

NephSAP[®]

Nephrology Self-Assessment Program

Primary Care for the Nephrologist

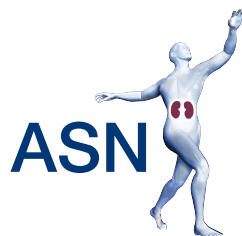
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LEADING THE FIGHT
AGAINST KIDNEY DISEASE

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Preface

NephSAP® is one of the three major publications of the American Society of Nephrology (ASN). Its primary goals are self-assessment, education, and the provision of Continuing Medical Education (CME) credits and Maintenance of Certification (MOC) credits for individuals certified by the American Board of Internal Medicine. Members of the ASN automatically receive *NephSAP* with their monthly issue of *The Journal of the American Society of Nephrology (JASN)*.

EDUCATION: Medical and Nephrologic information continually accrues at a rapid pace. Bombarded from all sides with demands on their time, busy practitioners, academicians, and trainees at all levels are increasingly challenged to review and understand all this new material.

Each bimonthly issue of *NephSAP* is dedicated to a specific theme, *i.e.*, to a specific area of clinical nephrology, hypertension, dialysis, and transplantation, and consists of an Editorial, a Syllabus, a Commentary on the Syllabus, and self-assessment questions. Over the course of 24 months, all clinically relevant and key elements of nephrology will be reviewed and updated. The authors of each issue digest, assimilate, and interpret key publications from the previous issues of other years and integrate this new material with the body of existing information.

SELF-ASSESSMENT: Twenty-five single-best-answer questions will follow the 50 to 75 pages of Syllabus text. The examination is available online with immediate feedback. Those answering >75% correctly will receive CME credit, and receive the answers to all the questions along with brief discussions and an updated bibliography. To help answer the questions, readers may go to the ASN web site, where relevant material from UpToDate in nephrology will be posted. Thus, members will find a new area reviewed every 2 months, and they will be able to test their understanding with our quiz. This format will help readers stay abreast of developing areas of clinical nephrology, hypertension, dialysis, and transplantation, and the review and update will support those taking certification and recertification examinations.

CONTINUING MEDICAL EDUCATION: Most state and local medical agencies as well as hospitals are demanding documentation of requisite CME credits for licensure and for staff appointments. A maximum of 36 credits annually can be obtained by successfully completing the *NephSAP* examination. In addition, individuals certified by the American Board of Internal Medicine may obtain credits towards Maintenance of Certification (MOC) by successfully completing the self-assessment portion of *NephSAP*.

BOARD CERTIFICATION AND INSERVICE EXAMINATION PREPARATION: Each issue will also contain 5 questions and answers examining core topics in the particular discipline reviewed in the Syllabus. These questions are designed to provide trainees with challenging questions to test their knowledge of key areas of nephrology.

∞ This paper meets the requirements of ANSI/NISO Z39.48-1921 (Permanence of Paper), effective with July 2002, Vol. 1, No. 1.

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Renal Bone Disease, Disorders of Divalent Ions, and
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*Kevin Martin, MBBCh, and Stanley Goldfarb, MD*September 2010

End-Stage Renal Disease and Dialysis—
*Rajiv Agarwal, MD, and Rajnish Mehrotra, MD*November 2010

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Program Mission and Objectives

The mission of the *Nephrology Self-Assessment Program (NephSAP)* is to regularly provide a vehicle that will be useful for clinical nephrologists who seek to renew and refresh their clinical knowledge and diagnostic and therapeutic skills. This Journal consists of a series of challenging, clinically oriented questions based on case vignettes, a detailed Syllabus that reviews recent publications, and an Editorial on an important and evolving topic. Taken together, these parts should assist individual clinicians undertaking a rigorous self-assessment of their strengths and weaknesses in the broad domain of nephrology.

Accreditation and Credit Designation

The American Society of Nephrology is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The ASN designates this educational activity for a maximum of 8.0 *AMA PRA Category 1 Credits*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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CME Credit: 8.0 *AMA PRA Category 1 Credits*[™]

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Audio Files Available: No audio files will be available for this issue.

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Answers: Correct answers with explanations will be posted on the ASN website in January 2011 when the issue is archived.

UpToDate Links Active: January and February 2010

Core Nephrology question links active: There are no core questions for this issue.

Target Audience: Nephrology Board and recertification candidates, practicing nephrologists, and internists.

Method of Participation:

- Read the syllabus that is supplemented by original articles in the reference lists, and complete the online self-assessment examination.
- Examinations are available online **only** after the first week of the publication month. There is no fee. Each participant is allowed two attempts to pass the examination (>75% correct).
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Editorial

The Nephrology–Primary Care Interface: Providing Coordinated Care for Chronic Kidney Disease

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The concept of a patient-centered medical home (PCMH) is being advanced by a number of specialty societies and by health care policy experts, as well as by both federal and nonfederal payers. The PCMH is a physician-directed practice that places the patient at the center of its focus to provide care that is accessible, continuous, comprehensive, and coordinated (1–3). The PCMH model of comprehensive health care delivery is now being tested in a number of pilot projects in various regions of the US. There are currently 22 projects in 16 states designed not only to test the applicability of the concept but also to provide much needed information on incremental cost estimates and savings that integrate the chronic care model and the PCMH concept. By the end of 2010, one of the deliverables from these pilots will be the establishment of a pay-for-performance approach using a consistent set of core measures. The reader is referred for more information on PCMH demonstration projects to the American College of Physicians (ACP) web site: http://www.acponline.org/running_practice/pcmh/demonstrations/index.html.

The patient-centered primary care collaborative formed in 2007 and has more than 610 member organizations including the American College of Physicians, American College of Cardiology, American Academy of Neurology, and a number of employer umbrella organizations representing more than 50 million employees, including individual companies such as IBM and General Motors. Most major health plans are represented as well as consumer organizations

such as AARP. So, in short, the notion of a PCMH is rapidly gaining traction as an idea to transform health care delivery in the United States (3,4).

The frequent use of subspecialists in the face of low use of primary care has been cited as one of the problems with our current health care delivery system in the United States. Because of the growing population of patients with stages 3 and 4 chronic kidney disease (CKD), in the face of an inadequate nephrology workforce to provide comprehensive care for such a large population, it is important for nephrologists to be involved in a collaborative and coordinated approach with primary care physicians (PCPs) to treat patients with CKD. To encourage a coordinated system of care, nephrologists have an opportunity through organizations such as the American Society of Nephrology and the Renal Physicians Association to *model* CKD from a coordinated care perspective. By defining how PCPs and nephrologists will coordinate the care for patients with CKD, it is hoped that the primary care–nephrology care interface will be improved and that specific means of reimbursement for the delivery of quality care will follow. The means by which PCPs, subspecialists, and patients might interact within the framework of the PCMH has been designated as the “medical neighborhood” (PCMH-N) (5). The key features of the “neighborhood” and the possible types of financial incentives or performance rewards for medical neighbors to participate in care coordination is just beginning to evolve. One of the pilots to test, presumably, the PCMH-N concept, was proposed recently by the Texas ACP Chapter, and

designated the “Texas Patient-Centered Medical Home Initiative.”

The American Society of Nephrology public policy board appointed a task force to formulate a position on the PCMH in 2008, and the initial report of the task force was published in *JASN* (6). In focusing on how the nephrologist might interact with a PCMH, the task force initially created four case scenarios to illustrate and elucidate how concerns that might arise with implementation would be considered (http://www.asn-online.org/policy_and_public_affairs/patient-care.aspx). The case scenarios included a patient with stage 3 CKD; a patient who has stage 4 CKD and is referred to a nephrologist for consultation and participation in treatment; and, finally, a patient who has a less common but a more complex autoimmune disorder that requires comprehensive management by a nephrologist and other subspecialists but requires less involvement by a PCP. This exercise demonstrated not only dilemmas that might arise in several areas but also illustrated clearly that a better definition of cooperative interaction between the nephrologist and the PCP would require a more comprehensive model. To accomplish this goal, the task force has focused on delineating the coordination of care around CKD that is caused by diabetes and hypertension.

With this background in mind, there are several questions that require careful consideration by nephrologists: First, what constitutes a good “neighbor,” and, second, how might a nephrologist participate? Several recent reviews have attempted to lay the groundwork for this relationship (5,7).

For these reasons, the task force is focusing presently on a more comprehensive model, specifically for the coordinated care of CKD, because this is by far the largest anticipated category of interaction between the PCMH and PCMH-N. Such an approach should fit within the framework of the modeling of chronic disease as initially proposed by Wagner and colleagues (8). If the nephrologist is to co-manage care for CKD with a PCP, then a spectrum of involvement by the specialist neighbor (PCMH-N) that extends from initial consultation at an earlier stage of CKD (*e.g.*, stage 3A) to the role of co-manager with shared care at stages 3B and 4 is envisioned. Ultimately, at later stages of CKD, the nephrologist could become responsible for providing principal care (*e.g.*, at stage 5 or late stage 4 CKD). Such a conceptual model is outlined in Figure 1 (this model also emphasizes that

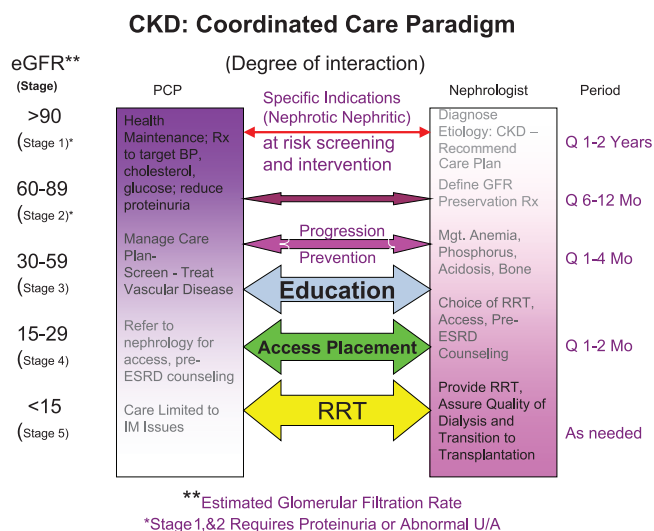


Figure 1. Model of coordinated care by CKD stage. RRT, renal replacement therapy; CKD, chronic kidney disease; Mgt, management; PCP, primary care physician; IM, internal medicine.

nondiabetic secondary and primary glomerulopathies would warrant immediate referral to a nephrologist). If the nephrologist becomes a co-manager with shared care, then he or she must share long-term management of CKD with a PCP. On the assumption that many patients who have CKD, for whom long-term treatment will be shared between the PCP and the nephrologist, have diabetes, it is apparent that guidelines that pertain to the involvement of the endocrinologist or any other subspecialist who is involved in the care of the patient will also be necessary.

For this relationship to improve care, accurate definitions of when the PCP should refer the kidney patient must be established. Because late referral is currently a major problem that results in poor outcomes for patients with CKD (6), the nephrologist PCMH-N should not be penalized for late referral by the PCP. Moreover, the accountability of the nephrologist must be clarified with the PCP for management tasks. Finally, timely communication of recommendations and changes in management should eventually flow through a mutually accessible electronic medical record for truly coordinated care to succeed. As CKD progresses, the nephrologist may assume a more active role as co-manager with principal care and assume total responsibility for the long-term management of the CKD/ESRD. In addition to providing evidence-based management, the PCMH-N (nephrologist) will then assume full accountability for the management of

the CKD as well as coordination of the involvement of other specialists (e.g., cardiology) as well as with the PCMH physician. If the nephrologist chooses to act in the capacity of a PCMH rather than to continue in the capacity as neighbor, it will be necessary for the nephrologist to assume responsibility for being the provider of “whole-person care” and as having overall responsibility for ensuring the coordination and integration of the care provided by all involved providers. Moreover, designation by the National Center for Quality Assurance as a PCMH would also be required. Designation as a PCMH, therefore, seems to be an option that many nephrologists may choose not to exercise.

Integrated health care delivery systems and multi-specialty group practices of the future will be compelled to develop systems for shared information, accountability, and rewards. Nephrologist PCMH-neighbors (PCMH-N) will need to develop referral guidelines that are evidence-based and provide better data regarding the impact of intervention and management on outcomes (e.g., progression of CKD to ESRD, and the development of complications such as cardiovascular disease). As a system of coordinated care is developed within the framework of the PCMH-N, it will be necessary to develop an approach that clearly delineates when a co-management approach should be used as opposed to either the PCP (PCMH), or the nephrologist (PCMH-N) playing a principle role. These guidelines, as well as quality metrics, are not yet available.

Up to this point, little attention has been given to communication regarding transitions of care, and certainly this includes the primary care–specialty care interface. Very few residency or fellowship programs focus on communication or transitions of care. A recent article by Forrest (9) attempted to describe the typology of specialists’ clinical roles on the basis of empirical evaluations of the specialty referral process and suggested ways of improving the effectiveness and efficiency of the primary care–subspecialist care interface. In an accompanying editorial (10), Chen and Yee indicated that “the Forrest typology has potential as a conceptual framework for establishing the respective and mutual duties and responsibilities of PCPs and specialists.” They also indicated that “implementation will require improvements in the delivery system and a clearer understanding of the application of co-management to clinical practice.”

The ACP Council on Subspecialty Societies is

developing a working agreement for the PCMH and the PCMH-N. At the operational level, the PCMH-N has been tentatively defined as a specialty practice that (1) is engaged in coordination and integration of care with a PCMH practice that is of high quality and efficiency; (2) complements the aims of the PCMH practice by facilitating appropriate and timely consultation; (3) facilitates the efficient, appropriate, and effective flow of necessary patient and care information; (4) effectively addresses issues of responsibility in co-management situations; (5) supports patient-centered care, enhanced care access, and high levels of care quality and safety; and (6) recognizes the PCMH practice as the provider of “whole-person primary care,” having overall responsibility for ensuring the coordination and integration of the care provided by all involved providers. From such definitions, service agreement principles between the PCMH and the PCMH-N are being developed. If such paradigms are to apply to CKD, then nephrology societies and individual nephrologists in general must be involved in the creation of chronic disease care models for CKD within the framework of the PCMH. This is why the American Society of Nephrology and the Renal Physicians Association are participating with the ACP, payers, and other health care organizations in discussions regarding the PCMH and PCMH-N interface.

In the interim, the most immediate goal for nephrology is to develop a clear paradigm for the management of the most common forms of CKD with emphasis on the interface between the PCP and the nephrologist as a function of CKD stage. To be precise, a definition of who does what and when is needed. Better guidelines regarding the timing of referral will be an absolute necessity. Extending the scope of care to CKD will represent a challenge for the PCP as well. A recent study emphasized that the “typical” PCP, on average, interacts with 229 other physicians who work in 117 practices with which care must be coordinated (11). For the primary care–nephrology interface to succeed, nephrologists should define how information will be exchanged and, ultimately, how outcomes can be measured fairly and improved. Such an approach is desirable when the patient with CKD is placed at the center of the health care delivery system, concordant with the stated core principle of the PCMH concept.

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Editorial

Beyond the Kidneys: The Nephrologist's Responsibilities as an Internal Medicine Specialist

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During the past year, reforming the American health care system has been one of the highest priorities of the federal government. A variety of driving forces have been behind this burgeoning interest in health care, including the large number of uninsured, the enormous financial burden of health care, widespread gaps in the quality of care, fragmentation and inadequate coordination of care across health care providers, and a looming—if not already present—crisis in the number and availability of primary care physicians. The primary care workforce shortage raises two important questions for subspecialists:

1. What is the subspecialist's responsibility to help fill this gap by providing care outside his or her subspecialty?
2. What is the subspecialist's responsibility to maintain competency and be current in the broader area of internal medicine outside the subspecialty?

The answers to these questions likely vary depending on the perspective of the person providing the answers. With that concern in mind, I fully disclose my perspective as a pulmonary and critical care subspecialist; however, in my current educational leadership role at the American College of Physicians (ACP), which I have held for more than 5 yr, I have acquired a much broader view of internal medicine, because the ACP represents both general internal medicine and all of the subspecialties of internal medicine. I suppose it is therefore fair to say that I am a subspecialist presenting a generalist's viewpoint or, perhaps even more accurate, that I am trying to present a viewpoint that takes into account the perspective of both subspecialists and generalists.

My personal answer to question 1 is that internal medicine subspecialists ideally should be capa-

ble of providing at least some care outside their subspecialty. This can perhaps be best illustrated by considering the patient who receives most of his or her care from a subspecialist for a chronic illness, such as a chronic kidney disease patient on dialysis who is treated by a nephrologist. Rather than fragmenting care between a nephrologist and a general internist, the patient's health care needs could be well served by a nephrologist who is able to handle many of the patient's other routine needs and common problems that might develop. If one accepts that premise, then the nephrologist has an obligation to update his or her knowledge in areas outside his or her subspecialty.

Subspecialists seem to vary in their interest in providing care and keeping updated outside their subspecialty. One marker of each subspecialty's view on this issue is the percentage of individuals in the subspecialty who have time-limited certification and have chosen to recertify in internal medicine in addition to their subspecialty. As it turns out, except for geriatricians, critical care physicians and nephrologists lead the pack among all internal medicine subspecialists, with 69 and 68%, respectively, of subspecialists in those fields holding time-limited certification and choosing to recertify in internal medicine (Figure 1). At the other end of the spectrum, only 33% of cardiologists with time-limited certification choose to recertify in internal medicine. Speaking for myself and probably for many of my pulmonologist colleagues, I know that one of the attractive features of a career in pulmonary and critical care medicine was the opportunity to remain a generalist by caring for a broad range of internal medicine problems in the critical care setting.

The second question I posed seems partially

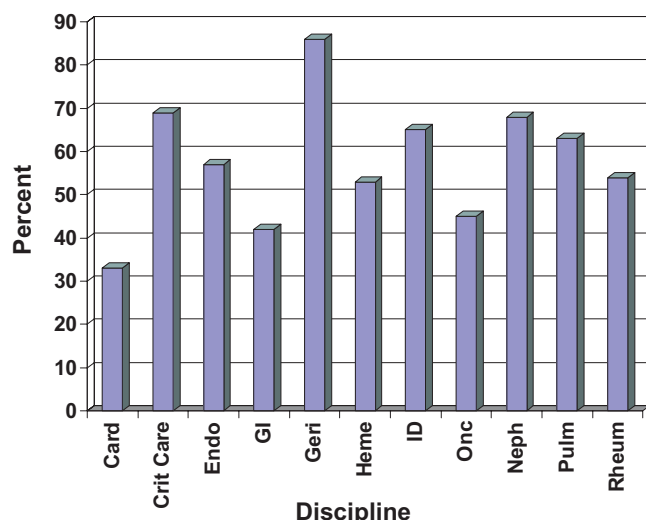


Figure 1. Rates of completing maintenance of certification in internal medicine by subspecialists. The data shown are for subspecialists who certified initially in 1990 through 1997 and have time-limited certificates in internal medicine. The data shown are as of February 2009. Data were kindly provided by Lorie Slass, American Board of Internal Medicine.

dependent on the answer to the first. Certainly, if a subspecialist has a responsibility to provide care outside his or her subspecialty, then it necessarily follows that the subspecialist has a responsibility to keep current in areas outside the subspecialty; however, even if a subspecialist does not intend to provide care outside the subspecialty, I believe that the subspecialist does have a responsibility to maintain competency in a “core” of internal medicine. The reason is that high-quality patient care is dependent on the physician’s having an understanding of the patient as a whole, not just the patient’s isolated disease within the subspecialist’s purview. Optimal evaluation and treatment of a patient involve consideration of a patient’s comorbid conditions, drug interactions, *etc.*, and are likely to be compromised by a disease-centric rather than a broader, patient-centric approach.

If one accepts the premise that subspecialists should maintain competency in a core of internal medicine, then the next question is what should be included within that core. The Alliance for Academic Internal Medicine, through its Residency Redesign Task Force, drafted a document outlining the broad areas of a core of internal medicine, along with more details within each of the broad areas. The composition of the Residency Redesign Task Force included educational leaders who represented various constitu-

encies of the Alliance for Academic Internal Medicine, specifically department chairs, residency program directors, student clerkship directors, and subspecialty division chiefs. In addition, there was representation from the American Board of Internal Medicine and ACP (I was the ACP representative).

The broad areas of core content within the medical knowledge competency for an internist are shown in Table 1, and further details within each of these broad areas can be found at the following web site: <http://www.im.org/PolicyAndAdvocacy/PolicyIssues/Education/Documents/FINALCoreCompetenciesandCoreContent.pdf>. When this document was drafted, the intent was to include areas that not only are core during training but also form a foundational knowledge base for all internists to maintain throughout their career, independent of their ultimate scope of practice.

The ACP’s Education Committee has been keenly interested in the process of maintenance of certification for internal medicine specialists and subspecialists. As described in a position statement developed by the Education Committee and approved by the ACP’s Board of Regents, the ACP’s favored model of recertification would be one in which subspecialists “maintain certification in both internal medicine and their subspecialty through a single process that evaluates and [en]sures the subspecialist’s competence in the subspecialty as well as the core components of internal medicine relevant to all internists.” This model is not currently in effect, and any decisions to transition to the model would ultimately need to be made and implemented by the American Board of Internal Medicine.

Table 1. Core content of internal medicine

1. Evaluation of the patient with an undifferentiated presentation
2. Treatment of common medical conditions
3. Basic preventive care
4. Basic interpretive skills
5. Recognition and management of emergency medical problems
6. Common pharmacotherapy
7. Cross-cutting, cross-disciplinary topics
8. Cross-cutting skills
9. Procedures

Source: Alliance for Academic Internal Medicine (<http://www.im.org/PolicyAndAdvocacy/PolicyIssues/Education/Documents/FINALCoreCompetenciesandCoreContent.pdf>).

Given the ACP's belief in the importance of core internal medicine for the subspecialist, we were pleased when we were approached by the editors of *NephSAP* to discuss our interest in collaborating to develop "Primary Care for the Nephrologist" as a new topic for *NephSAP*. We were particularly delighted when two outstanding general internists, Drs. Denise Dupras and Ericka Tung, both of whom are physicians and faculty members at the Mayo Clinic, agreed to spearhead this collaborative effort between the American Society of Nephrology and the ACP by writing this summary of selected generalist content for the subspecialist. Recognizing that it is impossible to cover all of general internal medicine in such a limited space, Drs. Dupras and Tung have chosen to focus on issues that relate to disease screening as well as coverage of several important clinical conditions that are

commonly encountered in patients who are seen by subspecialists.

Whether this type of review will change practice patterns among nephrologists or increase their comfort in addressing issues outside their subspecialty remains to be seen. In addition to hoping that it will, we would like to see it spark a wider discussion about the roles and responsibilities of subspecialists in the broader clinical area of internal medicine, which provides the foundation of clinical training for all subspecialists. Finally, the subspecialist who is able to consider a broader perspective on his or her patient's problems or even to care for these problems should be congratulated for both contributing to better patient care and for making a dent in solving America's health care needs in primary care.

Syllabus

Primary Care for the Nephrologist

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Learning Objectives:

1. To recognize the importance of family history in determining the most appropriate screening strategy for colon and breast cancer
2. To recommend the addition of pharmacotherapy to all patients who want to quit smoking
3. To recognize patients who are at risk for depression and use effective screening tools
4. To integrate evidence-based cancer screening guidelines into practice and determine when modification of screening guidelines is needed on the basis of patients' life expectancy, preferences, comorbidities, and functional status
5. To recognize the association between chronic kidney disease and cognitive impairment and to identify the risks, benefits, and limitations of Food and Drug Administration–approved medications that are used to treat dementia
6. To identify patients in your practice who are at high risk for falls and use evidence-based fall prevention interventions to prevent future falls for these individuals

Defining Primary Care

The term “primary care” was first introduced in 1967 (1). Alpert described the three fundamental functions of a primary clinician: To provide first-contact care, to assume responsibility for longitudinal care, and to coordinate care with subspecialty clinicians as needed (2).

In 1978, the Institute of Medicine defined primary care as “accessible, comprehensive, coordinated and continual care delivered by accountable providers of personal health services.” During the subsequent 20 yr, significant changes occurred in the field of medicine and the delivery of health care to individuals and society. The Institute of Medicine issued a final report defining primary care in 1996. The essential elements

of primary care were defined as the following: (1) Integrated and accessible health services; (2) accountability of clinicians and systems for quality of care, patient satisfaction, efficient use of resources, and ethical behavior; (3) the majority of personal health care needs, which include physical, mental, emotional, and social concerns; (4) a sustained partnership between patients and clinicians; (5) primary care in the context of family and community; and (6) recognition that services will be provided by a broader array of individuals in a primary care team, including nurse practitioners and physician assistants (3). The report also emphasized the need to focus on health promotion and disease prevention and care of the chronically ill, especially the elderly, with multiple problems. This definition is important because it specifies which types of activities are considered primary care and demonstrates that medical subspecialists may provide these activities. A recent review highlighted the importance of preventive services for patients with chronic kidney disease and ESRD (4).

The National Ambulatory Medical Care Survey, published in 2008, reported that of the 902 million visits made to physician offices in the United States, 22% of the visits were made to medical subspecialists. During these nearly 200 million visits, it is likely that there will be opportunities for the provision of primary care services, including disease screening and health maintenance (5).

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Screening for Disease

The idea of screening for unrecognized disease is a concept first developed in the early 1950s. The principles underlying appropriate screening were described in a World Health Organization publication, “Principles and Practice of Screening for Disease,” published in 1968 (1). The following is a summary of the 10 principles outlined in this document. The condition should be an important health problem, and the natural history of the condition should be adequately understood. There should be a suitable test that is acceptable to the patient population. There should be an early symptomatic stage and an accepted treatment for patients with recognized disease. There should be an agreed-on policy on whom to treat as patients. Screening should not be one-time but a continuous process, and the cost should be economically balanced relative to other health care expenditures. It is important to distinguish between screening—which involves asymptomatic individuals—and case-finding—which involves individuals with symptoms.

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Understanding Guidelines

The Institute of Medicine defines practice guidelines as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.” The report, published in 1990, described eight attributes of good guidelines (1). Subsequently, the National Health and Medical Research Council of Australia published its recommendations on the essential elements of a clinical guideline (2). They listed nine basic principles for developing guidelines: (1) Guidelines should focus on outcomes, (2) guidelines should be based on the best available evidence and include a statement about the strength of the recommendation, (3) the method that is used to synthesize the evidence should be the strongest applicable, (4) the process for guideline development should be multidisciplinary and include consumers, (5) guidelines should be flexible and adaptable to varying local conditions, (6) guidelines should be developed with the consideration of re-

Table 1. Factors that may influence the strength of the recommendation in the GRADE system

Factors that may decrease the strength of recommendation

1. Available randomized, controlled trials have a high likelihood of bias
2. Inconsistency of results
3. Indirect evidence
4. Sparse evidence
5. Reporting/publication bias

Factors that may increase the strength of recommendation when the evidence is based on observational studies

1. Large magnitude of effect
2. Plausible confounding would reduce a demonstrated effect
3. Dose-response gradient

Adapted from reference 11.

source constraints, (7) guidelines should be disseminated and implemented, (8) the impact and implementation of guidelines should be evaluated, and (9) guidelines should be revised regularly.

Efforts toward developing consensus on grading quality of evidence and strength recommendations have resulted in the development of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (3). The GRADE approach emphasizes the assessment of the quality of the evidence but also the uncertainty about the trade-offs, which can have a significant effect on whether the final recommendations are strong or weak. The quality of the evidence is rated as high, moderate, low, or very low and is based on whether future research is likely to change the estimate of the effect. Factors that can significantly affect the strength of the final recommendation are listed in Table 1.

The US Preventive Services Task Force (USPSTF), appointed by the Agency for Healthcare Research and Quality, published a series of articles describing their new method for developing guidelines and recommendations (4–6). Table 2 lists the system for grading recommendations. They further specify the level of certainty of net benefit associated with the recommendation as high, moderate, or low. One of the difficulties with interpreting these recommendations is the category of “insufficient evidence.” The USPSTF published an article to help clinicians make decisions on the basis of the balance of risk and benefit for individual patients in the setting of “insufficient evidence” recommendation (6). They define four domains of information that are relevant to clinicians in

Table 2. USPSTF grade definitions

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.	Offer or provide this service only if other considerations support the offering or providing of the service in an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, then patients should understand the uncertainty about the balance of benefits and harms.

Reprinted from reference 12.

making the decision of whether to recommend a preventive service: (1) The potential preventable burden of the disease; (2) the potential harms associated with the preventive service; (3) the costs, which include opportunity costs; and (4) the current practice of providers.

The challenge for clinicians is that multiple guidelines may exist for any given clinical situation, and often the guidelines come to different conclusions and recommendations, which serve to confuse rather than to clarify the most appropriate course of action for practitioners and patients. Oxman *et al.* (7) pointed out that clinicians need and use guidelines but that the recommendations should not be accepted uncritically. They stressed that it is essential that clinicians learn how to appraise clinical guidelines. The recommendations for prostate cancer screening using the prostate-specific antigen (PSA) test illustrate the challenges that providers face. The most recent guidelines from the USPSTF recommended against screening for early prostate cancer in men who are ≥ 75 yr and stated that there is insufficient evidence for screening men who are younger than 75 (8). The American Cancer Society recommends that providers have a discussion annually with men who are ≥ 50 yr of age and have a life expectancy of >10 yr regarding the risks and benefits of screening with PSA (9). They go on to recommend

that this discussion begin at age 45 for men who are at increased risk for prostate cancer. The American Cancer Society does not specify an upper age limit for screening. The American Urological Association recently published its recommendations (10), which include beginning PSA screening at age 40. They also state that their recommendations are designed to provide clinicians with information and should not be considered a fixed guideline. To understand the difference in the final recommendations, providers would have to look carefully at how the guideline was developed. One of the important differences in guideline development is often how "expert opinion" is incorporated into the guideline. For instance, in the case of the USPSTF, they explicitly state that expert opinion is not included in their guidelines.

Clinicians may access guidelines through the National Guideline Clearinghouse (<http://www.guidelines.gov>), which provides links to guidelines as well as synthesis of guidelines that cover similar topics and expert commentary on these topics. Another useful Web site is the Guidelines International Network (<http://www.g-i-n.net>), which has the world's largest guideline library and seeks to improve the quality of health care by supporting an international collaboration for the systemic development of clinical practice guidelines and their application.

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Cancer

Burden of Disease

Each year the American Cancer Society (ACS) publishes a report entitled “Cancer Facts & Figures.” The 2008 report estimated that 1,437,180 new cancer cases would be diagnosed that year. It is estimated that more than 1500 people a day die from cancer, and this disease accounts for one of every four deaths. Cancer is the second most common cause of death in the United States, exceeded only by heart disease (1).

As early as 1980, the ACS recommended a cancer-related checkup and screening for asymptomatic disease; however, this report emphasized the need

for decisions to be made between individual patients and providers and did not recommend mass screening at the public’s expense (1). The following sections include the current screening recommendations and guidelines for selected cancers.

Principles of Prevention and Cancer Screening for Older Adults

Counseling older adults about appropriate preventive services remains a complex task in the primary care practice. Guidelines put forth by specialty organizations and government agencies typically communicate the recommended age to initiate screening but often fail to recommend a firm end point or age level when it is appropriate to stop screening. As our population ages and life expectancies rise, it is essential for the primary care provider to feel comfortable tailoring health maintenance recommendations for the mature patient. These recommendations must be based not only on available evidence but also on the patient’s preferences, values, and prognosis.

Significant heterogeneity exists in the growing population of older adults. In addition, the prevalence and mortality rates that are associated with malignancies such as breast, colon, and prostate cancer increase with age. Approximately 30% of women and 43% of men who are older than 65 yr will develop cancer during their lifetime (2). When deciding how long to continue cancer screening, the clinician must first estimate the patient’s life expectancy, because life expectancy affects the individual’s likelihood of receiving benefit from the proposed screening modality (3,4). In general, older adults who have life expectancies of ≤ 5 yr are unlikely to receive survival benefit from cancer screening (5).

To determine life expectancy better, the clinician must assess chronologic age (and predicted median life expectancy) in conjunction with an individual’s functional status and comorbid conditions (see Table 3 for life expectancy at various ages). Functional status and the presence of comorbid conditions can be helpful in determining whether an individual’s life expectancy is lower, higher, or typical of other individuals in their age–gender cohort (5). Functional status refers to an individual’s ability to perform tasks that are required for living. Functional status not only is predictive of life expectancy but also is strongly correlated with risk for hospitalization and nursing home placement and quality of life (6–8). Assessment of basic

Table 3. Life expectancy at various ages

Age (yr)	Total (yr)	Men (yr)	Women (yr)
Birth	77.4	74.7	80.0
65	18.4	16.8	19.7
70	14.8	13.4	15.9
75	11.7	10.5	12.5
80	8.9	7.9	9.5
85	6.6	5.9	7.0
90	4.8	4.3	5.0
95	3.5	3.1	3.5
100	2.5	2.2	2.5

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activities of daily living such as transferring in and out of bed, toileting, bathing, grooming, dressing, and feeding oneself allow the clinician to appreciate his or her patient's level of disability.

Detection of asymptomatic disease with the use of available screening modalities requires lead time to benefit an older patient (9). Comorbid conditions such as ESRD, congestive heart failure, and dementia play a major role in predicting a patient's risk for dying before the benefits from the screening test outweigh the harms (see Table 4 for average life expectancy after diagnosis of selected diseases).

Next, the clinician must discuss the benefits and potential harms that are associated with the proposed screening test and weigh these factors against the patient's personal values, beliefs, and preferences. Possible adverse events, the potential need for additional testing or procedures, and the psychological distress of screening should be weighed. Studies that examined screening preferences of older adults revealed extensive heterogeneity in their values regarding cancer screening modalities (10). In addition, older adults with comorbid conditions, such as dementia, may find cancer screening tests to be overly burdensome or assaultive to their bodies (11). Specific guide-

lines and recommendations for cancer screening in the elderly are discussed in the context of each individual malignancy.

When deciding how long to continue cancer screening, the clinician must consider the patient's life expectancy, functional status, and comorbid conditions.

Cancer Screening in Chronic Kidney Disease

Currently, there are no specific cancer screening guidelines for the growing population of individuals with ESRD. Weighing the risks and benefits of cancer screening among patients with chronic kidney disease is often a challenging task and requires an individualized approach to the patient. Nephrologists must weigh their patient's increased risk for certain cancers (e.g., cervical cancer, tongue cancer, urothelial cancers) with the same patient's expected remaining lifetime. Assessment of whether a patient is on a transplant waiting list is also a factor to take into consideration (12).

Patients with ESRD have a highly variable, often reduced life expectancy. The estimated life expectancy for an adult between the ages of 65 and 69 yr at the onset of dialysis is 4.62 yr, whereas adults who are older than 80 yr when they start dialysis have an estimated mean life expectancy of only 2.59 yr (13). Given the increased mortality associated with ESRD, there are fewer life-years for screening to be of benefit (14). Consequently, many available cancer screening modalities may be of limited benefit for these individuals (12). The important impact of comorbidities and predicted life expectancy was highlighted in an analysis conducted by Kajbaf *et al.* (15). Using ESRD data from the Canadian Organ Replacement Registry combined with North American statistics for breast and cervical cancer, this group calculated the maximum increase in life expectancy (for a 60-yr-old woman)

Table 4. Average life expectancy after diagnosis of selected diseases

Disease	Age (yr)	Life Expectancy (yr)
ESRD: initiation of dialysis	65	4.6
Alzheimer's disease	Not specified	Men 4.2; women 5.7
Hip fracture	80	5.4
Congestive heart failure	>75	Men 3.9; women 4.5

Adapted from references 13 and 66.

from routine Papanicolaou (Pap) testing and mammography to be 3 and 2 d, respectively. These data are based on average results for the ESRD population. Clinicians must make decisions about cancer screening on an individual basis with their patients, weighing the aforementioned factors.

Lung Cancer

Burden of Disease. Cancer of the lung and bronchus is the leading cause of cancer death in men and women. The ACS estimated that 159,390 Americans would die of this cancer and that 116,090 men and 103,350 women would be diagnosed with lung cancer in 2009. It is the second most common newly diagnosed cancer in both men and women.

The most recent Surveillance, Epidemiology, and End Results (SEER) statistics reported that the median age at diagnosis of lung and bronchus cancer was 71 with an age-adjusted incident rate of 63.9 per 100,000 men and women per year. The median age at death was 72 and the age-adjusted death rate was 54.1 per 100,000 men and women per year (16).

Screening Recommendations. Both the US Preventive Services Task Force (USPSTF) and the American College of Chest Physicians have published guidelines and recommendations for lung cancer screening in asymptomatic patients (17,18). The USPSTF concluded that low-dose computerized tomography (LDCT) screening may result in diagnosing lung cancer earlier; however, significant false-positive results are associated with the test, and there is no evidence that earlier diagnosis leads to better patient outcomes. The overall recommendation was that the evidence was insufficient to recommend for or against screening asymptomatic individuals for lung cancer with LDCT, chest x-ray, sputum cytology, or a combination of these tests (17). The American College of Chest Physicians makes a strong recommendation against serial chest x-rays or sputum cytology and recommend LDCT only in the context of a clinical trial. A 2009 updated Cochrane Database of Systematic Reviews also concluded that there was no benefit from screening with serial chest x-rays or sputum. This review also found a statistically significant increase in lung cancer in those who were screened with serial chest x-rays (19).

Tobacco use is recognized as the primary risk factor for the development of multiple types of cancer, most commonly of the lung and bronchus. The most

Table 5. Gail model risk factors

Age at menarche
Age at first live birth
Number of previous breast biopsies
Presence of atypical hyperplasia in breast biopsy
Number of first-degree relatives with breast cancer
Race

Data from reference 21.

recent report from the National Center for Health Statistics estimated that 24% of men and 18% of women were smokers in 2006 (20). The incidence rate of lung cancer has been decreasing in men since 1990; however, in women, the rate has increased among those who are older than 75, reflecting differences in smoking patterns. The age-specific death rate from lung cancer has also been decreasing in men but has not yet leveled off in older women. There also are significant geographic variations in lung cancer mortality and incidence reflecting differences in smoking patterns. Treatment of tobacco use and dependence is discussed in a separate section.

Breast Cancer

Burden of Disease. Excluding skin cancer, breast cancer is the most frequently diagnosed cancer in women. The ACS estimated that 192,370 cases of invasive breast cancer and an additional 62,280 cases of carcinoma *in situ* of the breast would be diagnosed among US women in 2009. It was estimated that 40,170 women would die of breast cancer in 2009.

The most recent SEER statistics reported that the median age at diagnosis of breast cancer was 61 with an age-adjusted incident rate of 126.1 per 100,000 women per year. The median age at death was 69, and the age-adjusted death rate was 25.0 per 100,000 women per year (16).

Screening Recommendations. Breast cancer screening recommendations vary depending on a woman's estimated lifetime risk. Numerous models have been developed to estimate an individual's risk and are based primarily on family history. The most widely recognized is the Gail model. The Gail model was derived from data collected by the Breast Cancer Detection and Demonstration Project (BCDDP; see Table 5 for Gail model risk factors [21]). Using known risk factors, clinicians can calculate the estimated risk for an individual patient with an online tool developed by the National Cancer Institute (<http://www.cancer>.

Table 6. Risk assessment criteria for inherited breast-ovarian cancer syndrome

Non-Jewish families: Any of the following

- one case of breast cancer ≤ 40 yr old in an FDR or SDR
- one FDR or SDR with breast and ovarian cancer, at any age
- two or more cases of breast cancer in FDRs or SDRs if one is diagnosed at ≤ 50 yr old, or is bilateral
- one FDR or SDR with breast cancer at ≤ 50 yr old, or bilateral and one FDR or SDR with ovarian cancer
- three cases of breast and ovarian cancer (at least one case of ovarian cancer) in FDRs and SDRs
- >two cases of ovarian cancer in FDRs and SDRs
- one case of male breast cancer in an FDR or SDR if another FDR or SDR has (male or female) breast or ovarian cancer

Jewish families: Any of the following

- one or more cases of breast cancer ≤ 50 yr old in an FDR or SDR
- one or more cases of ovarian cancer at any age in an FDR or SDR
- one or more FDRs or SDRs with breast cancer at any age, if another FDR or SDR has breast and/or ovarian cancer at any age
- one or more cases of male breast cancer in an FDR or SDR

Adapted from reference 67. FDR, first-degree relative; SDR, second-degree relative.

gov/bcrisktool/). Additional algorithms have been developed to estimate the likelihood that a *BRCA* mutation is present. A recent review compared the models and their use (22). Table 6 lists the criteria used to assess the risk for inherited breast-ovarian cancer syndrome.

The ACS published guidelines for breast cancer screening in women of average risk. In their most recent guideline, they recommend beginning breast self-examination at age 20 and beginning clinical breast examinations (CBE) at least every 3 yr between ages 20 and 39 and annually after age 40. They recommend annual mammography beginning at age 40 (23). This recommendation differs from the recommendation of the USPSTF, which recommends against routine screening mammography among women aged 40 to 49 and suggests that biennial screening mammography before the age of 50 should be an individual decision, made after weighing potential risks and benefits (Grade C recommendation). The USPSTF recommends biennial screening mammogram for women

between the ages of 50 and 74 yr (Grade B recommendation). They found insufficient evidence for or against recommending breast self-examination or CBE alone among women aged 40 and older (I statement). The USPSTF also recommends against referring women who are not at increased risk for breast cancer for either genetic counseling or *BRCA* testing (25). The American College of Physicians recommends that for women between the ages of 40 and 49, clinicians perform an individualized risk assessment, discuss the risks and benefits of screening, and share the decision-making regarding which testing should be performed (26).

Extensive controversy exists among government agencies and medical societies about how often to screen and when to stop. The American Geriatrics Society outlines that women, up to age 85, should have an estimated 5-yr life expectancy for mammography to be considered for screening every 1 to 2 yr. Beyond age 85, only those in "excellent health and functional status" or patients who strongly value this screening test should be screened (27).

The genetic mutations *BRCA1* and *BRCA2* significantly increase the lifetime risk for breast cancer to 65 and 45% by age 70, respectively. These genes are inherited in an autosomal dominant pattern. Other, less common mutations that are associated with increased risk occur in the *TP53* gene and *PTEN* gene. Clinical situations that are associated with increased risk include a history of mantle irradiation, lobular carcinoma *in situ*, atypical lobular hyperplasia, increased breast density on mammography, and a history of breast cancer. The decision to get a genetic consultation and/or test a woman for the *BRCA* mutation should be made on the basis of the likelihood that a genetic mutation is present (28). Current recommendations from the USPSTF regarding who should be offered genetic screening for *BRCA* mutation are listed in Table 7.

In addition to *BRCA* testing, breast magnetic resonance imaging (MRI) has been suggested as an adjunct to mammography for breast cancer screening in these high-risk groups. The ACS recommended against using MRI in average-risk women but recommended an annual MRI in addition to mammography in women whose lifetime risk for breast cancer was 20 to 25%, based in part on the results of six studies that assessed the use of MRI in high-risk groups (29). The studies reported the sensitivity of MRI as 77 to 100%

Table 7. Recommendations from the USPSTF on who should be offered genetic testing for *BRCA* mutations: A family history of breast or ovarian cancer that includes a relative with a known deleterious *BRCA* mutation

For non-Ashkenazi Jewish women

- Two first-degree relatives with breast cancer, one of whom was diagnosed at age 50 or younger
- A combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis
- A combination of both breast and ovarian cancer among first- and second-degree relatives
- A first-degree relative with bilateral breast cancer
- A combination of two or more first- or second-degree relatives with ovarian cancer, regardless of age at diagnosis
- A first- or second-degree relative with both breast and ovarian cancer at any age
- History of breast cancer in a male relative

For women of Ashkenazi Jewish descent

- Any first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer

Adapted from reference 68.

and specificity as 81 to 99%. In contrast, the sensitivity of mammography was 16 to 40% and specificity was 93 to 99%, so although the detection rate is higher with MRI compared with mammography, there is also higher false-positive rate, leading to increased number of biopsies, only 20 to 40% of which are malignant. The cost-effectiveness of adding MRI to mammography and screening carriers with the *BRCA1/2* gene mutations annually beginning at age 25 is highly variable and greatly dependent on age. It is most cost-effective when used to screen women with the *BRCA1* mutation in addition to mammography between the ages of 35 and 54, with an estimated cost per quality-adjusted life-year of \$55,420 (25). A recent meta-analysis further reported the benefits of adding MRI to mammography for screening women at high risk for breast cancer (30). This study incorporated the American College of Radiology Breast Imaging and Reporting System (BI-RADS) to classify the tests as positive. This rating system incorporates five levels from 0 (indeterminate) to 5 (highly suspicious requiring biopsy). Using an estimate of 2% prevalence of disease and a BI-RADS score ≥ 4 , they calculated that the negative likelihood ratio for the combination of the

MRI and mammography was 0.14 compared with 0.70 for mammography alone. They concluded that the most accurate means of screening women at high risk for breast cancer on the basis of genetic predisposition or family history was to use both MRI and mammography annually.

Colon Cancer

Burden of Disease. Colorectal cancer is the third most commonly diagnosed cancer in men and women and the third most common cause of cancer-related death. The ACS estimated that 106,100 cases of colon and 40,870 cases of rectal cancer would be diagnosed in 2009. They also estimated that 49,920 individuals would die of colorectal cancer in 2009.

The most recent SEER statistics reported that the median age at diagnosis of colorectal cancer was 71 with an age-adjusted incident rate of 50.6 per 100,000 men and women per year. The median age at death was 75, and the age-adjusted death rate was 18.8 per 100,000 men and women per year (16). The lifetime risk for colorectal cancer in men is 5.7% and in women is 5.1%.

The cancer incidence rates have been decreasing for most of the past 2 decades, likely in part because of increased screening. Unlike most cancers, for which diagnostic testing is focused on early detection, screening with colonoscopy allows for the prevention of cancer by the removal of adenomatous polyps, which are precursors to malignancy.

Screening Recommendations. Both environmental and genetic risk factors can increase an individual's risk for developing colorectal cancer. A history of colorectal cancer in a first-degree relative or a personal history of inflammatory bowel disease doubles the risk for an individual's developing colon cancer. If the cancer occurs in more than one first-degree relative or if the relative is younger than 45 yr when the diagnosis is made, then the relative risk increases four-fold. Other factors that are reported to increase the risk slightly include obesity; diabetes; and high consumption of alcohol, red meat, or processed meat (31–33).

Recently, the ACS, American College of Radiology, and US Multi-Society Task Force on Colorectal Cancer collaborated and developed an updated consensus guideline on screening for colorectal cancer in average-risk individuals (34). In this guideline, there is a distinction between tests that are conducted primarily to detect cancer and those that are likely to detect

both cancer and adenomatous polyps. There are a number of options for testing, and patients and health care providers should discuss the benefits and risks of each approach when considering colorectal cancer screening (Table 8).

Studies that primarily detect cancer include the guaiac-based and immunochemical-based stool studies for fecal occult blood (FOBT) and the newer stool DNA (sDNA) test. The sensitivity and specificity of a guaiac-based FOBT has been shown to be highly variable and is based on a number of factors, including the number of samples collected, whether the specimen is rehydrated, how the specimen is collected, which brand of test is used, and other factors (35). One prospective study of asymptomatic average-risk patients with a positive FOBT result revealed that the predictive value of a positive FOBT result for clinically important colonic lesions increased as the severity of chronic kidney disease worsened (36). In addition, the reported sensitivity of a single guaiac-based FOBT varies considerably and led the task force to recommend against using a single FOBT in the office as a screen for colorectal cancer. The fecal immunochemical-based test has some advantages compared with the guaiac-based test; however, it does not seem to have increased diagnostic accuracy when compared with the highest sensitivity of currently marketed guaiac-based FOBT. Current recommendations for both tests are that they be performed yearly and any positive studies be followed up with a colonoscopy.

The sDNA test consists of a multiple-marker panel that includes 21 separate point mutations in the *kRAS*, *APC*, and *P53genes* and two additional probes. Studies reported that the first-generation test had sensitivities ranging from 52 to 91% and specificities ranging from 93 to 97% for the detection of colorectal cancer. A second-generation version of the sDNA is now available, but data on the sensitivity and specificity have not been released. The task force believed that there were insufficient data to recommend a testing frequency with the sDNA test (37).

Tests that detect adenomatous polyps and cancer require a structural examination of the colon. These tests include flexible sigmoidoscopy (FSIG), colonoscopy, double-contrast barium enema (DCBE), and computed tomography colonography (CTC). The FSIG examines the lower half of the colon. Evidence from case-control and cohort studies supports the use of FSIG for colorectal screening. The effectiveness of

FSIG depends on the completion of a high-quality examination. One criterion suggested as a measure of quality is insertion of the scope to 40 cm or beyond when screening for colorectal cancer. The primary limitation of FSIG is that it examines only a portion of the colon, and there are differences in the prevalence of distal and proximal lesions on the basis of age, gender, and ethnicity.

Colonoscopy is the most common procedure performed for colorectal cancer screening. Although there are no prospective, randomized, controlled trials of screening colonoscopy for reduction in incidence of colorectal cancer or mortality, there is indirect evidence that polypectomy performed at the time of colonoscopy has significantly decreased the incidence of colorectal cancer and, by extension, mortality (38,39). The primary benefit of colonoscopy is that it allows for a full examination of the colon and rectum in a single session and the detection of polyps or cancers with the opportunity for polypectomy or biopsy. Although rare, bowel perforation can occur. In general, the perforation rate is approximately 3.8 per 10,000 procedures in the United States (37). Finally, although colonoscopy is considered the “gold standard,” studies have found a miss rate for large adenomas (10 mm) to be 2.1% and for any size adenoma to be 22% (40).

The DCBE has been recommended for colorectal cancer screening since the late 1990s, although there is limited evidence about its efficacy as a primary screening modality. Like the colonoscopy, it provides a full structural examination of the colon and requires an extensive colonic preparation before the test. It is considered a relatively safe procedure with a lower perforation rate of 1 in 25,000. The task force recommended the DCBE every 5 yr as an acceptable option for colorectal cancer screening (37).

The final structural examination, the CTC, is also referred to as “virtual colonoscopy.” Adequate bowel preparation and gaseous distention of the colon are essential to ensure a successful examination. The study also requires an adequately prepared colon as with colonoscopy and DCBE. Since its introduction in the mid-1990s, there have been substantial advancements in the technology and computer imaging graphics, which allow for visualization of three-dimensional endoscopic flight paths through the colon. A meta-analysis found the pooled sensitivity for CTC to be 48% for small polyps (<6 mm), 70% for medium-

Table 8. Consensus recommendations and key issues to consider when discussing colon cancer screening methods

Test	Interval	Key Issues for Informed Decisions
Tests that detect adenomatous polyps and cancer		
FSIG with insertion to 40 cm or to splenic flexure	Every 5 yr	Complete or partial bowel prep is required Sedation usually is not used, so there may be some discomfort during the procedure The protective effect of sigmoidoscopy is primarily limited to the portion of the colon examined Patients should understand that positive findings on sigmoidoscopy usually result in a referral for colonoscopy
Colonoscopy	Every 10 yr	Complete bowel prep is required Conscious sedation is used in most centers; patients will miss a day of work and will need a chaperone for transportation from the facility Risks include perforation and bleeding, which are rare but potentially serious; most of the risk is associated with polypectomy
DCBE	Every 5 yr	Complete bowel prep is required If patients have one or more polyps ≥ 6 mm, colonoscopy will be recommended; follow-up colonoscopy will require complete bowel prep Risks of DCBE are low; rare cases of perforation have been reported
CTC	Every 5 yr	Complete bowel prep is required If patients have one or more polyps ≥ 6 mm, colonoscopy will be recommended; if same-day colonoscopy is not available, a second complete bowel prep will be required before colonoscopy Risks of CTC are low; rare cases of perforation have been reported Extracolonic abnormalities may be identified on CTC that could require further evaluation
Tests that primarily detect cancer		
gFOBT with high sensitivity for cancer	Annual	Depending on manufacturer's recommendations, two to three stool samples collected at home are needed to complete testing; a single sample of stool gathered during a digital exam in the clinical setting is not an acceptable stool test and should not be done
FIT with high sensitivity for cancer	Annual	Positive tests are associated with an increased risk for colon cancer and advanced neoplasia; colonoscopy should be recommended if the test results are positive If the test is negative, it should be repeated annually Patients should understand that one-time testing is likely to be ineffective
sDNA with high sensitivity for cancer	Interval uncertain	An adequate stool sample must be obtained and packaged with appropriate preservative agents for shipping to the laboratory The unit cost of the currently available test is significantly higher than other forms of stool testing If the test is positive, colonoscopy will be recommended If the test is negative, the appropriate interval for a repeat test is uncertain

Reprinted from reference 34, with permission from John Wiley and Sons. gFOBT, guaiac-based FOBT; FIT, fecal immunochemical test.

sized polyps (6 to 9 mm), and 85% for polyps >9 mm. The specificity was less dependent on the size of polyp identified and ranged from 92 to 97% (41). As with the other tests, there are significant limitations (see Table 8). There have been concerns of regarding the long-term potential risks associated with radiation involved in the test, and ongoing efforts are targeting techniques to limit the radiation dose further. A potential advantage is that the imaging also captures incidental extra-colonic findings, providing the opportunity to discover unsuspected disease.

The USPSTF published a targeted review of the evidence for the use of the new screening tests and concluded that there was insufficient evidence to assess the benefits and harms of CTC and sDNA (42). They continue to recommend screening in asymptomatic adults between the ages of 50 and 75 (A recommendation).

Although the incidence associated with colon cancer increases with age, the risk for dying *from this disease* declines with decreasing life expectancy (5). Similarly, the potential reduction of colon cancer-related mortality decreases with increasing age and comorbid health conditions (43). The USPSTF recommends against routine colon cancer screening in patients between the ages of 76 and 85 unless there are special considerations that would support screening the individual patient. The USPSTF does not recommend screening patients who are older than 85 because other, competing causes of death preclude any mortality benefit that would outweigh potential risks of the procedure (37).

Medicare coverage of the aforementioned screening tests varies on the basis of a Medicare beneficiary's risk for colon cancer. Medicare covers the following tests and procedures in various combinations: FOBT, FSIG, colonoscopy, and barium enema. Medicare provides coverage for one colonoscopy every 2 yr for high-risk beneficiaries regardless of age and covers one colonoscopy every 10 yr for beneficiaries who are not at high risk (44).

Surveillance after Polypectomy Recommendations. Adenomatous polyps are the most common neoplastic finding for people who undergo screening colonoscopy. In the 1970s, it was common practice for patients who had undergone a polypectomy to have a repeat colonoscopy in 1 yr. Data from the National Polyp Study led the development of guidelines published by a gastrointestinal consortium recommending repeat colonoscopy 3 yr after polypectomy in most

patients. A consensus update "Guidelines for Colonoscopy Surveillance after Polypectomy" was published in 2006 by the US Multi-Society Task Force on Colorectal Cancer and the ACS (45). The society critically reviewed all of the available evidence and proposed risk stratification for patients who undergo polypectomy to determine the appropriate surveillance schedule. The following factors were identified as conferring high risk: The presence of three or more polyps, polyps >1 cm, villous features, and high-grade dysplasia. Other factors for which the evidence suggested an increased risk included family history and proximal location of polyps. The low-risk group was categorized as having only one or two adenomas, all <1 cm in size, with no high-grade dysplasia or villous features (see Table 9 for a summary of the recommendations for surveillance in asymptomatic individuals). Additional considerations include quality of the colon preparation, quality of the colonoscopy, life expectancy of the patient, and ongoing evolution of the guidelines.

Recommendations for breast and colon cancer screening in asymptomatic individuals are strongly influenced by family history.

Prostate Cancer

Burden of Disease. Excluding skin cancer, prostate cancer is the most common cancer in men, but it accounts for only 10% of the cancer deaths in men. The ACS estimated that 192,280 cases of prostate cancer would be diagnosed and that 27,360 US men would die of cancer of the prostate in 2009.

The most recent SEER statistics reported that the median age at diagnosis of prostate cancer was 60 with an age-adjusted incident rate of 163.0 per 100,000 men per year. The median age at death was 80, and the age-adjusted death rate was 26.7 per 100,000 men per year (16).

Screening Recommendations. Prostate cancer screening is controversial, and continuing debate exists about whether screening increases or decreases morbidity and mortality. Traditionally, prostate-specific antigen (PSA) and digital rectal examination (DRE) are used in combination for screening; however, both modalities have low predictive values. The reported positive

Table 9. Recommendations for surveillance after polypectomy

1. Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 yr. An exception is patients with a hyperplastic polyposis syndrome. They are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow-up.
2. Patients with only one or two small (<1 cm) tubular adenomas with only low-grade dysplasia should have their next follow-up colonoscopy in 5 to 10 yr. The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician).
3. Patients with three to 10 adenomas, or any adenoma ≥ 1 cm, or any adenoma with villous features, or high-grade dysplasia should have their next follow-up colonoscopy in 3 yr providing that piecemeal removal has not been done and the adenoma(s) are completely removed. If the follow-up colonoscopy is normal or shows only one or two small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 yr.
4. Patients who have >10 adenomas at one examination should be examined at a shorter (<3 yr) interval established by clinical judgment, and the clinician should consider the possibility of an underlying familial syndrome.
5. Patients with sessile adenomas that are removed piecemeal should be considered for follow-up at short intervals (2 to 6 mo) to verify complete removal. Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment. Completeness of removal should be based on both endoscopic and pathologic assessments.
6. More intensive surveillance is indicated when the family history may indicate hereditary nonpolyposis colorectal cancer.

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predictive value of DRE ranges from 6 to 33% (46,47). The positive predictive value for a PSA level >4 ng/ml is approximately 25 to 30% (48,49). Potential harms that are associated with PSA screening include screening-related anxiety, the potential need for prostate biopsy, and the possibility of the diagnosis of a prostate cancer that would never have caused symptoms in a patient's lifetime (50).

In 2002, the USPSTF found insufficient evidence to recommend for or against screening for prostate cancer. The update published in 2008 focused on three questions: Does screening with PSA decrease morbidity or mortality? What are the harms associated with prostate cancer screening? What is the natural history of PSA-detected localized prostate cancer? They continued to find insufficient evidence for or against screening for prostate cancer in men who are younger than 75 (51). The USPSTF recommends against screening for prostate cancer in men who are aged ≥ 75 because the harms that are associated with screening likely outweigh the potential benefits.

The ACS does not support routine testing for prostate cancer at this time. Their current recommendation is that health care providers have a discussion regarding risks and benefits of prostate cancer screening and offer DRE and annual PSA testing to men who have a life expectancy of at least 10 yr beginning at age 50 (23).

Cervical Cancer

Burden of Disease. The ACS estimated that 11,270 US women would be diagnosed with cervical cancer in 2009 and that 4,070 women would die of this cancer. These cases represent approximately 1% of cancer-related deaths in women (52). In developing countries, the overall burden of this disease is more profound: Cervical cancer is the second most common cause of cancer death in women.

The most recent SEER statistics reported that the median age at diagnosis of cervical cancer was 48 with an age-adjusted incident rate of 8.4 per 100,000 women per year. In the United States, the median age at death was 57, and the age-adjusted death rate was 2.5 per 100,000 women per year (16).

Preventing Cervical Cancer. Infection with human papillomavirus (HPV), typically acquired through sexual activity, is the most important risk factor for cervical cancer. A recent advance in the prevention of cervical cancer has been the development of the HPV vaccine. The most commonly administered vaccination protects against HPV types 6, 11, 16, and 18 (quadrivalent) (53). This vaccination was designed with the recognition that the majority of invasive cervical cancers are the result of infection with HPV 16 or 18. These two types of HPV also are responsible for approximately half of the cases of cervical intraepithelial neoplasia grades 2 and 3, which are believed

to be precursors of invasive cervical cancer. These two types, 16 and 18, also cause 80 to 90% of anal cancers in the United States (54). In 2007, the ACS convened an expert panel and developed a “Guideline for HPV Vaccine Use to Prevent Cervical Cancer and Its Precursors” (55). This report described significant disparities in cervical cancer incidence and mortality among various groups of women, which seem to be directly related to a lack of appropriate screening that results from limited resources and poor access to health care. A dramatic burden of cervical cancer is still found in underserved populations of the world, with highest rates in Africa, Central America, South America, and Micronesia (55).

In determining the age at which to vaccinate female individuals, a key consideration (as with any vaccination) is that it be given before the exposure is likely to occur. Studies of the available vaccinations enrolled girls as young as 9 yr. The current ACS guidelines include routine HPV vaccination for girls aged 11 to 12. It is also recommended for girls aged 13 to 18 to catch up or complete the series. The data are considered insufficient to recommend for or against vaccination of women aged 19 to 26, and it is not recommended for women who are older than 26. Studies have shown that the vaccination did not provide protection from disease in individuals with current or previous infection with HPV type 16 or 18 (55). Important unanswered questions remain, including whether groups that are known to be at increased risk for anal cancer, such as HIV-positive men, should receive the vaccination.

Screening Recommendations. Regardless of whether a woman is vaccinated against HPV, most organizations recommend that cervical cancer screening begin within 3 yr of sexual activity or between the ages of 18 and 21. The USPSTF last updated its guideline in 2003 and recommended a standard Pap smear be obtained annually for 3 consecutive years before lengthening the interval to 3 yr (56). They reviewed the literature regarding the new liquid-based technology (*e.g.*, Thin Prep) and found that the high sensitivity combined with a lower specificity resulted in the new test’s being cost-effective when used for screening on a 3-yr interval. They also reviewed the evidence regarding the use of HPV testing for primary screening and found that its addition to routine screening with a Pap smear did not provide additional benefit.

There are differences between organizations in

their recommendations regarding when to stop screening for cervical cancer on the basis of age. The USPSTF recommends Pap testing older women who have not been screened previously for cervical cancer but suggests that clinicians stop testing at “age 65 if a woman has had adequate recent screening with normal Pap testing and is not otherwise at high risk” (56). The ACS guidelines suggest that providers can stop performing Pap testing on women who are older than 70 when they have had three or more normal cervical cytology tests within the past decade (57). Despite differences between organizations about recommended age of cessation, the USPSTF, American College of Obstetricians and Gynecologists, ACS, and American Geriatrics Society all recommend that cervical cancer screening may be stopped after surgical removal of the cervix for benign indications (56–58). They recommended against routine screening in women who had hysterectomies for benign disease on the basis of two large studies that documented the risk for dysplasia or cancer to be 1 in 10 of the average population of women who still had a cervix (23). (See Table 10 for a comparison of recommendations between societies.)

Skin Cancer

Skin cancer is the most commonly diagnosed cancer in the United States (59). Almost 95% of all skin cancers are either basal cell carcinoma or squamous cell carcinoma; however, malignant melanoma accounts for approximately 75% of the mortality from skin cancer. The lifetime risk for melanoma among Americans is 1.94% for men and 1.30% for women (60).

No randomized, controlled studies have examined whether clinician-initiated screening for skin cancer is associated with improved clinical outcomes; however, one evaluation of the American Academy of Dermatology’s Skin Cancer Screening Program found that lesions that were identified in the context of this program were more likely to be of early stage than those that were detected in usual care (61). The USPSTF reviewed the evidence for general screening for skin cancer and did not make a recommendation for or against clinical screening (I Statement) because of a lack of available evidence (60).

Some groups are at elevated risk for skin cancer. Patients who are aged ≥ 65 and have fair skin, patients with atypical moles, and patients with more than 50

Table 10. Comparison of cervical cancer screening recommendations (strength of recommendation)

Organization	When to Begin	How Often	When to Stop	Method of Screening
USPSTF	Age 21 or start of sexual activity (A)	Pap at least every 3 yr	Age 65 if previous screening is adequate (D), after hysterectomy for benign disease (D)	Evidence insufficient for use of new technologies (I)
ACS	Age 21 or within 3 yr of becoming sexually active	Yearly with Pap, every 2 yr with liquid-based technology until 30, then every 2 to 3 yr with either method	After hysterectomy; age 70 if three previous Paps normal and normal Pap in past 10 yr	Frequency based on which technology used including HPV DNA, conventional Pap, liquid-based
AAFP	After start of sexual activity (SR)	Pap at least every 3 yr (SR)	No recommendation	Evidence insufficient for use of new technologies
ACOG	Age 21	Pap every 2 yr between the ages of 21 and 29 Pap every 3 yr between the ages of 30 and 65 or 70 ^a	Between 65 and 70 if three prior Paps normal and no abnormal tests in past 10 yr. Women with multiple partners excluded.	The most recent guidelines suggest either conventional or liquid-based testing may be used

ACP, American College of Physicians; AAFP, American Academy of Family Physicians; ACOG, American College of Obstetrics and Gynecology; SR, strong recommendation. Letters A, D, and I represent grades of recommendation (see Table 2).

^a This recommendation applies to women with three consecutive negative cytologic tests. Exceptions include women with HIV, compromised immunity, history of cervical intraepithelia neoplasia grade 2-3, or exposure to diethylstilbestrol *in utero*.

moles are at increased risk for melanoma. Renal transplant recipients (RTRs) are at markedly increased risk for nonmelanoma skin cancers, particularly in regions with high ultraviolet radiation exposure (62). Other key risk factors for skin cancers among RTRs include use of immunosuppressive medications and history of HPV infections (63).

Up to 53% of all malignancies among transplant recipients are skin and lip cancers, with RTRs having an overall incidence of squamous cell carcinoma that is almost 250 times higher than that of the general population (64). In addition, nonmelanoma skin cancers are often more aggressive in RTRs and occur at a younger age in RTRs when compared with the general population (63). Accordingly, the American Society of Transplantation has developed guidelines for outpatient surveillance that recommends annual skin examinations by a physician for all RTRs and more frequent follow-up for patients with a history of skin cancer (65).

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Thyroid Disease

Burden of Disease

Thyroid disease affects up to 5% of the population. Subclinical thyroid disease, defined as a biochemical abnormal thyroid test without associated symptoms that can be detected by the thyroid-stimulating hormone (TSH) test, is much more common. Subclinical hyperthyroidism occurs in approximately 1% of men and 1.5% of women who are older than 60. Overt hyperthyroidism is associated with increased risk for atrial fibrillation and osteoporotic fractures, but data are less convincing for subclinical hyperthyroidism (1–4). A recent retrospective study of 75 patients at a mean age of 62.2 found through multivariate analysis that the low TSH values, especially those <0.10 mU/L, and development of symptoms were significant factors in the progression to overt hyperthyroidism (2). Unlike previous studies that found that it was rare for overt hyperthyroidism to develop, this study found that 45.3% of the patients went on to develop overt disease whereas 20% reverted to normal TSH values.

Subclinical hypothyroidism is more common in both men and women and varies depending on race and age. In a large population study with a 20-yr follow-up, the risk increased substantially in women from 4 to 5% at ages 18 to 44 to 17.6% in women who were older than 75 (4). Evidence from this study suggests that the risk that subclinical hypothyroidism will progress to overt hypothyroidism increases with higher TSH, age, presence of thyroid antibodies, and female gender and that a woman with a serum TSH of >10 mU/L has a high likelihood of developing symptomatic hypothyroidism within 5 yr. A more recent study of the natural history of spontaneous subclinical hypothyroidism in men and women aged ≥55 yr provided additional insights that can help in the clinical care of these patients (5). In that study, 107 patients (87% female) were followed for 6 to 72 mo (mean 31.7 mo) at 6-mo intervals. The individuals were categorized into three groups on the basis of TSH concentration. The underlying cause of the subclinical hypothyroidism was autoimmune on the basis of thy-

roid peroxidase antibody concentrations in the majority (75.7%) of participants. Univariate analysis suggested that four factors—symptoms of hypothyroidism ($P = 0.0146$), positive thyroid peroxidase antibody concentrations ($P = 0.035$), lower levels of free T_4 ($P = 0.0217$), and higher levels of TSH ($P < 0.0001$)—were associated with progression to overt hypothyroidism. In the multivariate analysis, only the serum TSH concentration was significant ($P < 0.0001$). Similar to the previous study, the risk increased substantially with a TSH >10 mU/L (hazard ratio 10). The hazard ratio increased to 28 when the baseline TSH was >15 mU/L. An additional result with practical importance is that the majority who went on to develop definite hypothyroidism did so within the few months of the study. One limitation is that all of the patients who were enrolled in the study were part of an endocrine referral practice, so it is unclear whether the results generalize to other referral or primary care practices.

Screening Recommendations

One of the underlying tenets of screening for disease is that early detection of disease will result in significant health gains. A systematic review by Helfand (6) was unable to find evidence that treatment of either subclinical hyperthyroidism or hypothyroidism resulted in significant health improvements. A systematic review found good evidence for an association between TSH levels and the progression to overt hypothyroidism but no or insufficient evidence that treatment of subclinical hypothyroidism is of any benefit (3). With regard to subclinical hyperthyroidism, that review found an association between TSH levels <0.10 mU/L and the progression to clinical hyperthyroidism, some evidence of an association with the development of atrial fibrillation, and weaker evidence suggesting that the suppressed levels are associated with bone and cardiac disease. Again, there was no strong evidence that treatment of subclinical hyperthyroidism resulted in significant health gains (1).

The USPSTF reviewed the evidence and concluded that there were insufficient data to make a recommendation for or against routine screening for thyroid disease in nonpregnant adults (7). The consensus development conference, composed of members of the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endo-

crine Society, also recommended against the routine screening for thyroid disease in asymptomatic adults (3).

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Hyperlipidemia

Background

Cardiovascular disease (CVD) accounts for nearly half of all deaths in the United States. Lipid abnormalities are recognized as a significant risk factor for the development of CVD. Although multiple tools can be used to calculate risk for coronary heart disease (CHD), few data are available on their use in clinical practice and impact on patient outcomes (1). Factors that are used in calculating overall risk with the Framingham tool are listed in Table 11. Some authorities consider obesity, sedentary lifestyle, and metabolic syndrome risk factors as well. Lifetime risk for a cardiovascular event has been estimated at 49 and 32% in men and women, respectively (2).

In patients with ESRD, the risk for CVD is 10 to 20 times that in the general population, and 50% of the mortality is due to CVD (3). A Framingham offspring study found that patients with mild to moderate chronic kidney disease (CKD) had increased rates of known CVD risk factors, including hypertension, diabetes, and hyperlipidemia, and that individuals were less likely to reach treatment goals (4). Given this increase in the risk for CVD, patients with CKD should be assessed for cardiovascular risk factors at

Table 11. Factors included in Framingham Risk Assessment Calculator

1. Hypertension
2. Lipid abnormalities
 - a. Elevated total cholesterol (TC)
 - b. Elevated low-density cholesterol (LDL)
 - c. Low high-density cholesterol (HDL)
3. Diabetes
4. Smoking
5. Family history of premature coronary artery disease
 - a. 1st-degree male relative with event before age 55
 - b. 1st-degree female relative with event before age 65
6. Age (men ≥ 45 , women ≥ 55)
7. Male gender

Adapted from reference 15.

their visits with physicians who are providing their primary care. Many may not be candidates for “screening” but should have their lipid levels measured as part of their overall cardiac risk assessment.

Screening Recommendations

There are differences in the recommendations for screening men and women for lipid abnormalities. As with screening for colon cancer and breast cancer, the recommendations for screening for lipid disorders differ on the basis of age and the presence of other risk factors. The USPSTF updated their recommendations in 2008 (2). They strongly recommend (grade A) screening for lipid disorders all men who are aged ≥ 35 and women who are aged ≥ 45 and have additional risk factors for CHD. They gave grade B recommendations to screening for lipid disorders in men and women beginning at age 20 when they have risk factors for CHD. The grade C recommendation for screening for lipid disorders in women who are aged ≥ 20 or men who are aged 20 to 35 and do not have risk factors for CHD recognizes that there are few data supporting a net benefit to these individuals. The USPSTF recommends obtaining nonfasting total cholesterol (TC) and HDL levels as the first test for screening and confirming with a repeat test at a separate time. When elevated, they recommend a full fasting lipid profile.

The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) was published in 2002 (5) and updated in 2004

(6). The update continues to emphasize the use of three risk categories in determining the approach to treatment and setting goals for LDL levels, which remains the primary target for treatment. Their recommendations are based on the panel’s best interpretation of the empirical evidence and issues of clinical intervention, which explains why the final recommendations differ from those of the USPSTF. The Framingham risk assessment that was used to estimate the 10-yr risk for hard CHD end points is available at <http://hp2010.nhlbihin.net/atp3iii/calculator.asp?user-type=prof>.

The ATP III recommends screening all adults who are aged ≥ 20 with a fasting lipoprotein panel (TC, HDL, LDL, and triglycerides) every 5 yr (6). When nonfasting TC and HDL levels are obtained, they recommend getting the full fasting lipoprotein panel to determine the LDL. This screening recommendation for asymptomatic adults remains unchanged in the updated document. These recommendations are endorsed by the National Heart, Lung, and Blood Institute; the American College of Cardiology Foundation; the American Heart Association; and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Underlying their recommendations are the results of multiple studies showing that interventions to lower blood lipids, targeting LDL levels, have successfully decreased secondary and, more recently, primary CVD events (7–9). Importantly, in patients with CKD, the standard screening tests recommended by the ATP III and USPSTF often reveal unimpressive levels of TC and calculated LDL levels. Patients with kidney disease often have high triglyceride levels and low HDL levels, which more closely correlate with their risks for CVD. Additional abnormalities include elevation of highly atherogenic remnants of chylomicrons and very-low-density lipoproteins. This has led to the suggestion to use the non-HDL cholesterol rather than LDL level in assessing the risk for CVD in patients with CKD (10). Three recent meta-analyses from the Cochrane Collaboration specifically assessed the benefits of treating hyperlipidemia with statins in patients with CKD. They reviewed studies of individuals who had CKD that did not require dialysis, those who were on dialysis, and patients after renal transplantation. All three studies showed that statin therapy resulted in significant drops in TC and LDL levels and

that statins were well tolerated (11–13). There was a significant decrease in all-cause (relative risk 0.81) and cardiovascular mortality (relative risk 0.80) in patients who had CKD and were not on dialysis (13) but no significant differences in the other two studies. The implications of these findings are outside the scope of this document but raise important issues about whether LDL is the appropriate target for treatment in the prevention of CVD in these high-risk groups. These results extend and support the findings of a previous meta-analysis of the effect of statins in patients with CKD (14).

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Abdominal Aortic Aneurysm Screening Recommendations

Burden of Disease

Aneurysmal degeneration of the abdominal aortic and iliac arteries, commonly referred to as an abdominal aortic aneurysm (AAA), is a common age-related disease process in men and women who are older than 60 yr. Each year, thousands of Americans die of this condition, typically from rupture of a previously undetected aneurysm. The prevalence of AAA steadily increases with age. Among individuals who are aged ≥ 60 , approximately 4 to 8% of men and 1.5% of women are affected (1); however, prevalence rates are two to five times as high among individuals with cardiovascular risk factors (2). Major risk factors for AAA include a history of smoking (defined as 100 cigarettes in an individual's lifetime), advanced age, male gender, and family history. Among these, smoking is the most potent risk factor (3). Other contributing factors include treated and untreated hypertension, hyperlipidemia, intermittent claudication, and coronary artery disease (4). The male-to-female ratio is 4:1 to 5:1 among those aged 60 to 70; however, this ratio approaches 1:1 in patients who are older than 80 (5). Caucasian men are more frequently affected than African American men (5).

The normal infrarenal aortic diameters in patients who are older than 50 are approximately 1.7 cm in men and 1.5 cm in women. An AAA is present when the infrarenal diameter of the aorta exceeds 3.0 cm (6,7). The iliac arteries are involved in 40% of patients with AAAs, with the majority of these cases involving the common iliac arteries (5). Larger aneurysm diameter confers increased risk for rupture. The annual risk for rupture of AAAs that measure 4.0 to 5.4 cm is 0.5 to 1.0%, whereas the annual risk for rupture of AAAs that measure 5.5 to 6.0 cm is 5 to 10% (5). Other important risk factors for rupture include growth rate, history of smoking or chronic obstructive pulmonary disease, family history, poorly controlled hypertension, female gender, and eccentric shape (8,9).

Ruptured AAA and complications after surgical treatment are the cause of at least 15,000 deaths annually in the United States; however, it is believed that this figure might actually underestimate the true burden of this condition given the large number of Americans who have sudden death annually (10). After rupture, half of patients will die before reaching the hospital, and among those who reach the hospital, one study found that 17% died during the operation (11). Conversely, a recent prospective registry analysis of patients who had undergone elective AAA repair revealed that the 30-d mortality rates of open repair and endovascular repair were approximately 2.3 and 0.5%, respectively. One-year mortality rates were 5.8 and 5.7% for open and endovascular repair, respectively, making the case for early detection and intervention (12).

Screening Recommendations

Abdominal ultrasound is the standard screening modality for individuals who are at increased risk for AAA. When performed in a setting with adequate quality assurance, abdominal ultrasound has excellent test characteristics for diagnosing AAA, with a sensitivity of 95% and a specificity of nearly 100% (13). Multiple prospective, randomized studies have established the benefit of screening for AAA. In the Multicenter Aneurysm Screening Study (MASS), Caucasian men who were aged 65 to 74 and were screened with AAA and referred to surgery when AAAs with diameter >5.4 cm were identified had a 42% (95% confidence interval [CI] 22 to 58%) lower AAA-related mortality compared with the nonscreened population (14). Similarly, another large, randomized, controlled trial of Danish men aged 64 to 73 were randomly allocated to receive an invitation to be screened for AAA with ultrasound or to the control group. The cumulative 5-yr mortality in the invited group was reduced by 67% (15). Currently, the US Preventive Services Task Force (USPSTF) and a consortium of leading professional organizations recommend a one-time ultrasound for men who are aged 65 to 74 and have ever smoked (grade B recommendation). The USPSTF recommends against routine screening for women because the prevalence of AAA-related death for women who are younger than 80 is low (13). In 2006, the Screening for Abdominal Aortic Aneurysms Very Efficiently (SAAAVE) Amendment was passed, leading Centers for Medicare and Medicaid Services to add screening AAA ultrasound to the list of covered preven-

Table 12. Recommended ultrasound surveillance for patients with AAA

Diameter of Aneurysm	Interval for Follow-up
Less than 3 cm	No further testing
3 to 4 cm	Every 12 months
4 to 4.5 cm	Every 6 months
Greater than 4.5 cm	Consider referral to vascular subspecialist

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tive services. CMS allows men who are between the ages of 65 and 75 and have smoked at least 100 cigarettes in their lives and men and women who are aged 65 to 75 and have a strong family history of AAA to undergo screening ultrasound once (16).

Although the majority of effectiveness trials have examined the short-term benefits of screening for AAA, Kim *et al.* (17) analyzed the sustained benefits of AAA screening. In their multicenter, randomized trial, they found that men who were aged 65 to 74 and were invited to undergo AAA screening ultrasound had lower mortality rates (hazard ratio 0.53; 95% CI 0.42 to 0.68) at 7 yr than their counterparts who were not screened. In addition, the cost effectiveness of AAA screening was estimated to be \$19,500 (95% CI \$12,400 to \$39,800) per year of life gained. To date, AAA screening has not been found to be cost-effective in patients who are older than 84 (18).

Asymptomatic patients who are found to have an AAA should be triaged on the basis of the diameter of the aneurysm (Table 12). The rate of growth for small AAAs is relatively predictable. Multiple independent prospective trials have found that observation with longitudinal surveillance of patients with AAA diameters >4.0 and <5.5 cm is safe. Conversely, individuals with aneurysm diameters ≥ 5.5 cm should be considered for AAA repair (19,20). In the Consensus Statement from the Society for Vascular Surgery, it was recommended that individuals with aneurysm diameters ranging from 3.0 to 4.0 cm be followed with ultrasound every 12 mo. Individuals with aneurysm diameters between 4.0 and 4.5 cm should be screened every 6 mo, and individuals with aneurysms >4.5 cm should be considered for referral to a vascular subspecialist (1) (see Table 13 for a summary of AAA screening recommendations).

Table 13. Summary recommendation from USPSTF for AAA screening

One-time screening for AAA by ultrasonography in men aged 65 to 75 yr who have ever smoked more than 100 cigarettes. Grade B recommendation
No recommendation for or against AAA screening for men who have never smoked. Grade C recommendation
Recommend against routine screening for AAA in women. Grade D recommendation

Information from reference 13.

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Screening for Type 2 Diabetes

Definition and Burden of Disease

Type 2 diabetes, previously known as non-insulin-dependent diabetes mellitus, accounts for 90 to 95% of diabetes in adults. In 2007, the prevalence of diagnosed and undiagnosed diabetes was 23.6 million people, or 7.8% of the total population. Of these, approximately 25% had undiagnosed disease, which is less than the 30% undiagnosed in previous estimates on the basis of an earlier National Health and Nutrition Examination Survey (NHANES). Prevalence increases with age: Approximately 2.6% of adults aged 20 to 39, 10.8% of adults aged 40 to 59, and 23.1% of adults aged ≥ 60 have diabetes (1). There are also differences in prevalence on the basis of ethnicity (2). Not only is the disease prevalent, but it also is associated with significant morbidity and mortality. Diabetes was the seventh leading cause of death listed on death certificates in 2006 and listed as contributing to death on 233,619 death certificates in 2005. Given the prevalence and serious health consequences associated with diabetes, many organizations have developed recommendations for screening for this disease in asymptomatic individuals.

Type 2 diabetes develops insidiously and usually is preceded by a period when a person could be categorized as having prediabetes. Individuals with prediabetes have either an impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). The presence of an elevated blood sugar level of 140 to 199 mg/dl

after a 2-h oral glucose tolerance test defines IGT. A blood sugar level between 100 and 125 mg/dl after an overnight fast is diagnostic of IFG. Prediabetes is associated with an increased risk for developing type 2 diabetes, heart disease, and stroke. The results of the Diabetes Prevention Program study demonstrated that lifestyle intervention is effective in reducing the development of diabetes in high-risk individuals, such as those with prediabetes (3). The 2007 estimate is that 57 million American adults have prediabetes (1).

Screening Recommendations

The US Preventive Services Task Force reviewed the evidence and updated their recommendations for screening for type 2 diabetes in 2008 (4). They assessed the evidence that screening asymptomatic individuals for diabetes with any of the three most commonly used screening tests—fasting plasma glucose, oral glucose tolerance test, and hemoglobin A_{1c}—were associated with improved health outcomes (5). There are no direct randomized, controlled trials of screening for diabetes, so they based their recommendations on indirect evidence. They concluded that among adults who had sustained BP >135/80 mmHg or who were being treated for hypertension, there was sufficient evidence to recommend screening for type 2 diabetes. They did not recommend which test should be used but found evidence that the oral glucose tolerance test did identify more individuals with abnormal tests than did the plasma fasting glucose test; however, this is not used routinely as a screening test in practice. This grade B recommendation was based on the evidence that in patients with known diabetes, lowering the BP is associated with a significant decrease in cardiovascular events. They concluded that there was insufficient evidence to recommend for or against mass screening in adults whose BP was <135/80 mmHg; however, clinicians may consider screening in adults who have other significant risk factors for cardiovascular disease, for whom the detection of diabetes or IFG would result in significant changes in their care, such as the institution of lipid-lowering therapy.

A study of Framingham offspring found that diabetes was more prevalent in patients with chronic kidney disease (stage 3 or greater), especially in patients aged <65 yr, and often not diagnosed (6). On the basis of these data, it may be reasonable to consider testing patients with chronic kidney disease for diabetes.

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Depression

Burden of Disease

Data from the National Health and Nutrition Examination Survey (NHANES) 2005 through 2006 suggested that depression is a common disease affecting more than one in 20 Americans who are aged ≥12 yr (1). The prevalence is highest in the age group 40 to 59 (7.3%). It is also more common in women, non-Hispanic African American individuals, and those with income below the federal poverty level. Importantly, the survey found that 80% of respondents reported that the depression interfered with their ability to work, to maintain a home, and to be socially active. Depression was measured in this study using a validated tool, the Patient Health Questionnaire (PHQ-9) (2). It is estimated that by 2020, depressive illness will be the second leading cause of disability, with considerable societal cost (3).

Depression has been associated with higher rates of diabetes; coronary heart disease; asthma; obesity; and unhealthy habits of smoking, inactivity, and excessive alcohol. Similarly, studies of patients with chronic disease including chronic kidney disease (CKD), especially ESRD, have reported high but variable rates of depression. One article reviewed the epidemiology of depression in patients with ESRD and highlighted the difficulty with differentiating the diagnosis of depression from depressive symptoms that reflect the underlying disease, such as fatigue, sleep disorders, and loss of appetite (4). This is a problem that Chilcot *et al.* (5) called “criterion contamination,”

Table 14. American College of Physicians recommendation for management of major depression

1. For initial treatment, select a second-generation antidepressant based on adverse effect profile, cost, and patient preference (strong recommendation; evidence—moderate quality)
2. Patients should be reassessed on a regular basis starting 1 to 2 wk after initiating therapy (strong recommendation; evidence—moderate quality)
3. In patients with major depression, therapy should be modified if the response has been inadequate within 6 to 8 wk after beginning therapy (strong recommendation; evidence—moderate quality)
4. Therapy should continue for 4 to 9 mo after successful treatment of 1st episode of major depression and be continued for a longer time after 2 or more episodes (strong recommendation; evidence—moderate quality)

Information from reference 10.

which makes the diagnosis of depression more complicated in patients with chronic disease. Although studies report variable rates in the prevalence of depression in patients with ESRD, the evidence suggests that the rate is high and differences can likely be explained on the basis of screening tools. A recent report assessed the prevalence of major depression in patients with earlier stages of CKD (6). The overall prevalence of a major depressive episode was 21% and did not vary between stages 2 through 5 CKD. The primary limitation of the study is that it was performed at a single center, a Veterans Administration Medical Center, and almost exclusively included men. The authors concluded that all patients with CKD should be screened for depression.

Screening Recommendations

In 1996, the US Preventive Services Task Force found insufficient evidence to recommend for or against screening for depression. They published an updated recommendation on the basis of a systematic review of the evidence in 2002 (7). They reviewed 14 randomized, controlled trials of the effect of depression screening in primary care practices using a variety of tools. They found the internal and external validity in these trials to be fair to good. Various outcomes were measured in these studies, including recognition of the diagnosis of depression, treatment of depression, and clinical outcomes. Overall screening did result in increased detection and diagnosis of depression by 10 to 47% in the studies in which it was measured. The results of the studies that assessed clinical outcomes were mixed, and the authors were unable to identify consistent relationships between factors and outcomes. A review of screening tools found that many practical questionnaires that can be completed in 1 to 5 min can reliably identify and diagnose major depression (8).

On the basis of the evidence review, the US Pre-

ventive Services Task Force recommends screening adults for depression in clinical practices that have systems in place to ensure accurate diagnosis, effective treatment, and follow-up (B recommendation). Important clinical considerations are that all positive screening tests should have a full diagnostic interview, the optimal screening interval is unknown, and screening without systems in place for effective treatment and follow-up is less likely to result in positive clinical outcomes. Commonly used screening scales for depression have been validated in patients with CKD (9). Given the prevalence of depression in patients with CKD, in particular those with ESRD, assessing these patients for depression should be a component of their primary care.

The American College of Physicians has published recommendations to guide clinicians in the initial treatment and management of diagnosed depression (see Table 14) (10). A review by Cohen *et al.* (4) listed the options for treatment of depression in patients with ESRD and provided a review of trials of drug therapy and dosage adjustment recommendations required in ESRD. In general, the selective serotonin reuptake inhibitors are preferred to older agents, not because of increased effectiveness but because of their adverse effect and safety profiles (11,12). When prescribing these drugs in the setting of CKD, it is important to determine whether dosage adjustment is required (13–15).

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Obesity

Burden of Disease

The prevalence of obesity in adults aged ≥ 20 is increasing on the basis of National Health and Nutrition Examination Survey (NHANES) data last obtained in the 2005 through 2006 survey. The current estimate is that 34% of the American population is obese and has increased significantly since the first NHANES survey done in the late 1980s. The percentage of overweight individuals has remained essentially constant at 32.7% during this same time (1). Definitions of normal, overweight, obese, and extremely obese are based on the body mass index (BMI; Table 15). BMI, calculated as weight in kilograms divided by height in meters squared, is highly correlated with percentage of body fat and body fat mass. It is least correlated but still significant in the elderly and does take into consideration weight of muscle compared with fat in a heavily muscled individual. BMI is also age dependent. A BMI calculator is available from the National Institutes of Health at <http://www.nhlbisupport.com/bmi/>.

A recent systematic review and meta-analysis assessed the comorbidities that are associated with overweight and obesity (2). Table 16 contains the summary of

Table 15. Classification of excessive body weight based on BMI

Category	BMI			
	25.0 to 29.9	30.0 to 34.9	35.0 to 39.0	≥ 40
Overweight	X			
Obese				
class 1		X		
class 2			X	
class 3				X

their findings (3). There is evidence that obesity may be an independent risk factor for ESRD. A large cohort study of 177,570 individuals who were followed for nearly 10 yr found that the two most potent risk factors for the development of ESRD were proteinuria and excess weight. The evidence was strengthened by the finding of a dose-response gradient with a hazard ratio of 4.39 for classes 2 to 3 obesity, 3.11 for class 1 obesity, and 1.65 for overweight versus normal weight (4). In addition to the increase in hypertension that is associated with obesity and contributes to renal dysfunction, other suggested mechanisms underlying this association include physical compression of the kidneys by visceral obesity and glomerulopathy related to hemodynamic and metabolic abnormalities (5); however, more recent studies have found that obesity is not an independent risk factor for the development of stage 3 chronic kidney disease (CKD) after adjustment for other known cardiovascular risk factors (6).

Screening Recommendations

In the update of the US Preventive Services Task Force recommendation for screening for obesity, researchers reviewed the evidence on the effectiveness of detection and intervention and also the effectiveness of interventions on weight loss and subsequent intermediate or clinical outcomes (7). They were unable to find any randomized, controlled trials that evaluated the effectiveness of screening for obesity in improving health outcomes, so they based their recommendations on indirect evidence. They gave a grade B recommendation to screening all adult patients for obesity and offering intensive counseling and behavioral interventions. Intensive intervention was defined as more than one person-to-person or group session monthly for the first 3 mo. They found insufficient evidence to recommend for or against a lower intensity intervention to promote sustained weight loss in individuals who were obese or

Table 16. Comorbidities associated with excess body weight

Comorbidity	Measure	Overweight		Obesity	
		Male	Female	Male	Female
Type 2 diabetes ^a	BMI	2.40 (2.12 to 2.72)	3.92 (3.10 to 4.97)	6.74 (5.55 to 8.19)	12.41 (9.03 to 17.06)
	WC	2.27 (1.67 to 3.10) ^b	3.40 (2.42 to 4.78)	5.13 (3.81 to 6.90) ^b	11.10 (8.23 to 14.96)
Cancer					
breast, postmenopausal	BMI	–	1.08 (1.03 to 1.14)	–	1.13 (1.05 to 1.22)
colorectal	BMI	1.51 (1.37 to 1.67)	1.45 (1.30 to 1.62)	1.95 (1.59 to 2.39)	1.66 (1.52 to 1.81)
endometrial	BMI	–	1.53 (1.45 to 1.61)	–	3.22 (2.91 to 3.56)
esophageal	BMI	1.13 (1.02 to 1.26)	1.15 (0.97 to 1.36)	1.21 (0.97 to 1.52)	1.20 (0.95 to 1.53)
kidney	BMI	1.40 (1.31 to 1.49)	1.82 (1.68 to 1.98)	1.82 (1.61 to 2.05)	2.64 (2.39 to 2.90)
ovarian	BMI	–	1.18 (1.12 to 1.23)	–	1.28 (1.20 to 1.36)
pancreatic	BMI	1.28 (0.94 to 1.75)	1.24 (0.98 to 1.56)	2.29 (1.65 to 3.19)	1.60 (1.17 to 2.20)
prostate	BMI	1.14 (1.00 to 1.31)	–	1.05 (0.85 to 1.30)	–
Cardiovascular diseases					
hypertension ^a	BMI	1.28 (1.10 to 1.50)	1.65 (1.24 to 2.19)	1.84 (1.51 to 2.24)	2.42 (1.59 to 3.67)
	WC	NA	1.38 (1.27 to 1.51)	NA	1.90 (1.77 to 2.03)
coronary artery disease ^a	BMI	1.29 (1.18 to 1.41) ^b	1.80 (1.64 to 1.98)	1.72 (1.51 to 1.96) ^b	3.10 (2.81 to 3.43)
	WC	1.41 (1.16 to 1.72) ^b	1.82 (1.41 to 2.36)	1.81 (1.45 to 2.25) ^b	2.69 (2.05 to 3.53)
congestive heart failure ^a	BMI	1.31 (0.96 to 1.79)	1.27 (0.68 to 2.37) ^b	1.79 (1.24 to 2.59)	1.78 (1.07 to 2.95) ^b
pulmonary embolism	BMI	1.91 (1.39 to 2.64)	1.91 (1.39 to 2.64)	3.51 (2.61 to 4.73)	3.51 (2.61 to 4.73)
stroke ^a	BMI	1.23 (1.13 to 1.34) ^b	1.15 (1.00 to 1.32) ^b	1.51 (1.33 to 1.72) ^b	1.49 (1.27 to 1.74) ^b
Other					
asthma	BMI	1.20 (1.08 to 1.33) ^b	1.25 (1.05 to 1.49) ^b	1.43 (1.14 to 1.79) ^b	1.78 (1.36 to 2.32) ^b
gallbladder disease ^a	BMI	1.09 (0.87 to 1.37) ^c	1.44 (1.05 to 1.98) ^c	1.43 (1.04 to 1.96) ^c	2.32 (1.17 to 4.57) ^c
	WC	1.61 (1.40 to 1.85) ^b	NA	2.38 (2.06 to 2.75) ^b	NA
osteoarthritis	BMI	2.76 (2.05 to 3.70)	1.80 (1.75 to 1.85) ^b	4.20 (2.76 to 6.41)	1.96 (1.88 to 2.04) ^b
chronic back pain	BMI	1.59 (1.34 to 1.89) ^b	1.59 (1.34 to 1.89) ^b	2.81 (2.27 to 3.48) ^b	2.81 (2.27 to 3.48) ^b

Reprinted from reference 2, with permission. WC, waist circumference.

^a WC measures were considered to be the better risk predictor than BMI measures.

^b Relative risks were calculated from the ratios of proportions (RR-Ps).

^c Both the RR-Ps and the incidence risk ratios (IRRs) were used to calculate relative risks.

overweight. A systematic review of intensive counseling and lifestyle modifications in adults who were older than 60 also found evidence of modest sustained weight loss (3). The 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children gave a strong recommendation (grade A) to measuring BMI in all adults to screen for obesity and to measure waist circumference in all adults to measure obesity-related health risks on the basis of the evidence from observational studies (8). The method used for screening may be particularly important in patients with CKD. A recent study compared the utility of waist-to-hip ratio (WHR), waist circumference, and BMI in the measurement of obesity as it related to the risk for cardiovascular events in patients with CKD. In the univariate analysis, only the WHR was associated with an increased

risk for cardiac event, which was not statistically significant in the multivariate analysis (9). Another study found that waist circumference was highly correlated with visceral fat as measured by the gold standards of dual-energy x-ray absorptiometry and computerized tomography, suggesting that measures other than BMI should be used to assess obesity in patients with CKD (10).

Treatment Guidelines

A Cochrane review of the effect of psychological interventions on overweight or obesity found evidence that behavioral therapy, especially when combined with a program of diet and exercise, was effective in reducing weight (11); however, the magnitude of the effect was small at 2.5 kg (95% confidence interval

[CI] -1.7 to -3.3). The increased intensity of the intervention resulted in weight loss of an additional 2.3 kg (95% CI -1.4 to -3.3).

Exercise was also shown in a systematic review to result in modest weight loss (12). The weight loss was increased with higher intensity exercise and when combined with dietary changes. The review found that exercise resulted in significant reductions in diastolic BP (-2 mmHg; 95% CI -4 to -1), triglycerides (-0.2 mmol/L; 95% CI -0.3 to -0.1), and fasting blood sugar (-0.2 mmol/L; 95% CI -0.3 to -0.1) even when not associated with weight loss.

The US Preventive Services Task Force reviewed the evidence for pharmacotherapy and obesity surgery as methods of promoting weight loss. They concluded that Food and Drug Administration–approved use of orlistat or sibutramine can produce a modest weight loss of 2.6 to 4.8 kg that can be sustained with continued use of the medication; however, the use is limited to 2 yr on the basis of the lack of long-term safety data (13). A Cochrane systematic review of pharmacotherapy with orlistat or sibutramine found that both drugs compared with placebo resulted in significant weight loss: 2.7 kg (95% CI 2.3 to 3.1 kg) and 4.3 mg (95% CI 3.6 to 4.9 kg), respectively (14). At least 10% weight loss was achieved by 12% more of those who took orlistat and 15% more of those who took sibutramine compared with placebo. A significant number of participants dropped out of the studies, including 33% in the orlistat trials and 43% in the sibutramine studies. The main adverse effects included gastrointestinal symptoms with orlistat and small increases in BP and pulse in those who were taking sibutramine.

Surgical interventions can result in substantial weight loss but generally has been limited to those with class 3 obesity or those with medically complicated class 2 obesity on the basis of the recommendations of an expert panel of the National Heart, Lung, and Blood Institute. A Cochrane systematic review was done to assess the effects of surgery for morbid obesity (15). The review found and evaluated 26 trials, most of poor quality and with the potential for significant bias. Studies included in the review enrolled patients who had BMI >40 or had BMI > 35 and one or more obesity-associated comorbidities. The majority of participants were women in their late 30s to early 50s, which limits the generalizability of the results. Surgery resulted in significant sustained weight loss at 8 yr (21 kg) compared with conventional treatment. Although the review ad-

ressed comparisons of various surgical procedures, the poor quality of the limited evidence prevents any firm conclusions about safety and effectiveness of these procedures. A review of studies that enrolled patients with moderate obesity (BMI >30) also found evidence that surgery results in more weight loss than conventional treatment (15). Another systematic review compared laparoscopic adjustable gastric band with Roux-en-Y gastric bypass (16). As in the Cochrane analysis, the majority (80%) of patients were women and the studies were generally of low quality. Operative mortality was low in both procedures at $<0.5\%$. Hospitalization and operative times were shorter with the laparoscopic procedure; however, overall, the weight loss was greater in the gastric bypass group and associated with increased resolution of diabetes, hyperlipidemia, sleep disorders, and hypertension. Separate analysis of the highest quality studies found the same results favoring greater weight loss with gastric bypass.

A recent systematic analysis specifically examined the impact of bariatric surgery on type 2 diabetes (17). The majority (78.1%) of patients had resolution. When improvement in diabetes control was included, the percentage increased to 86.6%. The beneficial changes were maintained for at least 2 yr. The studies that were included in the meta-analysis had significant between-study heterogeneity, but the magnitude of the effect—resolution of diabetes—was similar in most of the studies. No studies to date have assessed the impact of weight loss on the development of CKD.

Excessive weight increases risk for serious disease. Obesity and overweight, defined by BMI, are associated with increased risk for type 2 diabetes, cardiovascular disease, and multiple cancers.

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Smoking

Background

In 2000, the US Public Health Service published a clinical guideline, “Treating Tobacco Use and Dependence,” which was updated by the US Preventive Services Task Force in 2003 (1). The Clinical Practice Guideline: Treating Tobacco Use and Dependence, which was updated in 2008, is a comprehensive systematic review and meta-analysis of topics related to effective tobacco cessation strategies (2). The expert panel developed key recommendations with an overriding goal that clinicians

strongly recommend the use of effective tobacco cessation counseling and medications to all patients who are smokers. They further recommend that other components of the health care system, such as insurers and suppliers, assist clinicians in making the therapy available.

Screening Recommendations

The guideline reaffirms the recommendation that all providers ask all adult patients about tobacco use, document this use, and provide tobacco cessation interventions. The evidence shows that having in place a system that documents tobacco use increases the likelihood that clinicians will intervene and also results in a slightly higher abstinence rate. The guideline recommends that all health care providers ask five questions to assess smoking behavior. These are known as the “5 A’s”: (1) Ask about use, (2) advice to quit, (3) assess willingness to quit, (4) assist quitting, and (5) arrange follow-up and offer support. The guideline provides practical strategies for implementing these actions during a clinical encounter. Variables that are associated with higher rates of abstinence include high motivation to quit, a belief that the individual will be successful, a smoke-free workplace and home, and a readiness to change (defined by a plan to quit within 1 mo). A meta-analysis of 43 studies demonstrated that even brief interventions—<3 min—can result in increased quitting rates. Importantly, interventions by health care providers other than physicians are as effective, and as more providers advise the smoker to quit, the effectiveness of the intervention increases (2).

Treatment Recommendations

The evidence shows that pharmacotherapy in addition to counseling will improve quit rates (1,3). All smokers who are trying to quit should have medications offered unless there are specific contraindications to specific medications. Contraindications to the use of bupropion include a history of seizures or eating disorders. Varenicline requires dosage adjustment in the setting of chronic kidney disease and should not be prescribed in the setting of serious psychiatric disease, such as major depression. Additional considerations when prescribing drug therapy include costs, adverse effects, and previous experience with drug therapy for tobacco cessation. Seven Food and Drug Administration–approved medications are considered first-line therapy for smoking cessation: Nicotine replacement (lozenge, in-

haler, gum, nasal spray, patch), bupropion sustained release (SR), and varenicline. Clonidine and nortriptyline are considered second-line agents for tobacco cessation and are not Food and Drug Administration approved for this use. Other studies found that naltrexone and selective serotonin reuptake inhibitors are not effective in smoking cessation.

A recent meta-analysis evaluated the effectiveness of nicotine replacement therapy (NRT) to assist in reducing smoking (4). The authors examined the outcomes of sustained reduction, defined as a reduction of 50% in number of cigarettes smoked and abstinence at 7 d and 6 mo. They found that NRT significantly increased the abstinence rate two-fold, with a number-needed-to-treat (NNT) of 29 for 6 mo of replacement therapy; however, the overall abstinence rate was only 6.75% in the treatment group. In addition, they found that it did not depend on the type of NRT. Use of NRT also resulted in more smokers' achieving a sustained reduction at all time points. Nausea was significantly more common in the treatment arm (8.7%) compared with the control arm (5.3%). There was no difference in the number of serious adverse effects, including death in the two study arms. They concluded that NRT is effective—nearly doubling the quit rate—and safe and should be offered to smokers who want to quit smoking.

The Cochrane review of varenicline for smoking cessation found that the drug increased the quit rate compared with placebo by a factor of 2 to 3. Studies also found it slightly more effective at 1 yr than bupropion SR (relative risk 1.50; 95% confidence interval 1.22 to 1.88) and NRT (relative risk 1.31; 95% confidence interval 1.01 to 1.71) (3). Assuming a 7.5% quit rate, the NRT compared with placebo was 10, 18, and 23 for varenicline, bupropion SR, and NRT, respectively. Although the predominant adverse effects reported in the trials was mild to moderate nausea, recent concerns regarding safety and the potential for adverse psychiatric events led to amended labeling of the drug (5).

Dosage adjustment is required for varenicline in patients with chronic kidney disease. Pharmacokinetic studies found an increase in varenicline exposure of 1.5-fold in patients with creatinine clearance of 30 to 50 ml/min and 2.1-fold in those with creatinine clearance of <30 ml/min. The drug is efficiently removed by hemodialysis, so these patients should use the standard dose of 1 mg twice a day (5). Caution should also be used when prescribing bupropion.

Pharmacotherapy with NRT or partial nicotine agonists doubles the tobacco cessation quit rate compared with placebo.

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Falls: Assessment and Prevention

Scope of Problem

Falls are a frequent, dreaded occurrence among older people and often lead to serious health consequences and substantial economic burden (1). Almost one third of community-dwelling older adults fall annually, and up to 20% of inpatients will fall at least once during their hospital stay (2,3). Older dialysis patients have been found to have a fall incidence that is twice as high as that of nondialysis patients (4). A fall is one of the most injurious yet preventable complications that an older adult might experience (1,5). Although death is a less frequent consequence, falls remain the primary cause of accidental death among US seniors who are older than 75 yr. Centers for Disease Control and Prevention data revealed that between 2001 and 2003, the age-adjusted rate of fatalities from falls increased by 13.3%. This increasing trend was observed for all races (6). One recently conducted longitudinal cohort study of older dialysis patients found that after adjusting for known predictors of dialysis mortality, falls were a significant independent predictor of death (hazard ratio 1.63; 95% confidence interval [CI] 1.02 to 2.28) (7).

Falls contribute greatly to excess morbidity, loss of independence, and premature institutionalization among the geriatric population (8). Specific injurious

consequences of hospital falls include soft tissue injuries, traumatic brain injuries, and fractures (9). Although <10% of falls in older adults result in fracture (10), studies have suggested that up to 20% of fall occurrences require medical attention (11,12). In addition to the substantial physical morbidity, many older adults will experience significant fall-related anxiety and may restrict their activities to prevent future falls (13). This fall-related withdrawal from social networks has been associated with increased risk for social isolation and depression (14). Older adults who are injured by a hospital fall experience longer hospitalizations, greater resource use, and higher rates of discharge to long-term institutional care than their nonfalling counterparts (15). Inpatients who have fallen may take legal action against their providers and the institution itself (16).

It is critical that ambulatory care and hospital-based providers understand how to assess older patients' risk for falling and implement evidence-based interventions that may prevent future falls. Here, we present a practical approach to the evaluation and prevention of inpatient falls with emphasis on appropriate risk factor reduction.

Assessment

Successful fall prevention involves screening all older adults for falls and promoting targeted interventions aimed at fall risk factor reduction. In their clinical practices, providers often fail to identify and evaluate patients who are falling (17). Clinicians must ask their older patients about falls on a regular basis because many individuals may be hesitant to share this information with their health care providers.

Numerous fall risk assessment tools have been developed (18). The suggested purpose of these instruments is to identify older adults who are at highest risk for falls so that resources can be targeted toward individuals who are most likely to benefit (19). Appropriate fall risk assessment requires the evaluator to identify whether key intrinsic risk factors, extrinsic risk factors, and risk-taking behaviors are present (Table 17). As such, these tools can be used as a framework for clinicians to implement individualized risk reduction plans for all of their patients.

In particular, older patients with chronic kidney disease have numerous risk factors for falls. Older patients with chronic kidney disease have a high prevalence of diabetes, anemia, heart disease, sleep-related disorders, polypharmacy, and peripheral and auto-

Table 17. Common risk factors for falls

Risk Factor	Mean Risk Ratio
Muscle weakness	4.4
History of falls	3.0
Gait deficit	2.9
Balance deficit	2.9
Inappropriate use of assistive device	2.6
Visual deficit	2.5
Arthritis	2.4
Impaired ADL	2.3
Depression	2.2
Cognitive impairment	1.8
Age >80 yr	1.7
Medication use	NA
Fear of falling	NA

Adapted from reference 40. ADL, activities of daily living.

nomous neuropathies (4,20). Patients who receive dialysis are also at risk for rapid fluid and electrolyte shifts that could result in orthostatic hypotension (20). One prospective longitudinal study of patients who were aged ≥ 65 and receiving hemodialysis revealed that in this population, male gender, previous history of falls, low mean predialysis systolic BP, and higher comorbidity were key risk factors for falls (4).

Interventions

Multifactorial Risk Reduction Strategy. Many studies have examined the efficacy of multicomponent strategies as a means of reducing intrinsic and extrinsic risk factors. These programs typically involve an initial assessment by a trained nurse or physician. On the basis of the results of the initial assessment, recommendations for targeted strength, balance, gait training, medication optimization, patient education, home safety evaluation, and treatment of orthostatic hypotension are provided (Table 18).

Previous studies of the multifactorial risk reduction strategy suggested that this type of intervention was among the most effective (11). One well-done systematic review and meta-analysis of fall interventions found that a multifactorial fall risk assessment and management program reduced the risk for falling by 28% (95% CI 0.72 to 0.88; number needed to treat 11) and reduced the monthly fall rate by 37% (95% CI 0.49 to 0.83) by simultaneously mitigating patients' intrinsic and extrinsic risk factors (21). Accordingly, in their Guideline for Prevention of Falls in Older Adults, the American Geriatrics Society, British Geriatrics Society, and American

Table 18. Recommended components of assessment and individualized management of older adults who are at risk for falls

Risk Factor	Intervention Strategy
Gait disturbance or balance abnormalities	<ol style="list-style-type: none"> 1. Consider referral to physical therapy for gait training and assistive device instruction. 2. Encourage patients to bring their typical gait device to each visit to ensure proper form. 3. Consider referral for a professionally delivered home safety evaluation to reduce environmental hazards at the patient's home. 4. Refer appropriate patients to physical therapy for tailored exercise programs that focus on strengthening, balance, and endurance. The preferred method of exercise has not been established. Tai Chi C'uan has shown some benefit, but further studies are needed.
Muscle weakness	<ol style="list-style-type: none"> 1. Evaluation for underlying cause 2. Refer appropriate patients to physical therapy for tailored exercise programs that focus on strengthening, balance, and endurance. The preferred method of exercise has not been established. Tai Chi C'uan has shown some benefit, but further studies are needed. 3. Vitamin D supplementation (1000 IU/d orally) can be considered.
High risk medication regimen	<ol style="list-style-type: none"> 1. Encourage patients to bring their over-the-counter and prescription medications to each visit. 2. Taper all medications to the lowest effective dosage. 3. Taper or discontinue psychotropic medications (antidepressant, antipsychotic, and anticholinergic medications) whenever possible. 4. Reduce the total number of medications when possible. Reduction of medications to four or fewer has resulted in risk reduction.
Postural hypotension	<ol style="list-style-type: none"> 1. Evaluate for underlying cause. 2. Review medications for possible culprits. 3. Encourage good hydration habits in patients. 4. Educate patients on how to rise slowly from a seated or supine position. 5. Pressure stockings 6. Pharmacologic therapy
Circumstances of falls reveal environmental culprit	<ol style="list-style-type: none"> 1. Counsel patient about environmental hazards (<i>e.g.</i>, loose rugs, cluttered walkways/stairs, slippery surfaces). 2. Professionally delivered home safety assessment (occupational therapy, physical therapy) and environmental modification
Cardiovascular disease	<ol style="list-style-type: none"> 1. Targeted cardiovascular assessment and optimization of treatment.
Inappropriate shoe wear or foot problems	<ol style="list-style-type: none"> 1. Suggest low-heeled shoes with thin, nonslippery sole. 2. Recommend daily self-examination of the feet and regular foot care.
Vision impairment <20/60, decreased depth perception, decreased contrast sensitivity, cataracts	<ol style="list-style-type: none"> 1. Recommend ample lighting without glare. 2. Avoid multifocal glasses while ambulating. 3. Refer to specialist when appropriate.

Adapted from references 2 and 22.

Academy of Orthopaedic Surgeons recommended this type of strategy for community-dwelling older adults. Review and modification of medications, exercise programs with balance training, and treatment of postural hypotension were designated as grade B recommendations. Modification of environmental hazards was designated as a grade C recommendation (22). Similarly, the

National Institute for Health and Clinical Excellence (NICE) has recommended that older adults with recurrent falls be considered for multifactorial individualized interventions (grade A recommendation). In addition the NICE guideline recommends that after an injurious fall, older adults be offered a multidisciplinary intervention aimed at promotion of independence and function (23).

Vitamin D Supplementation. Recent studies have suggested that vitamin D may also play a role in fall prevention and musculoskeletal performance. 1,25-Hydroxyvitamin D binds to a highly specific nuclear receptor in muscle tissue, and it has been hypothesized that this active metabolite may lead to improved muscle function and subsequent reduction of falls (24). One meta-analysis of double-blind, randomized, controlled trials that evaluated the impact of vitamin D on fall prevention found that vitamin D reduced the risk for falling by 22% (odds ratio 0.78; 95% CI 0.64 to 0.96) compared with patients who received calcium supplementation or placebo (25). This group's subsequent 3-yr randomized, controlled trial revealed that community-dwelling older adults who were given 700 IU of cholecalciferol plus 500 mg of calcium citrate malate per day were less likely to fall (odds ratio 0.54; 95% CI 0.30 to 0.97) compared with individuals who received a placebo tablet. Fall reduction benefit was independent of baseline 25-hydroxyvitamin D level (26).

Challenging these findings, the Randomized Evaluation of Calcium or Vitamin D (RECORD) trial randomly assigned ambulatory older adults to oral 800 IU of vitamin D₃, 1000 mg of calcium, 800 IU of vitamin D₃ plus 1000 mg of calcium, or placebo. It is interesting that the incidence of new, low-trauma fractures and the number of falls did not differ between those who received vitamin D and those who did not (27). Similarly, in the recent Cochrane Collaboration review of Interventions for Preventing Falls in Elderly People, pooled data from three trials of oral vitamin D supplementation did not show convincing evidence that vitamin D supplementation reduced the number of older adults who fell (28). These two last analyses raise several important questions about who benefits most from vitamin D supplementation (27).

Medication Optimization. There is strong evidence that the use of psychotropic medications or the use of greater than four medications is linked to falls (2). Benzodiazepines, antidepressants, and neuroleptic medications are associated with an almost two-fold increased risk for falls (29,30). Takkouche *et al.* (31) assessed the risk for fracture with specific types of psychotropic medications. In that meta-analysis, the random effects relative risk (RR) for fractures was 1.34 (95% CI 1.24 to 1.45) for benzodiazepines, 1.60 (95% CI 1.38 to 1.86) for antidepressants including selective serotonin reuptake inhibitors, 1.59 (95% CI 1.27 to 1.98) for antipsychotic/neuroleptic medications, and 1.38 (95% CI 1.15 to 1.66) for opioid

medications. Benzodiazepines impair postural sway, delay reaction time, cause ataxia, and reduce proprioception, even in studies of normal volunteers (32). Sedation with psychomotor retardation is the most likely cause of falls among older adults who are on antidepressants. In addition, older adults who take tricyclic antidepressants are at increased risk for orthostatic hypotension and cardiac arrhythmia, which may lead to falls (33). Neuroleptic medications may increase fall risk by causing excessive sedation, orthostatic hypotension, cognitive impairment, extrapyramidal dysfunction, or α blockade (33–35).

Campbell *et al.* (36) designed a randomized, controlled intervention study aimed at assessing the effectiveness of psychotropic medication withdrawal. Individuals in the intervention group underwent gradual withdrawal of psychotropic medications, and, after 44 wk, the intervention group had a significantly reduced relative hazard for falling (hazard ratio 0.34; 95% CI 0.16 to 0.74).

Benzodiazepines, antidepressants, and neuroleptic medications are associated with an almost two-fold increased risk for falls.

Exercise. Randomized trials have examined the impact of specific types of exercise on fall risk. Pooled data from studies that examined the effectiveness of untargeted exercise interventions in community-dwelling older people have failed to show a reduction in the number of older adults who fall (28); however, studies that provide individually tailored programs of strength, balance, and gait retraining have been shown to reduce significantly the number of individuals who fall during a 1-yr period and reduce the number of people who sustain a fall-related injury (36–38). Trials that specifically examined Tai Chi, a Chinese martial art technique, have also yielded promising results with significant reduction in rate of falls (0.63; 95% CI 0.52 to 0.78) and risk for falling (RR 0.65; 95% CI 0.51 to 0.82) (39). These studies suggest that referring patients to therapy professionals who can individualize exercises to the needs of the patient may be an effective fall prevention tool.

Conclusions

Clinical nephrologists who care for older patients who are treated with long-term dialysis can play an

important role in the identification of patients who are falling or are at risk for falling. This population of patients is globally at risk for falls, fall-related fractures, and subsequent functional disability (4). Nephrologists can identify modifiable fall-related risk factors and refer to appropriate members of the multidisciplinary team for individualized interventions (e.g., physical therapy, medication reduction, home safety evaluation) to prevent their patients from these morbid complications.

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Dementia

Scope of Syndrome

Dementia is a clinical syndrome characterized by acquired cognitive impairment that results from central neurodegenerative and ischemic processes. Signs and symptoms of the syndrome include difficulty with memory and impairments in language, visuospatial skills, or executive function with resultant impairment in function (Table 19) (1). On the basis of estimates for the Aging, Demographics, and Memory Study (ADAMS), 14% of American adults aged ≥ 71 have dementia. Approximately 5% of individuals aged 71 to 79 have the syndrome, but this prevalence increases to 37.4% among those aged ≥ 90 (2). Because most patients with dementia have a relatively long survival with the syndrome, the prevalence of dementia far exceeds the incidence rate. It is projected that, by 2010, 454,000 Americans annually will receive a diagnosis of Alzheimer disease and, by

2050, $>950,000$ older adults per year will receive a diagnosis of Alzheimer disease (3).

The most common types of dementia include Alzheimer disease, dementia associated with cerebrovascular disease (vascular dementia), dementia with Lewy bodies, and mixed-type dementia (4). Frontotemporal dementia and normal pressure hydrocephalus are less common causes of chronic cognitive impairment (4). In the general population, 60 to 70% of individuals with dementia have Alzheimer disease, whereas vascular dementia accounts for approximately 17% of all cases of dementia (2); however, among hemodialysis patients, dementia associated with cerebrovascular disease or mixed Alzheimer disease and cerebrovascular dementia seem to be more common than Alzheimer disease alone (5). Pneumonia is the most commonly identified cause of death among individuals with dementia, because patients with advanced dementia may experience undernutrition, immobility, and dysphagia (6).

The relationship between chronic kidney disease and cognitive impairment has recently received closer attention. Cardiovascular risk factors such as age, diabetes, hyperlipidemia, and hypertension have been associated with both cognitive impairment and chronic kidney disease (7,8). Studies have suggested that kidney disease is also an independent risk factor for cognitive impairment (9). Among menopausal women, each 10-ml/min per 1.73 m^2 decrement in estimated GFR corresponded to an approximately 15 to 25% increase in risk for cognitive dysfunction in the Heart, Estrogen/Progesterone Study (10). In a study of hemodialysis patients, Kurella *et al.* (11) found that almost 40% had severe impairment in executive function and 33% had severe memory impairment. Similarly, another study of 338 hemodialysis patients revealed that although 13.9% of patients were classified as having mild cognitive impairment, 36.1% as having moderate impairment, and 37.3% as having severe impairment, only 2.9% of the cohort had a documented history of cognitive impairment in their medical record (12). As such, clinical nephrologists need to be familiar with the array of evidence-based assessment tools and treatment modalities that are available for patients with cognitive impairment.

Dementia is one of the main causes of late-life disability, and, accordingly, individuals who have this syndrome use health care services frequently. Medicare beneficiaries with dementia are three times more likely to have a hospital stay and eight times more likely to require admission to a skilled nursing facility than their age-

Table 19. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for dementia

Criteria for dementia

1. memory impairment
2. at least one of the following
 - aphasia
 - apraxia
 - agnosia
 - disturbance in executive functioning
3. disturbance in 1 and 2 significantly interferes with work, social activities, or relationships
4. disturbance does not occur exclusively during delirium

Additional criteria for dementia type

dementia of the Alzheimer type
gradual onset and continuing cognitive decline
not caused by identifiable medical, psychiatric, or neurologic condition

vascular dementia

focal neurologic signs or laboratory evidence of cerebrovascular condition

dementia from other medical conditions

evidence from history, physical examination, or laboratory findings of a specific medical condition that causes cognitive deficits (*e.g.*, HIV disease, head trauma, Parkinson disease, Huntington chorea, Pick disease, Creutzfeldt-Jacob)

Adapted from reference 1.

matched counterparts without dementia (13). In 2005, direct costs to Medicare and Medicaid and indirect costs to businesses for employees who lost work days (caring for patients with dementia) exceeded \$148 billion (13). The total indirect costs associated with unpaid caregiving from family members, friends, and neighbors is difficult to measure but has been estimated to exceed \$18 billion annually in the United States (14).

Recognition of the Syndrome and Screening

The early recognition of dementia can be beneficial, because clinicians may be able to provide additional psychosocial support and resources to the patient and his or her family and may initiate pharmacologic treatments in a timely manner. In addition, early recognition may afford patients and families the time needed to plan for the future. They may be able to develop and communicate their advance care plan to their loved ones and may be able to designate individuals to exercise power of attorney for their health care and financial decisions. Although screening potential hemodialysis patients for cognitive impairment is not currently required by Centers for Medicare and Medicaid Services, identification of this syndrome could potentially guide nephrologists about the appropriateness of starting dialysis (5).

The potential drawbacks that are associated with early detection also deserve mention. Individuals who receive an early diagnosis of dementia may experience anxiety or depressed mood about this diagnosis. Furthermore, individuals who receive a diagnosis of dementia may have difficulty obtaining long-term care insurance or residence in certain retirement communities.

Recognition of the syndrome depends on patient report, informant report, and the assessment of cognitive function. A number of mental status examinations have been described and validated in the literature. The Mini-Mental Status Examination (MMSE) is the most widely used dementia screening tool. The MMSE evaluates the domains of orientation, learning, language, and construction (15). Using a cut point of 24 of a total of 30 points, this test has a reported sensitivity that ranges from 71 to 92% and a specificity that ranges from 56 to 96% in English-speaking populations (16). The accuracy of this test is dependent on age, education, and ethnicity of the individual being assessed. Another, more recently developed test is the Kokmen Short Test of Mental Status (STMS), which has a sensitivity of 81.0 to 86.4% and specificity of

90.0 to 93.5% (16,17) and is also appropriate for the ambulatory setting. A criticism of assessment tests such as the MMSE and the STMS is that they may not assist the clinician in determining severity of the disease or reflect the individual's functional limitations in a meaningful way (18).

In the most recent guideline, the US Preventive Services Task Force concluded that there is *insufficient* evidence to recommend for or against routine screening for dementia in the general population of asymptomatic older adults (I statement) (19). The American Academy of Neurology and Canadian Task Force on Preventive Health have echoed the US Preventive Services Task Force conclusions (20,21).

In symptomatic patients, evaluation for potentially reversible causes of memory loss is recommended. The American Academy of Neurology has published recommendations about the appropriate laboratory assessment. Initial investigations include a full blood count, basic electrolyte panel, liver enzymes, thyroid function tests, and evaluation for vitamin B₁₂ deficiency. Individuals with suspected cognitive impairment also should be screened for depression and substance abuse (22). Brain imaging with magnetic resonance imaging or computed tomography to exclude structural causes of cognitive impairment, such as normal pressure hydrocephalus or mass lesions, also is recommended (4). Other investigations should be guided by the individual's history (HIV testing, syphilis serology, cerebrospinal fluid examination, or electroencephalogram) when less common infectious causes of dementia are suspected (see Table 19 for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for dementia*).

Treatment

At this time, there is no cure for dementia; however, an array of pharmacologic and nonpharmacologic therapies have been used to alleviate symptoms and to delay syndrome progression. The Food and Drug Administration (FDA) has approved five drugs for the management of dementia: cholinesterase inhibitors (donepezil, rivastigmine, galantamine, and tacrine), which degrade acetylcholinesterase and increase levels of acetylcholine, and memantine, which partially blocks the N-methyl-D-aspartate (NMDA) receptor and prevents excess stimulation of the glutamate system. In studies to assess efficacy of the five drugs, outcomes typically include cognition, global

function, dementia-related behavior, quality of life, institutionalization, and functional status.

Cholinesterase Inhibitors. In their recent meta-analysis, Raina *et al.* (18) pooled data from 24 distinct studies that examined donepezil *versus placebo* or vitamin E and found that donepezil consistently resulted in improved cognition and global function among patients with Alzheimer disease and vascular dementia. The summary estimates for the Alzheimer Disease Assessment Scale Cognitive Subset (ADAS-cog)—a validated assessment scale for attention, memory, orientation, language ability, and praxis—were small with a mean decrement of 2.80 points (95% confidence interval -3.28 to -2.33). A decrement in the ADAS-cog suggests a reduced degree of cognitive decline in individuals who took the cholinesterase inhibitor compared with those who took the placebo. A decrement of ≥ 4 points is believed to be clinically significant on this 70-point scale (23). This analysis found that donepezil reduced rates of transition from mild cognitive impairment to Alzheimer disease in the short term (<36 mo), but effects were not sustained (18).

Similarly, studies that evaluated galantamine and rivastigmine showed a favorable impact on cognition, as measured by the ADAS-cog in patients with various severity levels of Alzheimer dementia, but most studies did not show a consistent improvement in functional or behavioral outcomes. Studies that examined the efficacy of tacrine *versus placebo* have been challenging to interpret because of small sample sizes and low dosages of the medication. The evidence for the impact of cholinesterase inhibitors on functional status has been mixed (16). The most commonly reported adverse effects of cholinesterase inhibitors are gastrointestinal symptoms (diarrhea, nausea, vomiting, and weight loss) and dizziness. Clinicians should use caution when prescribing cholinesterase inhibitors to patients with orthostatic hypotension, obstructive lung disease, cardiac conduction abnormalities, concurrent use of nonsteroidal anti-inflammatory medications, history of peptic ulcer disease, or seizure. No dosage adjustment is required for donepezil, rivastigmine, or tacrine in patients with impaired renal function. Galantamine should not be used in patients with severe renal impairment.

Memantine. The effect of memantine, a medication that typically is reserved for moderate to severe dementia, has also been evaluated in several studies. Memantine does improve global assessment and cognition, but the effect size for the ADAS-cog does not suggest clinical significance (18,24,25). Early studies

of this medication do suggest that it might favorably improve quality of life for older adults with moderate to severe Alzheimer disease (18). The most commonly reported adverse effects of memantine are nausea, dizziness, diarrhea, and agitation. Clinicians should use caution when prescribing NMDA antagonist medications to individuals who are on other drugs that alkalinize the urine, those who have moderate to severe renal impairment, and those with seizure disorders. Dosage reduction is required for patients with creatinine clearances <29 ml/min.

Nonpharmacologic Interventions. Studies that examined multicomponent nonpharmacologic interventions on caregiver outcomes have been promising. Components typically include caregiver training, family counseling, and educational sessions (16). Two studies found that intensive caregiver interventions allowed caregivers to continue caring for loved ones for 11 to 19 mo longer than those in the control group (26,27).

Summary Recommendations for Treatment of Dementia

In summary, each of the five FDA-approved medications discussed here have been shown to have a significant impact on validated dementia assessment instruments; however, determining clinical significance is more challenging. Clinical significance requires that the result be meaningful to the patient, caregiver, or clinician and, accordingly, is variable between individuals. In addition, there is not sufficient evidence to determine the optimal duration of pharmacologic therapy.

On the basis of the aforementioned findings, the American College of Physicians and the American Academy of Family Physicians recommend that “clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment” after carefully weighing the risks, benefits, limitations, and preferences of the patient and the family. This was deemed to be a weak recommendation with moderate-quality evidence (28). The American College of Physicians and the American Academy of Family Physicians also have recommended that “clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication” because the evidence comparing different agents of the treatment of dementia is insufficient (28).

Each of the five FDA-approved medications for the treatment of dementia have shown statistically significant impact on assessment instruments; however, determining impact on clinically significant outcomes has been more challenging to establish.

Behavioral Problems in Dementia

The majority of patients who have Alzheimer disease and other dementias will experience neuropsychiatric and behavioral disturbances at some time during the course of their illness. These disturbances can include delusions, hallucinations, agitation, wandering, and aggression toward others and frequently precipitate nursing home placement. In addition, these symptoms can contribute to caregiver stress and increased health care costs (29).

Assessment of the patient with behavioral disturbance requires a history from the patient and the caregiver or other informant. Obtaining a clear description of the behavior is important because the most successful interventions are symptom specific. Inquiring about temporal onset, course, associated circumstances, environmental factors, caregiver changes, and physical symptoms should be undertaken. Environmental disruptions such as schedule changes, time zone changes, travel, or changes in the caregiving environment can precipitate behavioral symptoms. In patients with dementia, behavioral changes often are the initial presenting symptom for acute conditions such as urinary tract infections, pain, angina, and ischemia. In addition, mood disorders such as depression may precipitate behavioral changes, and treatment of the underlying condition with antidepressant therapy and activity therapies can often result in improved behavior (29).

After medical, psychosocial, and environmental causes have been excluded, it might be concluded that the behavior is a manifestation of the underlying dementing syndrome. Data from trials that examined the role of pharmacologic modalities have been challenging to interpret because the medications typically chosen for treatment, namely atypical antipsychotic drugs, have been associated with increased risk for cerebrovascular events (30) and death (31).

Pharmacologic and Nonpharmacologic Interventions for Behavioral Disturbance

Second-generation antipsychotic drugs, the so-called atypical antipsychotic drugs, have been used extensively to treat negative behaviors that are associated with dementia. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) project was a multisite, double-blind, placebo-controlled trial of patients with Alzheimer disease-related psychosis, aggression, or agitation aimed at measuring the overall effectiveness of atypical antipsychotic medications (32). Patients were randomly assigned to receive olanzapine, quetiapine, risperidone, or placebo and were followed up to 36 wk for improvement on the Clinical Global Impression of Change (CGIC) scale. This group found that there were "no significant differences noted among the groups with regard to improvement on the CGIC scale" and concluded that "adverse effects offset advantages in efficacy" of these medications for the treatment of negative behaviors in patients with Alzheimer disease. Notably, the median time to discontinuation of assigned therapy, including placebo, was 5 to 8 wk, with no significant differences between treatment groups. Sedation was reported with each of the active medications, whereas extrapyramidal symptoms and weight gain were more commonly reported with risperidone and olanzapine (32). A follow-up analysis of the CATIE-AD trial revealed that atypical antipsychotic medications did not result in improvement of functional abilities, quality of life, or caregiving requirements (33).

Notably, the free fraction of risperidone may be increased in patients with severe renal impairment; dosage adjustment is necessary. Dosage adjustment is not required with quetiapine and olanzapine.

Alternative agents such as antiepileptic drugs and benzodiazepines also have also evaluated for their use in treating behavioral symptoms of dementia. Individual studies of carbamazepine and valproate have shown mixed results; however, a systematic review concluded that there is not enough evidence to support its use in the treatment of neuropsychiatric symptoms (34). Because of their unfavorable adverse effect profile and limited utility, benzodiazepines are not recommended for the management of behavioral dyscontrol in dementia (35).

Nonpharmacologic interventions may also be effective in reducing agitation and anxiety in patients with dementia. Small trials with therapies using aromas, ex-

ercise, music, and touch/massage have been conducted and have generally shown good compliance and minimal associated risk. Behaviors that seem to be most responsive to nonpharmacologic therapies include repetitive questioning, wandering, and hiding objects. Despite the lack of strong, consistent evidence from large clinical trials, nonpharmacologic therapies are recommended as first-line treatment, given the potential for adverse events associated with other medication classes (36).

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Immunizations

An important component of the primary care of patients is the provision of appropriate immunizations. Each year, the Centers for Disease Control and Prevention (CDC) provides an updated Recommended Adult Immunization Schedule. The recommendations are based on patient age and also provide specific recommendations and contraindications for patients with other conditions, including pregnancy, chronic diseases including ESRD, and compromised immune systems. An understanding of the composition of the vaccine, whether it contains live, attenuated, or inactivate substrate, is a critical factor in determining whether an individual can receive a vaccination. Specific recommendations for immunization can be obtained at <http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm>.

The following recommendations reflect the 2009 guidelines and refer to adults who are aged ≥ 19 yr with the assumption that the individual has received the appropriate primary series of vaccinations as a child (1). Adults should receive a tetanus/diphtheria booster every 10 yr, and one of the boosters before the age of 65 should include acellular pertussis. The series of human papillomavirus vaccinations is indicated in women and recently was approved for use in boys and men to prevent genital warts. Ideally, the series should be given before the individual becomes sexually active. There are no data supporting the use after age 26 in either gender. Adults without evidence of immunity should receive two doses of the varicella vaccine, unless they are immunocompromised or pregnant. Adults who were born before 1957 are considered immune, whereas those who were born in 1957 or after should receive one dose of the measles-mumps-rubella vaccination. There are additional recommendations for a second dose in selected populations. Contraindications for this vaccine are the same as those for the varicella vaccination. A herpes zoster vaccination is indicated for adults who are aged ≥ 60 , regardless of whether they have had a previous episode of herpes

zoster. Because the vaccine is not inactivated, it is contraindicated in pregnant or immunocompromised patients. All adults should receive an annual influenza vaccination, but those with ESRD and other underlying chronic illnesses should preferentially receive the inactivated rather than the live, attenuated influenza vaccine. The pneumococcal polysaccharide vaccine is routinely indicated for all adults who are aged ≥ 65 yr. Many groups, including patients with nephrotic syndrome or chronic renal failure, should receive the vaccination irrespective of age. Revaccination after 5 yr is appropriate for these patient populations as well as those who are immunocompromised or received the vaccination before the age of 65. There are specific indications for the meningococcal, *Haemophilus influenzae* type b, and hepatitis A vaccinations, which do not generally include patients with renal disease. The hepatitis B vaccination is recommended for patients with ESRD, including those who are on hemodialysis. Evidence suggests that the immune response is better when patients are vaccinated before beginning hemodialysis. The Centers for Disease Control and Prevention has published specific recommendations for the Recombivax HB and Enegerix B dosing on the basis of age and whether the patient is dialysis dependent (<http://www.cdc.gov/vaccines/spec-grps/conditions.htm>).

The initial recommendations of the Advisory Committee on Immunization Practices on the use of the 2009 Influenza A (H1N1) were published in August 2009 (2). These were updated in October and include recommendations for the use of the live attenuated and the inactivated vaccines. The recognition of increased mortality in pregnant patients who contract H1N1 resulted in a “Dear Colleague” letter urging providers to encourage pregnant patients to get both the seasonal and H1N1 vaccinations in 2009. Recommendations regarding patient eligibility for vaccination continue to evolve. Providers are urged to access the Center for Disease Control website for the latest recommendations (<http://www.cdc.gov/h1n1flu/vaccination/>).

References

1. Advisory Committee on Immunization Practices: Recommended adult immunization schedule: United States, 2009*. *Ann Intern Med* 150: 40–44, 2009
2. National Center for Immunization and Respiratory Diseases, CDC; Centers for Disease Control and Prevention (CDC): Use of influenza A (H1N1) 2009 monovalent vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep* 58: 1–8, 2009

Nephrology Self-Assessment Program

Examination Questions

Instructions to obtain 8 AMA PRA Category 1 Credits™

Credit expiration date: December 31, 2010

Continuing Medical Education (CME) Information

Date of Original Release: January 2010

Examination Available Online: on or before Monday, January 11, 2010

Audio Files Available: No audio files will be available for this issue.

CME Credit Eligible Through: December 31, 2010

Answers: Correct answers with explanations will be posted on the ASN website in January 2011 when the issue is archived.

UpToDate Links Active: January and February 2010

Core Nephrology question links active: There are no core questions for this issue.

CME Credit: 8.0 AMA PRA Category 1 Credits™

Target Audience: Nephrology Board and recertification candidates, practicing nephrologists, and internists.

Method of Participation:

- Read the syllabus that is supplemented by original articles in the reference lists, and complete the online self-assessment examination.
- Examinations are available online **only** after the first week of the publication month. There is no fee. Each participant is allowed two attempts to pass the examination (>75% correct).
- Your score and a list of question/s (by number) answered incorrectly can be printed immediately.
- Your CME certificate can be printed immediately after passing the examination.
- **Answers and explanations are provided ONLY with a passing score on the first or second attempt.**
- Your ASN transcript will be updated in 6 to 8 weeks after passing the examination.

Instructions to access the Online CME Center to take the examination and complete the evaluation:

- Access the ASN website: www.asn-online.org
- Click on “**CME**” tab at the top of the homepage and then click on the **Online CME Center** icon to go to the login page.
- After login, click on the icon for “**NephSAP**”
- Select a topic and click on “**Start Now**”
- On the CME Information page, click on “**Continue**”
- On the MOC page, select whether or not you want MOC points.
- On the next page, click on “**Examination Questions/Evaluation**” to answer the questions.
- Your score and a list of question numbers answered incorrectly can be printed immediately.
- Follow the prompts to retake the examination if you failed, or print your certificate and the correct answers if you passed.
- You can retake the examination at any time. Each participant is allowed two attempts.

Instructions to Obtain American Board of Internal Medicine (ABIM) Maintenance of Certification (MOC) Points:

Each issue of *NephSAP* provides 10 MOC points. Respondents must meet the following criteria:

- Be certified by ABIM in internal medicine and/or nephrology and must be enrolled in the ABIM–MOC program *via* the ABIM website (www.abim.org).
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- Designate the issue for MOC points by clicking on the MOC link on the CME certificate page after passing the examination. You will be leaving the ASN-CECity site and transferring the information directly to the ABIM in real-time.
- Provide your ABIM Certificate ID number and your date of birth.
- You will receive a confirmation message from the ABIM indicating the receipt of your information.

MOC points will be applied to only those ABIM candidates who have enrolled in the program. It is your responsibility to complete the ABIM MOC enrollment process.

Volume 9, Number 1, January 2010—Primary Care for the Nephrologist

- ★ 1. You are seeing a 68-yr-old woman in the ambulatory setting for follow-up of her multiple chronic illnesses. She has a known history of hypertension, diabetes, and chronic renal disease and remote history of left middle cerebral artery stroke. She has been very compliant with her medication regimen, and both her BP and blood sugar levels are under tight control. She does share with you that she continues to smoke approximately 10 cigarettes daily and has done so for the past 50 yr. At this time, she is not interested in quitting. Her family history is significant for chronic obstructive pulmonary disease in her father and Alzheimer disease in her mother. As you review her preventive services, she asks you whether you will be “looking for aneurysms” in the abdomen. She has a close friend who recently died from a ruptured aortic aneurysm, and she knows that there is a screening test for this.

Which ONE of the following statements is TRUE about screening for abdominal aortic aneurysm (AAA)?

- On the basis of the recommendation of the US Preventive Services Task Force (USPSTF), women who are between the ages of 65 and 74 and have smoked >100 cigarettes in their lifetime should be screened once with ultrasound for AAA.
- On the basis of the recommendation of the USPSTF, women who are between the ages of 65 and 74 and have smoked >100 cigarettes in their lifetime should be screened annually with ultrasound for AAA, given their increased risk for rupture.
- On the basis of the recommendation of the USPSTF, women should not be screened with ultrasound for AAA.
- Ultrasound is not an effective method of screening for AAA.

E. Overall, women are at higher risk for the development of AAA than men.

- You are seeing an 86-yr-old woman in the office for her annual general medical examination. She has a history of degenerative joint disease, coronary artery disease, and hypertension and was recently admitted to the hospital with an exacerbation of her congestive heart failure. She is now back to her baseline and residing at home with her husband. The patient is completely independent with all instrumental activities of daily living but needs considerable assistance with bathing herself because of her arthritis. She is very motivated to optimize her health and prevent future hospitalization. She wonders what sort of preventive services she should be receiving. Specifically, she wonders whether you will be ordering a screening mammogram for her.

How should you proceed in counseling this patient about the utility of mammogram?

- Explain that mammography is never appropriate for women who are older than 85 yr.
 - Explain that on the basis of her prognosis, chronologic age, and history of congestive heart failure, a mammogram is not indicated.
 - Explain that the American Geriatrics Society has outlined that women should receive a mammogram annually until age 75.
 - Order a screening mammogram for this patient, because mammography has been shown to decrease mortality among women who are older than 85 yr.
- A 78-yr-old man presents after sustaining a fall in his home. He is accompanied by his daughter, who observed the event. The patient was walking from the kitchen table to his sink, when he

stumbled and fell onto his right hip. The patient did not lose consciousness and denied any dizziness. The patient has moderate pain around his right hip but is doing well otherwise. He has a history of chronic kidney disease (CKD), hypertension, atrial fibrillation, and generalized anxiety disorder. His current medications include lisinopril 10 mg/d, metoprolol 50 mg twice daily, warfarin 3 mg/d, and fluoxetine 20 mg/d. His supine BP in the office is 130/88 with a pulse of 64 bpm, and his standing BP is 125/82 with a pulse of 66 bpm.

Which ONE of the following of the patient's medications confers the greatest risk for falling?

- A. Lisinopril
 - B. Metoprolol
 - C. Warfarin
 - D. Fluoxetine
4. An 82-yr-old community-dwelling woman is seeing you for follow-up of her CKD and hypertension. Before the visit, her daughter pulls you aside privately and states that her mother has been falling at home. She is concerned about her mother's ability to continue living at home independently. The patient's daughter asks you to do what you can to prevent her mother from falling again.

Which ONE of the following therapies is MOST effective in fall prevention?

- A. Hip protectors
 - B. Multifactorial risk factor assessment and intervention
 - C. Use of an assistive gait device
 - D. Home safety assessment
 - E. Patient and family education about fall prevention
5. You are seeing a 70-yr-old man in an outpatient setting for his CKD. The radiologist reading his renal ultrasound describes an incidentally found infrarenal AAA that measures 3.5 cm in greatest diameter. The common iliac arteries are also aneurysmal.

How should you treat this patient?

- A. Immediately refer him to a vascular surgeon for consideration of elective open repair.
 - B. Immediately refer him to an interventional radiologist for consideration of endovascular repair.
 - C. Order a follow-up abdominal ultrasound in 3 mo.
 - D. Order a follow-up abdominal ultrasound in 6 mo.
 - E. Order a follow-up abdominal ultrasound in 12 mo.
6. A 69-yr-old woman presents for a hypertension follow-up. She has a history of diabetes, depression, and peripheral vascular disease. Her husband accompanies her and mentions that his wife repeats herself frequently, and he is concerned about her memory. He provides further history that she has made several accounting errors, which is most unusual for her. The patient denies any concerns about her own memory and seems insulted by her husband's observations. She scores 24 of 30 points on the Mini-Mental Status Examination, but the remainder of her neurologic examination is normal. Laboratory results are as follows: Hemoglobin 13 g/dl; leukocyte count $10 \times 10^9/L$; platelet count $146 \times 10^9/L$; aspartate aminotransferase 35 U/L; thyroid-stimulating hormone (TSH) $1 \mu U/L$, and creatinine 1 mg/dl.

Which other investigations should you recommend?

- A. Positron emission tomography scanning to rule out frontotemporal dementia
 - B. Syphilis serology
 - C. Cerebrospinal fluid evaluation for cell count, oligoclonal bands, and protein
 - D. Magnetic resonance imaging (MRI) of the brain
 - E. Electroencephalogram to rule out Prion disease
- ★ 7. You are seeing an 88-yr-old woman with a history of moderately advanced Alzheimer disease for a number of worsening symptoms. She

is accompanied by her son, who is her primary caregiver. He explains that his mother has continued to lose weight over the past year and has little interest in eating. In addition, she often complains of vague epigastric discomfort and belching. He states that he has not noted any blood in his mother's stool but notices that she has frequent loose stools. Upon further review of her chart, you find that she has lost approximately 5 kg in the past year. Her current body mass index (BMI) is 22. Her medications include diltiazem, donepezil, sertraline, omeprazole, and vitamin E. These medications have been stable over the past year.

Which ONE of the following is the MOST appropriate next step in the treatment of this patient?

- A. Order esophagogastroduodenoscopy of this patient to rule out gastric malignancy.
- B. Order computed tomography (CT) scan of the abdomen and pelvis.
- C. Discontinue donepezil.
- D. Discontinue vitamin E.
- E. Begin therapy with rotating antibiotics.

- ★ 8. A 79-yr-old man is seen in the clinic setting for his annual general medical examination. He has enjoyed good health, and at this time his only medical problems are hypertension and obstructive sleep apnea. The patient continues to jog several times per week and eats a healthy diet. His family medical history is significant for a brother with prostate cancer in his late 80s. The patient wonders whether he should be screened for prostate cancer.

Which ONE of the following statements is TRUE?

- A. Prostate-specific antigen (PSA) has a moderately high positive predictive value and will likely be of utility in this gentleman with excellent functional status.
- B. PSA has a low positive predictive value but will be of utility in this gentleman with excellent functional status.
- C. The USPSTF recommends screening all men aged 50 to 80 for prostate cancer with annual PSA and digital rectal examination.

- D. The USPSTF recommends against screening for prostate cancer in men aged ≥ 75 yr.

9. A 64-yr-old woman seeks advice in the clinic setting for dyspareunia. She has a history of cervical intraepithelial neoplasia grade 1 on a Papanicolaou (Pap) test approximately 10 yr ago and recently underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for menorrhagia.

Which ONE of the following statements is CORRECT?

- A. The patient needs to undergo vaginal Pap testing every 3 yr until age 70.
- B. The patient needs to undergo vaginal Pap testing at least once after hysterectomy, and then cervical cancer screening may be stopped.
- C. The patient does not need further cervical cancer screening because of her previous surgery.
- D. On the basis of the patient's age, she does not need further cervical cancer screening.

10. An active 70-yr-old woman comes to the office for a physical examination. Approximately 10 yr ago, she had three colon polyps removed. The pathology from these polyps was consistent with tubular adenomas. She underwent a follow-up colonoscopy 6 yr ago, and this was negative for colon polyps.

Which ONE of the following is the MOST appropriate colon cancer screening recommendation for this patient?

- A. No further screening
- B. Flexible sigmoidoscopy
- C. Virtual colonoscopy
- D. Colonoscopy
- E. Fecal occult blood testing

11. A 77-yr-old woman with a history of chronic renal disease and Alzheimer-type dementia is on your hospital service with a urinary tract infection. You are called to assess her because her nurse notes that she has been aggressive toward

the allied health staff and has struck her roommate without provocation. The nursing staff has tried redirecting the patient and engaging the patient without success. After a call to the patient's assisted living facility, you find out that this patient has exhibited aggressive, physical behaviors during the past 3 mo. They are concerned that she may not be able to return to the facility if her behaviors continue.

Which ONE of the following medication regimens is MOST appropriate for this patient?

- A. Lorazepam 0.5 mg by mouth every 6 h as needed for agitation
 - B. Clonazepam 1 mg by mouth every 8 h
 - C. Buspirone 10 mg by mouth every 8 h
 - D. Quetiapine 12.5 mg by mouth twice daily
 - E. Trazodone 25 mg by mouth at bedtime
12. A 65-yr-old man comes to the office with his wife for follow-up of hypertension. He has been your patient for the past 10 yr since he was diagnosed with CKD and has had increasing trouble with BP control. He has been on stable doses of losartan, metoprolol, hydrochlorothiazide, and amlodipine. On his current medications, his home BPs have been averaging 138/78 mmHg. He has been trying to be more active and is watching his diet. His weight has remained unchanged at 220 lb (100 kg). His BMI is 31 kg/m². He denies any problems, but his wife states that he has been more fatigued than usual and is taking naps. She tells you that he does not seem to want to go out to dinner anymore and wonders whether this is related to his medications. He had a general physical examination with his primary doctor 3 mo ago, and tests done at that time were satisfactory. His creatinine was stable at 2.5 mg/dl, and blood urea nitrogen was not increased. His hemoglobin was stable at 11.5 g/dl. Additional testing included assessment of thyroid function and overnight oximetry, which were normal. Today in the office, his BP is 134/74 mmHg and pulse is 66 bpm.

At this point, which ONE of the following is the MOST appropriate next step?

- A. Recheck serum TSH concentration
- B. Screen for depression
- C. Schedule an exercise treadmill test

- D. Reduce the dosage of metoprolol
- E. Check pulse oximetry

- ★13. A 54-yr-old man with type 2 diabetes and CKD and a baseline creatinine of 2.1 mg/dl comes to the office complaining of fatigue. This is not a new complaint but now is interfering with his ability to work. He says he “has no energy” but denies shortness of breath, chest pain, edema, lightheadedness, or other symptoms of cardiac disease. He is single and has no children. He quit smoking 10 yr ago and rarely uses any alcohol. His current medications include glipizide, metformin, lisinopril, aspirin 81 mg, and simvastatin. His last hemoglobin A_{1c} was 6.5%, and LDL cholesterol (calculated) was 97 mg/dl. On examination, his BP is 128/70 mmHg and pulse is 72 bpm. His BMI is 28.9 kg/m². His examination is otherwise normal. He admits to being sad and feeling hopeless at times.

In addition to setting him up for a follow-up visit, which ONE of the following medications should be started?

- A. Amitriptyline
 - B. Trazodone
 - C. Venlafaxine
 - D. Fluoxetine
 - E. No medication is indicated
14. A 35-yr-old man comes to your office for recommendations about a healthy lifestyle. He does not smoke, exercises 4 to 5 d/wk on an elliptical machine, and has one to two alcoholic drinks per week. His father is alive at age 75, had a myocardial infarction at age 72, and developed prostate cancer last year. His mother is 74 yr old and had a mastectomy for breast cancer at age 68. Recently, she was told to watch her diet more carefully because her blood sugar was higher than normal. On examination, his pulse is 68 bpm and his BP is 132/80 mmHg. His BMI is 25.8 kg/m². His physical examination is otherwise normal.
- Which ONE of the following tests is MOST appropriate at this time?**
- A. Fasting blood sugar
 - B. PSA

- C. Serum TSH
- D. Serum lipid panel
- E. Electrocardiogram

15. A 54-yr-old woman comes to the office to discuss breast cancer screening. Her mother developed breast cancer at age 62. She has three maternal aunts, one who developed breast cancer at age 72, and four paternal aunts, none of whom have had breast cancer. She has two sisters. An older sister had a biopsy for “dense breast tissue” but has not been told she has breast cancer. Her younger sister, age 45, has refused to get a mammogram.

At this time which ONE of the following is the MOST appropriate recommendation?

- A. Order a mammogram.
- B. Send for a genetic consultation.
- C. Order *BRCA1/2* gene testing.
- D. Order breast MRI.

16. A 28-yr-old woman who has type 1 diabetes and has been on hemodialysis for the past 2 yr asks you what additional things she needs for preventive services when you see her for a recheck at a hemodialysis run. She does not smoke or drink. Her past medical history is otherwise significant for a tonsillectomy at age 8 and wisdom teeth removal at age 14. Her current insulin regimen consists of lispro and glargine. She also takes a multivitamin, lisinopril, simvastatin, and aspirin 81 mg/d. Her menstrual cycles are regular and occur every 28 d. She is not sexually active and never had a Pap smear. Her BP is 112/68 mmHg, and pulse is 64 bpm. Her BMI is 26 kg/m².

Which ONE of the following is indicated?

- A. Human papillomavirus vaccination
- B. Pap smear
- C. Mammogram
- D. Hepatitis A vaccination series
- E. Herpes zoster vaccination

17. A 57-yr-old man comes to the office for evaluation of an elevated creatinine: 1.4 mg/dl. He admits to using ibuprofen for knee pain on a daily basis for the past 2 mo after twisting his knee while working

in the yard. His BP has been labile for the past few years, but he has never been put on medication nor received a diagnosis of hypertension. He drinks approximately 6 cans of beer every few days and says he is working on cutting down on his smoking. He currently smokes 1 pack per day. He has tried the nicotine patches in the past when he was trying to quit but could not tolerate the adhesive.

In addition to advising him to quit, which ONE of the following is MOST likely to help him stop smoking?

- A. Nortriptyline
- B. Clonidine
- C. Varenicline
- D. Bupropion
- E. Nicotine nasal spray

18. A 62-yr-old woman comes to your office for follow-up of CKD with a baseline creatinine of 1.8 mg/dl. She continues to smoke, despite your repeated recommendations to stop. Today she requests a chest x-ray to look for lung cancer. She had pneumonia 5 yr ago and a bout of bronchitis that required antibiotics 18 mo ago. Her current medications include lisinopril and albuterol metered-dose inhaler as needed. On examination, her BP is 148/70 mmHg and pulse is 84 bpm. Her cardiac examination is normal, and there is mild prolongation of expiration on chest examination. You obtain peak flows in the office, which are 85% of predicted (>80% is normal).

At this time, which ONE of the following tests is MOST appropriate?

- A. Obtain sputum for cytology.
- B. Order a chest x-ray.
- C. Order low-dosage CT.
- D. Order spirometry.
- E. No test is needed.

19. A 56-yr-old man with a history of IgA nephropathy comes to the office for a recheck and to discuss cancer screening. At age 50, his previous doctor ordered a PSA test and a colonoscopy. The PSA was slightly elevated, but a recheck 6 mo later was normal. At the time of colonoscopy, three small polyps 2 to 4 mm in diameter

were found and removed. On pathology, the polyps were found to be hyperplastic. His paternal grandfather and paternal uncle had prostate cancer, but no one has had breast, ovarian, or colon cancer. He tells you that he has been recently healthy and denies any hematuria. He takes enalapril daily and an occasional aspirin for a headache. He does not drink. He continues to smoke 1 to 2 packs per day and is not interested in quitting. His BP is 128/82 mmHg, pulse is 78 bpm, and BMI is 27.4 kg/m². His creatinine is 1.2 mg/dl, and his urinalysis shows 1 to 3 red blood cells per high-power field.

Which ONE of the following should be done at this time?

- A. Order a PSA.
- B. Order a colonoscopy.
- C. Advise him to quit smoking.
- D. Order a chest x-ray.
- E. Prescribe nicotine replacement therapy.

★20. A 55-yr-old woman whom you see for management of hypertension comes to the office to discuss weight reduction therapies. Her twin sister “just had a heart attack, and I don’t want this to happen to me.” She has tried to lose weight in the past but given up after a few weeks. She takes lisinopril daily, and her creatinine has been stable at 1.6 mg/dl for the past 3 yr. Her BP is 124/78 mmHg, and pulse is 84 bpm. Her BMI is 38 kg/m². Her fasting blood sugar was 121 mg/dl on laboratory testing obtained before her appointment.

Which ONE of the following would be the MOST effective to prevent the development of diabetes in this patient?

- A. Oral sibutramine therapy
- B. Oral metformin therapy
- C. Intensive diet and exercise program
- D. Laparoscopic adjustable gastric band
- E. Roux-en-Y gastric bypass

21. A 32-yr-old woman who is on long-term peritoneal dialysis comes to the office to discuss her thyroid results. She had complained about fatigue, and the TSH concentration test came back

elevated at 5.5 μ U/L (normal 3.5 to 5.0 μ U/L). There was no elevation in the thyroid peroxidase antibody concentration. Her BP is 128/88 mmHg, pulse is 78 bpm, and BMI is 27.4 kg/m².

Which ONE of the following is the MOST appropriate next step?

- A. Begin low-dosage thyroid replacement therapy.
- B. Reassure her that she is at low risk for developing clinical hypothyroidism.
- C. Check a free T4 level because it is likely falsely elevated by the peritoneal dialysis.
- D. Recheck a TSH concentration in 6 wk.
- E. Assess for goiter with thyroid ultrasound.

22. Evidence-based guidelines require developers to interpret and evaluate the evidence contained in clinical studies. For studies that assess the value of diagnostic tests, both the sensitivity and the specificity are important considerations in developing the guidelines. The American Cancer Society reviewed six studies that assessed the value of adding MRI to mammography for women whose lifetime risk is 20 to 25%. Their review reported the sensitivity of MRI as 77 to 100% and the specificity as 81 to 99%. In contrast, the sensitivity of mammography was 16 to 40% and the specificity was 93 to 99%. Twenty to 40% of biopsies done after MRI are malignant.

Which ONE of the following is the MOST accurate interpretation of these results?

- A. MRI has lower sensitivity for malignancy than mammography.
- B. MRI has a higher false-positive rate than mammography.
- C. Mammography is more accurate in patients who are at higher risk for breast cancer.
- D. MRI is cost-effective for patients who are at high risk for breast cancer.
- E. No conclusion can be made on the basis of these results.

23. A recent effort toward developing a consensus on grading the quality of evidence and strength of recommendations resulted in the Grading of Recommendations Assessment, Development

and Evaluation (GRADE) system. This system emphasizes the quality of evidence as well as the uncertainty of trade-offs. The quality of evidence is based on the strength of study design and whether future research is likely to change the estimate of the effect.

Which ONE of the following is likely to DECREASE the strength of a recommendation when the quality of evidence is rated as high?

- A. Absence of a dose-response gradient
 - B. Inclusion of studies with negative results in the analysis
 - C. A narrow confidence interval around the estimate of effect
 - D. Heterogeneity in study outcomes
 - E. Studies that are funded by the pharmaceutical industry
- 24.** A 62-yr-old man comes to the office for an insurance physical. His last physical examination was at age 55 and included age-appropriate preventive services. He takes no medications but smokes one to two packs of cigarettes daily and drinks a 12-pack of beer weekly. He tells you that he is doing fine and is not interested in quitting smoking. He enjoys golf and usually walks when he plays. On physical examination, his BP is 138/88 mmHg, pulse is 88 bpm, and BMI is 29.7 kg/m². His examination is satisfactory. You recommend checking his lipids. The patient then asks, "Will you order a chest x-ray to check me for lung cancer?"

Which ONE of the following is the MOST appropriate response to this question?

- A. If you are concerned about lung cancer, then you should quit smoking.
- B. A low-dosage CT scan of the chest is a better screening test.

- C. A sputum cytology test is more specific for lung cancer.
- D. Repeated chest x-rays cause an increase in lung cancer in smokers.
- E. Chest x-rays have not been shown to diagnose cancer early enough to make a difference.

- 25.** A 63-yr-old man comes to the office for follow-up of benign prostatic hypertrophy and elevated creatinine. One month ago, he presented to your office with urinary hesitancy and nocturia. On examination, he had moderate prostatic hypertrophy without nodules. Laboratory testing showed an elevated creatinine at 1.4 mg/dl. His PSA concentration and urinalysis were normal. His symptoms are much improved on terazosin 5 mg nightly. He has no symptoms of orthostatism. His BP in the office today is 118/82 mmHg, and pulse is 76 bpm. In reviewing his records, you determine that he is due for colon cancer screening. There is no history of colon cancer or polyps that he is aware of, but his brother had diverticulitis that required emergent surgery because of a perforation.

Which ONE of the following statements is the MOST accurate?

- A. Colonoscopy should be avoided because of his brother's history.
- B. A CT colonography is generally a better test because a significant amount of disease outside the colon is found during the examination.
- C. A fecal occult blood test done at the time of his digital rectal examination is sufficient to screen him this year.
- D. A stool DNA test done every 5 yr will be an adequate screen.
- E. A colonoscopy would be the most appropriate test.



For all questions highlighted in green, access to related *UpToDate* topic reviews is available on the ASN web site (www.asn-online.org). See the CME Information page for instructions.