficacy and Safety Study) clinical trial, which followed men with BPH for 4 years.11 Mean annual prostate growth was 1.8 cc and ranged from 1.5 cc in men ages 50 to 59 years to 2.4 cc in men ages 70 to 79 years.

**Symptoms**

Consistent with the progressive nature of BPH, community- and clinic-based studies generally show a gradual, age-related worsening of irritative and obstructive symptoms. The deterioration in symptoms parallels the progressive increase in prostate volume and decrement in urinary flow rate.12-14 For example, in the Forth Valley Study, which followed a community-based cohort of 217 Scottish men with untreated BPH for 3 years, prevalence of symptoms, symptom bothersomeness, and symptom-related interference in daily activities increased over the study period.12 It is estimated, on the basis of data from several studies, that symptoms worsen over years in approximately 55% of patients with untreated BPH; remain stable in 30% of patients, and improve in 15%.15

**Urinary Flow Rate**

Data from the Olmsted County study also demonstrate that maximum urinary flow rate (Q_max) and voided volume progressively decrease over time and as a function of age.16 In this analysis, Q_max and voided volume were assessed in a sample of 492 men over a 6-year follow-up period. The median decrease in peak urinary flow rate was 2.1% per year. Rapid decrease in peak urinary flow rate (ie, at least 4.5% decrease per year) was most likely to occur in men at least 70 years of age.
of age. Similar results have been observed in other studies of BPH and LUTS.17,18

SEQUELAE OF BPH

Like the signs and symptoms of BPH, the incidence of serious sequelae of BPH increases over time and is directly related to age as well as to other parameters such as prostate volume and symptom severity.1,19 In the Olmsted County study, for example, the incidence of acute urinary retention over a 4-year period was directly related to severity of symptoms measured using the American Urological Association Symptom Index.19 This effect was particularly marked in older individuals. Among those ages 70 to 79 years, the frequency of acute urinary retention per 1000 patient-years increased from 9.3 in the presence of mild to moderate symptoms to 34.7 in the presence of moderate to severe symptoms.19

The likelihood of needing BPH-related prostate surgery also increases over time. In the Baltimore Longitudinal Study of Aging, which prospectively followed 1057 men for up to 30 years, the 10-year probability of prostate surgery for BPH was directly related to age among both those with prostatic enlargement and obstructive symptoms and among those without prostatic enlargement and obstructive symptoms.20 The risk of surgery was particularly high for older men with prostatic enlargement and obstructive symptoms. The 10-year probability of BPH-related prostate surgery among 60- to 69-year olds with prostate enlargement and obstructive symptoms was 16%. For 70- to 79-year olds with prostate enlargement and obstructive symptoms, the 10-year probability of BPH-related prostate surgery was 34% (Figure 3).20

CONCLUSIONS: BPH AS A PROGRESSIVE DISEASE

These data show that BPH is progressive. Over time, prostate volume increases while urinary flow rate decreases and symptoms worsen. Moreover, the risk of serious BPH sequelae such as acute urinary retention and prostate surgery increases over time. The progressive nature of BPH is supported by the results of several studies ranging from clinical trials following patients for up to 4 years to cross-sectional and longitudinal community-based studies following individuals for up to 7 years.9,17,19,20 That these varying approaches, each associated with unique advantages and disadvantages (Table), consistently show BPH to be a progressive condition renders the evidence compelling. While the studies show that signs and symptoms of BPH gradually worsen and the risk of sequelae increases across groups of men, they also show considerable variability between individuals in the rate and extent to which BPH progresses. Research to be reviewed in the following sections shows that serum PSA is useful in gauging risk of progression in the individual patient.

PSA

PSA, a single-chain glycoprotein with a molecular weight of 34 kilodaltons, is produced by all prostatic epithelial cells whether benign or malignant.21 In men with enlarged prostates associated with BPH, prostate cancer, or prostatitis, serum PSA levels are believed to be elevated through leakage of intraprostatic PSA into the systemic circulation.7 In the systemic circulation, PSA occurs in both a free form (free PSA) and a form complexed to endogenous protease inhibitors such as alpha-1-antichymotrypsin. A common, reliable, reproducible test that is easy to obtain in nearly any clinical setting, serum PSA is the best biomarker available for prostate cancer. However, it is not cancer specific in

Figure 3. 10-year probability of BPH-related surgery as a function of age in patients with or without prostatic enlargement and obstructive symptoms in the Baltimore Longitudinal Study of Aging.20

![Figure 3. 10-year probability of BPH-related surgery as a function of age in patients with or without prostatic enlargement and obstructive symptoms in the Baltimore Longitudinal Study of Aging.20](image-url)
that it is elevated in the presence of both benign and malignant prostate disease.

**Serum PSA: A Biomarker for BPH Progression**

The utility of serum PSA as a biomarker for disease progression arises from the ability to use serum PSA values as a proxy for prostate volume, which is well established as a primary predictor of progression and outcomes in BPH. While PSA and total prostate volume are both strong predictors of disease progression in BPH, PSA may be more useful in the clinical setting than is total prostate volume. PSA can be accurately measured with a simple clinical test whereas total prostate volume is generally difficult to estimate accurately without sophisticated techniques such as trans-rectal ultrasound or magnetic resonance imaging. Digital rectal examination, the most common means of assessing prostate volume in the clinic, often underestimates prostate volume. Given that PSA predicts outcomes in BPH at least as robustly as does prostate volume, that it can be more easily and accurately measured, and that it is available in the medical records of any patient screened for prostate cancer, it constitutes an important tool to use alone or in conjunction with other clinical assessments in managing the patient with BPH.

**Relationships Among Serum PSA, Age, and Prostate Volume**

Both PSA and total prostate volume increase with advancing age. PSA and total prostate volume have an age-dependent, log-linear relationship; that is, the logarithms of the 2 variables are linearly related, and that relationship depends on age. That serum PSA and prostate volume are closely related is not surprising given that the age-related increase in serum PSA is most likely attributed to the increase in prostate volume (arising from increased epithelial mass) that occurs as men age.

The direct relationship between age and serum PSA as well as between age and prostate volume is illustrated by the results of an analysis of data from

### Table. Advantages and Disadvantages of the Primary Study Designs Employed in Assessing the Predictive Value of Serum PSA in BPH

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Clinical trial</td>
<td>Follow-up is consistent from patient to patient so that influence of extraneous variables is minimized</td>
<td>• Inclusion and exclusion criteria may render sample unrepresentative</td>
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<td></td>
<td></td>
<td>• Placebo effect</td>
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<td>• Hawthorne effect (i.e., behaviors change as a consequence of being studied)</td>
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<td>• Volunteer bias</td>
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<td></td>
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<td>• Significant numbers of participants are often lost to follow-up in studies employing prolonged observation periods</td>
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<td>• Data may not be generalizable to samples from communities with other demographic and clinical characteristics</td>
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<td>• Selection bias (i.e., sample differs from population in measured or unmeasured baseline characteristics because of the way participants were selected or assigned)</td>
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<td>• Cannot establish timing and directionality of events</td>
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<tr>
<td>Longitudinal, community-based cohort study</td>
<td>Sample is representative of reference population so “real world” meaningfulness of data is enhanced</td>
<td>• Inclusion and exclusion criteria may render sample unrepresentative</td>
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<td>• Volunteer bias</td>
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<tr>
<td>Cross-sectional community-based study</td>
<td>Sample is representative of reference population so “real world” meaningfulness of data is enhanced</td>
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clinical trials in which baseline prostate volume was measured by either transrectal ultrasound or magnetic resonance imaging in 4627 men with no prostate cancer. Both the log of baseline serum PSA and the log of baseline prostate volume were directly related to age throughout the adult life span (Figure 4). Data from this analysis show that PSA cut-off values for detecting men with prostate volume exceeding 30 mL were PSA >1.3 ng/mL, >1.5 ng/mL, and >1.7 ng/mL for men with BPH in their 50s, 60s, and 70s, respectively. These criteria had 70% specificity and 65% to 70% sensitivity for detecting men with prostate volume exceeding 35 mL. These findings show that serum PSA values were closely related to current prostate volume in men enrolled in clinical trials. Whether or not serum PSA predicted future prostate volume changes associated with disease progression was not assessed in this analysis.

**SERUM PSA PREDICTS PROSTATE GROWTH**

That serum PSA values can indeed predict future prostate growth was established in subsequent analyses of clinical trials data and in a community-based study. In the PLESS clinical trial, 164 men in the placebo group had yearly evaluations of prostate volume via pelvic magnetic resonance imaging over a period of 4 years. Baseline PSA values more strongly predicted prostate growth than either age or baseline prostate volume (both of which also predict prostate growth). Annualized growth rates in mL/year were 0.7 for those with baseline PSA of 0.2 to 1.3 ng/mL (low tertile), 2.1 for those with baseline serum PSA of 1.4 to 3.2 ng/mL (middle tertile), and 3.3 for those with baseline serum PSA of 3.3 to 9.9 ng/mL (high tertile) (Figure 5).

Baseline PSA values also predicted subsequent prostate enlargement in the community-based Baltimore Longitudinal Study of Aging. Over a 30-year period, the long-term risk of prostate enlargement among men ages 40 to 49.9 years (n=194), 50 to 59.9 years (n=191), and 60 to 69.9 years (n=144) was predicted by serum PSA quartile at baseline. The relationship was particularly strong for those ages 50 and older:

- Among those ages 50 to 59.9 years, the risk of an enlarged prostate was 8.6 times higher when serum PSA level exceeded 1.4 ng/mL than when serum PSA was 0.5 ng/mL or below (Figure 6).
Among those ages 60 to 69.9 years, the risk of an enlarged prostate was 11.1 times higher when serum PSA level exceeded 1.7 ng/mL than when serum PSA was 0.5 ng/mL or below (Figure 6).

The authors concluded that “risk stratification based on PSA level may be useful to identify men at greatest risk for adverse events due to prostate enlargement.”

Both the observation that PSA predicts future prostate growth and the age-dependent, log-linear relationship between baseline PSA and baseline prostate volume support the use of PSA as a proxy for prostate volume in predicting progression of BPH.

Serum PSA Predicts Changes in Symptoms and Urinary Flow Rate

Serum PSA also predicts changes in symptoms and urinary flow rate. In the PLESS trial, mean changes in American Urological Association Symptom Index (AUA-SI) scores at the end of 4 years of treatment with placebo were inversely related to baseline serum PSA levels. Mean changes in AUA-SI score were -2.4, -0.4, and -0.2 in men with BPH and baseline serum PSA of 0 to 1.3 ng/mL, 1.4 to 3.2 ng/mL, and 3.3 to 12 ng/mL, respectively. A similar relationship was observed between baseline serum PSA levels and changes in maximum urinary flow rate over 4 years.

Serum PSA Predicts Incidence of Sequelae of BPH

Besides predicting increases in prostate volume and changes in symptoms and urinary flow rate, serum PSA predicts 4-year incidences of either acute urinary retention or BPH-related surgery at least as well as does prostate volume. Among 312 placebo-treated patients in the 4-year PLESS study, the incidence of acute urinary retention was directly related to both baseline prostate volume and baseline serum PSA (Figure 7). Baseline prostate volume and baseline serum PSA were more powerful predictors of the occurrence of acute urinary retention than were symptom scores, urinary flow rates, or residual urine volume. The need for BPH-related surgery, like the risk of acute urinary retention, was strongly predicted by baseline prostate volume and baseline serum PSA.

PSA also strongly predicted the incidence of acute urinary retention in another analysis of data.
from clinical trials of men with LUTS and BPH. The ability of 110 variables to predict acute urinary retention was assessed by logistic regression analysis and classification and regression tree methods with data from 5335 patients. The occurrence of acute urinary retention was predicted by several variables including prostate volume, serum PSA, frequency of urination, symptom problem index, maximum urinary flow rate, and hesitancy. Serum PSA alone was as strongly predictive of the occurrence of acute urinary retention as was the combination of PSA, urinary frequency and hesitancy, flow rate parameters, and symptom problem index.

CONCLUSIONS: PSA AS A BIOMARKER OF BPH PROGRESSION

Considered in aggregate, the data on the relationships among PSA, prostate volume, and BPH progression show that PSA is a powerful predictor of disease progression in BPH. The strong predictive utility of PSA—combined with the fact that it, unlike other clinical markers of BPH status, can be accurately and easily measured—renders it an important tool for the clinician seeking to optimize outcomes for patients with BPH. These conclusions should be interpreted with the knowledge that most of the data supporting the predictive value of serum PSA levels are derived from retrospective analyses rather than studies prospectively designed to examine the ability of serum PSA to predict progression of BPH. This caveat notwithstanding, the consistency of data from various sources ranging from clinical trials to longitudinal community-based studies lends credence to the conclusion that serum PSA is a powerful marker of disease progression in BPH.

The precise PSA value above which risk of progression can be considered to be clinically significant may vary from patient to patient depending on factors such as the patient's age, individual goals, general health status, and socioeconomic circumstances. Generally and for practical purposes, patients with PSA values of 1.5 ng/mL or above can be considered at high risk of disease progression. The findings reviewed above show that, above this PSA cut-off point, the risk of BPH-associated sequelae increases significantly. Patients with PSA values of 1.5 ng/mL or above may benefit from close monitoring and may be appropriate candidates for pharmacotherapy that can delay or prevent progression of BPH. Early pharmacotherapeutic intervention can improve patients' health and quality of life, decrease the risk of serious sequelae of BPH, and reduce the economic and personal costs of surgery.

FUTURE APPLICATIONS

Understanding of the possible applications of PSA in the management of BPH continues to evolve. Free (noncomplexed) PSA exists in several forms in serum. Serum levels of one of these forms, benign PSA (BPSA), are closely associated with the transition zone enlargement that occurs in BPH and may constitute a specific marker for the biochemical changes associated with BPH. BPSA can be accurately measured in serum and may eventually prove to be a more specific and sensitive marker for the presence of BPH than serum PSA.

CONCLUSIONS

The data reviewed herein establish that BPH is a progressive condition characterized by increases in prostate volume, decreases in urinary flow rate, worsening symptoms, and increasing risk of acute urinary retention and BPH-related surgery. While BPH is progressive and follows a predictable course, the rate and extent of BPH progression vary among patients. Progression-modifying therapy is therefore not warranted for everyone. For optimum management of patients with BPH, it is valuable to predict which patients are likely to progress and which are not likely to progress so that those at high risk of progression can be monitored closely and/or administered preventive therapy. A large body of research from both clinical trials and community-based studies demonstrates that serum PSA levels are a useful predictor of disease progression in BPH. Men with PSA levels above 1.5 ng/mL are particularly likely to show rapid disease progression and are at increased risk of acute urinary retention and BPH-related surgery. These men, more than those whose disease is unlikely to progress rapidly or to cause adverse sequelae, are appropriate candidates for early intervention with pharmacotherapy that can delay or prevent disease progression. On the other hand, patients with a small prostate gland, low serum PSA, and bothersome lower urinary tract symptoms might benefit most from symptomatic...
treatment but should be periodically monitored to assess for changes in clinical status. The strong predictive utility of PSA—combined with the fact that it, unlike other clinical markers of BPH status, can be accurately and easily measured—renders it an important tool for the clinician seeking to optimize outcomes for patients with BPH.

REFERENCES


