Medicare Coverage of Routine Screening for Thyroid Dysfunction

Marc B. Stone and Robert B. Wallace, Editors, Committee on Medicare Coverage of Routine Thyroid Screening

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Committee on Medicare Coverage of Routine Thyroid Screening
Board on Health Care Services

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Barbara J. McNeil, M.D., Ph.D., Ridley Watts Professor and Head Department of Health Care Policy, Harvard Medical School**, and **Joseph P. Newhouse, Ph.D., John D. MacArthur Professor of Health Policy and Management Harvard University.** Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

When the Medicare program was established in 1965, it was viewed as a form of financial protection for the elderly against catastrophic medical expenses, primarily those related to hospitalization for unexpected illnesses. The first expansions to the program increased the eligible population from the retired to the disabled and to persons receiving chronic renal dialysis. It was not until 1980 that an expansion of services beyond those required "for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member"[1] was included in Medicare. These services, known as *preventive services,* are intended either to prevent disease (by vaccination) or to detect disease (by diagnostic test) before the symptoms of illness appear.

Our Committee was formed "to conduct a study on the addition of coverage of routine thyroid screening using a thyroid stimulating hormone test as a preventive benefit provided to Medicare beneficiaries under Title XVIII of the Social Security Act for some or all Medicare beneficiaries."[2] We approached this task in the context of another Institute of Medicine report published in 2000, *Extending Medicare Coverage for Preventive and Other Services*. In addressing this issue, we were aided by a background paper commissioned by the United States Preventive Services Task Force that reviewed the evidence published in peer-reviewed scientific papers, heard from a broad range of experts in relevant fields,

[1]Title XVIII of the Social Security Act, Section 1862(a)(1)(A).
[2]Consolidated Appropriations Act for 2001, Section 123.

and looked at the current state of thyroid disease and testing among Medicare beneficiaries through both an analysis of Medicare claims data and a population-based study of Medicare beneficiaries.

Robert B. Wallace, M.D.
Chair

Acknowledgments

The Committee would like to express its appreciation for the fine assistance it received from a number of individuals:

David Atkins and the United States Preventive Services Task Force, in response to the legislation ordering this volume, commissioned the Systematic Evidence Review that is the principal background paper for this document as well as part of the process for the Task Force's new clinical practice recommendations for screening for thyroid disease.

Mark Helfand developed the comprehensive Evidence Review (presented in Appendix B) and provided additional advice and insight.

Robert Lindeman provided additional data and analysis pursuant to his work on the New Mexico Elder Health Survey.

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Summary

The Medicare program was established in 1965 under Title XVIII of the Social Security Act. The program has become the principal means of providing health insurance coverage to the American population aged 65 and older as well as covering individuals with permanent disabilities or end-stage renal failure. Notwithstanding the enormous scale of the Medicare program, Congress has explicitly excluded a number of health care services. Section 1862(a)(1)(A) of Title XVIII states that the program may not pay for services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Section 1862(a)(7) excludes routine physical examinations. These provisions have amounted to an exclusion of preventive services. In subsequent years Congress has overridden this exclusion for specific preventive services, adding them to the Medicare program.

Section 123 of the Consolidated Appropriations Act for 2001 commissioned the National Academy of Sciences, now known as the National Academies, "and as appropriate in conjunction with the United States Preventive Services Task Force, to conduct a study on the addition of coverage of routine thyroid screening using a thyroid stimulating hormone test as a preventive benefit provided to Medicare beneficiaries under Title XVIII of the Social Security Act for some or all Medicare beneficiaries" and to "consider the short-term and long-term benefits, and costs to the Medicare program, of such addition." The serum thyroid stimulating hormone (TSH) assay is a common blood test that is already covered by the Medicare program for the diagnosis and treatment of illness. This volume, prepared by a committee appointed by the Institute of Medicine of the National

Academies, is an inquiry into the additional costs and benefits of also offering this test as a preventive service.

MEDICARE AND PREVENTIVE SERVICES

The initial focus of the Medicare program was to provide financial relief through substantial, if partial, reimbursement for the largest expenses of serious illness, particularly hospitalization. The original Medicare legislation excluded preventive services and routine physical examinations because they were not seen as part of the care of serious illness. These services were performed at the discretion of patients and doctors; their expense was foreseeable and not substantial.

Over time patterns of illness and treatment have changed. Illness is more commonly chronic and ongoing instead of acute and episodic. Most care is now provided outside the hospital. The Medicare program has adapted to most of these changes and covers most outpatient care. Coverage of preventive services (and prescription drugs) has been a significant exception. Individual preventive services have been added on an ad hoc basis through specific acts of Congress.

THYROID DYSFUNCTION AND ITS DIAGNOSIS

The thyroid gland produces and releases into the circulation hormones that influence basal metabolic processes in nearly all body tissues. Hypothyroidism, the lack of adequate production of thyroid hormones, can result in fatigue, lethargy, cold intolerance, slowed speech and intellectual function, slowed reflexes, hair loss, dry skin, weight gain, and constipation. Hyperthyroidism, the production of excessive amounts of thyroid hormones, can cause nervousness, anxiety, heart palpitations, rapid pulse, fatigability, tremor, muscle weakness, weight loss with increased appetite, heat intolerance, frequent bowel movements, increased perspiration, and often thyroid gland enlargement (goiter).

Thyroid gland function and hormone synthesis and release are regulated by thyroid stimulating hormone (TSH) that is secreted by the anterior pituitary gland. Inadequate thyroid gland output leads to high levels of TSH, while excessive thyroid hormone production suppresses production of TSH. Levels of serum TSH are generally the most sensitive indicator of thyroid gland function: Abnormal levels of TSH are often found even when serum levels of thyroxine, the principal hormone produced by the thyroid gland, are normal. By convention, abnormal levels of TSH in the presence of normal serum levels of free thyroxine are described as *subclinical* thyroid dysfunction; abnormal levels of TSH in the presence of abnormal serum levels of free thyroxine are described as *overt* thyroid dysfunction. This terminology can be confusing. Persons with "subclinical" thyroid dysfunction by this biochemical definition may display clear symptoms or signs of thyroid dysfunction while those with biochemically defined "overt" hypothyroidism may show no other evidence of thyroid dysfunction.

PREVALENCE AND CONSEQUENCES OF THYROID DYSFUNCTION

Thyroid dysfunction is common, especially in elderly people. Most people found to have abnormal serum levels of TSH in surveys have normal serum free thyroxine levels and are thus classified as having subclinical thyroid dysfunction, particularly subclinical hypothyroidism. Among people with subclinical thyroid dysfunction, most have very small increases or decreases in serum TSH concentrations. When asked, some of these people with subclinical thyroid dysfunction have symptoms that are compatible with, though not specific for, thyroid dysfunction, or have another indication for testing for thyroid dysfunction. Some people have biochemical or physiological abnormalities that are ameliorated by thyroid hormone therapy, in the case of people with subclinical hypothyroidism, or antithyroid therapy, in the case of subclinical hyperthyroidism. Among people with thyroid dysfunction, therapy may have beneficial effects on intermediate outcomes, such as reduction in serum lipid concentrations and improvement of myocardial contractility. However, appropriate therapy has not been proven to alter long-term morbidity or mortality in people with subclinical thyroid dysfunction. Similarly, while it is accepted that treatment will benefit patients with biochemically overt thyroid dysfunction who present with significant symptoms or complications, the lack of well designed studies makes it difficult to determine whether treatment would provide significant net benefit in persons who have biochemically defined overt thyroid dysfunction but little evidence of illness; the potential for harm is similar but potential for benefit is less. These uncertainties make it difficult to assess the value of a screening program for thyroid dysfunction.

SCREENING FOR THYROID DYSFUNCTION

Screening is the process of testing for a clinical condition when symptoms or other evidence of the presence of that condition either do not exist or, if present, are unrecognized by the health professional who orders the test. If a clinician suspects that clinically manifest thyroid dysfunction is present, TSH testing would not be considered screening; this is a diagnostic process that is already covered by Medicare. Under current coverage, a patient may be tested for thyroid dysfunction because of a broad range of symptoms associated with thyroid dysfunction; because thyroid dysfunction is a known cause or aggravating factor for many conditions such as atrial fibrillation, diabetes, hypertension, or hyperlipidemia; or because of a history of any kind of thyroid disease or exposure to an agent known to be thyrotoxic.

For a screening program to be successful, a number of important conditions must be satisfied. The natural history of the condition being screened must be understood so there is good evidence the disease outcome will be favorably influenced by further diagnosis and treatment. The screening test must be suit-

ably reliable and valid so that most of those tested are accurately classified as to the current presence or absence of the disease in question. The screening test must be acceptable when applied to most persons for whom it is indicated. If not, the test will not effectively reach its intended target population and fail as a disease prevention measure. If a screening test indicates the possibility of a disease being present, there must be suitable, definitive tests to make a formal diagnosis of that condition. There must be proven, effective treatments for the conditions identified—treatments that lead to increased survival, function, or quality of life. Finally, there must be value to early intervention; diagnosis as a result of screening must provide a better chance of cure, less disability, a reduction in the development of pain or other significant symptoms, or enable treatment that is less arduous or expensive.

In the case of serum TSH screening for thyroid disease, these conditions are not fully satisfied. In its favor, the serum TSH test is reliable, valid, and acceptable to patients. The diagnosis of thyroid dysfunction can usually be made definitively. However, the natural history is not highly predictable; a large proportion of subjects screened who have positive test results will not develop significant morbidity from thyroid dysfunction. Available treatments can improve biochemical and physiological indications of thyroid dysfunction, but there are no studies of treatment of subjects identified through screening that show significant benefits from treatment in terms of improved survival, function, or quality of life. Treatment begun at the time of screening also has not been demonstrated to provide benefits greater than treatment initiated when the disease is clinically manifest.

THE COST OF COVERAGE

Estimates of the costs of screening require an estimate of the number of subjects who will be screened and the net costs incurred (or saved) as a result of screening.

Historically, the use of preventive services by Medicare beneficiaries has been considerably less than universal among those covered for the service; important factors have limited demand or created other barriers to use. In the case of serum TSH testing, more than 90 percent of Medicare beneficiaries have indications for testing that are already covered by the Medicare program. Aside from beneficiaries with known thyroid disease, fewer than 25 percent of beneficiaries with these indications are tested annually. On this basis, it is estimated that a relatively small number of Medicare beneficiaries would take advantage of a serum TSH screening benefit; our best estimate is 250,000 annually.

The Committee found a widespread lack of information necessary to make a meaningful assessment of the true economic costs of screening. It could not estimate costs avoided or other possible benefits resulting from screening or whether any costs incurred would be postponed rather than avoided if screening were not done. The Committee's estimate of the cost of health care resources

likely to be expended for the initial screening test for 250,000 elderly beneficiaries was $5.9 million. The Medicare program would pay this entire amount. The Committee's estimate of the lifetime cost of evaluating and treating those people with positive test results suggesting hypothyroidism was $24.7 million. The Medicare program would pay $11.6 million of this total; supplementary insurance or the beneficiaries themselves would pay the remaining $13 million. The Committee's estimate of the lifetime cost of evaluating and treating those people with positive test results suggesting hyperthyroidism was $2.8 million. The Medicare program would pay $2.1 million of this total; supplementary insurance or the beneficiaries themselves would pay the remaining $0.6 million.

CONCLUSIONS AND RECOMMENDATIONS

The Committee reached two conclusions and makes a recommendation.

There is insufficient evidence to recommend periodic, routine screening for thyroid dysfunction among asymptomatic persons using serum TSH levels.

The basic reasons for this conclusion stemmed from several general considerations. It is uncertain whether asymptomatic persons with abnormal TSH levels actually have some degree of physiologically meaningful abnormalities that would benefit from early treatment in the absence of clinical manifestations. Some of the potentially important consequences of thyroid disease, such as altered blood cholesterol and lipid levels and bone density levels, are themselves the subject of recommended routine clinical screening procedures; these should be performed as part of a general program of preventive care regardless of a potential relation to possible thyroid dysfunction. While some individuals with unrecognized clinical or physiological abnormalities associated with thyroid dysfunction do progress to more severe thyroid disease over several years, the rates, timing, and risk factors for this progression are only partly understood. Finally, routine TSH screening of asymptomatic persons over 65 years of age may lead to large numbers of persons receiving thyroid hormone therapy, but no randomized clinical trials have been performed that assess the long-term benefits or adverse effects of early treatment of thyroid dysfunction.

Given insufficient evidence about the health benefits of a serum TSH screening program, the net cost implications for the Medicare program are uncertain.

Because evidence is lacking on the likely health benefits of screening, there is no reasonable basis for estimating whether a screening program would detect thyroid dysfunction more effectively than usual care and hence how the costs of treating thyroid dysfunction under these alternative strategies would compare. We do not have an adequate basis for estimating whether there would be any net

savings or additional costs associated with treating future consequences of thyroid dysfunction.

The Medicare program at this time should not cover screening for thyroid dysfunction as a preventive services benefit. This recommendation is based on the lack of sufficient evidence of either net benefit or harm. Additional evidence is required for a definitive conclusion.

1

Introduction

The Medicare program was established in 1965 under Title XVIII of the Social Security Act. The program has become the principal means of providing health insurance coverage to the American population aged 65 and older as well as covering individuals with permanent disabilities or end-stage renal failure. The program covered more than 40 million people in 2001 (Centers for Medicare and Medicaid Services, 2002). Fiscal 2001 expenditures were $238 billion, or 2.4 percent of gross domestic product (GDP). The Congressional Budget Office projects Medicare expenditures to double by 2012 (Congressional Budget Office, 2002) and constitute 5.5 percent of GDP by 2030 (Crippen, 2001).

Notwithstanding the enormous scale of the Medicare program, Congress has explicitly excluded a number of health care services. Section 1862(a)(1)(A) of Title XVIII states that the program may not pay for services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Section 1862(a)(7) excludes routine physical examinations. These provisions have amounted to an exclusion of preventive services. In subsequent years Congress has overridden this exclusion for specific preventive services, adding them to the Medicare program.

Section 123 of the Consolidated Appropriations Act for 2001 commissioned the National Academy of Sciences, now known as the National Academies, "and as appropriate in conjunction with the United States Preventive Services Task Force, to conduct a study on the addition of coverage of routine thyroid screening using a thyroid stimulating hormone test as a preventive benefit provided to Medicare beneficiaries under Title XVIII of the Social Security Act for some or all Medicare beneficiaries" and to "consider the short-term and long-term benefits,

and costs to the Medicare program, of such addition." Because the issue is framed as a question of coverage, the commission of this study required examination of both Medicare coverage policy and the clinical utility of the thyroid stimulating hormone test in the Medicare population. The serum thyroid stimulating hormone (TSH) assay is a common blood test that is already covered by the Medicare program for the diagnosis and treatment of illness. This volume, prepared by a committee appointed by the Institute of Medicine of the National Academies, is an inquiry into the additional costs and benefits of also offering this test as a preventive service.

The remaining sections of this chapter summarize the evolution of the Medicare program and the processes that Medicare uses to determine what services it will cover. Subsequent chapters summarize the clinical concepts of thyroid disease, its diagnosis, and treatment; describe and execute an analytic framework for the assessment of TSH testing as a preventive measure; and discuss the specific effects of current Medicare coverage of TSH testing and implications of its expansion.

THE ORIGINS OF MEDICARE

The Medicare program emerged after decades of debate about whether the United States should adopt a European-style model of comprehensive universal coverage through compulsory social insurance. The results were very different from most government-sponsored health insurance programs established outside the United States; the Medicare program had much narrower goals. Instead of a program that distributed medical services to the entire population, Medicare was intended initially only to pay some of the hospital costs of pensioners receiving Social Security (Marmor and Marmor, 1973).

The initial focus of the Medicare program was to provide financial relief through substantial, if partial, reimbursement for the largest expenses of serious illness, specifically hospitalization (Medicare Part A). The final legislation also included an optional program to help pay for physician services (Medicare Part B). There was strong political opposition to the idea of the government influencing the distribution of medical services. The problem of the retired was not seen as the inaccessibility of health care services, but the financial consequences of using those services (Marmor and Marmor, 1973); in principle, they could access the same services available to them before retirement.

Like most private insurance plans in America at that time, the Medicare program did not cover preventive services. The primary purpose of these plans was pooling of risk to protect against large financial losses that are unpredictable as to whether or when they might occur. Medical insurance under this model assumes that illness is unpredictable (so it cannot be budgeted), and the resource requirements for treatment are well defined and out of the control of the insured

(or his agent, the physician). This was thought to be true for major illnesses that required hospitalization; the patient could manage the expense of minor illnesses by himself. The insurer does not obtain or provide services; it provides financial reimbursement to the patient after the fact. There is no need for direct contact between the insurer and the health care provider (e.g., doctor, hospital); the insurer takes no responsibility for the quality of services provided. Plans limited their costs by excluding discretionary expenses and sharing costs with subscribers through limits on total outlays and specific payments for individual services, copayments, and deductibles (Starr, 1982).

The original Medicare legislation excluded preventive services and routine physical examinations because they did not involve the diagnosis and treatment of an existing condition. Their expense was foreseeable and not substantial. Their use did not follow the unpredictable dictates of illness; they were performed at the discretion of patients and doctors.

MEDICARE AND HEALTH INSURANCE TODAY

In the nearly 40 years since the establishment of the Medicare program, health insurance in America has undergone dramatic changes. This has come about as a result of changes in the understanding of how the demand for medical care arises and in consumer expectations for care.

One of the most significant changes in the practice of medicine since the establishment of Medicare has been in the recognition, prevalence, and treatment of chronic disease. Patients with grave illnesses such as heart and kidney failure, cancer, emphysema, AIDS, and severe atherosclerosis that previously resulted in rapid death now live much longer; much of their treatment occurs on a steady basis outside the hospital. Diseases with less immediate consequences such as hypertension and diabetes are more widely recognized and aggressively treated. Longer life expectancies resulting from better treatments, health-related behaviors, and preventive measures have allowed degenerative conditions such as arthritis and dementia to affect more of the population for greater periods of time. The care of chronic illness does not fit the original insurance model. The treatment requirements for chronic disease are neither unusual nor episodic; they involve large numbers of small expenditures on a continuing basis. This concept of proactive health maintenance also resulted in greater recognition of the potential value of preventive measures for adults.

The second reason for change has been the recognition that the evidence base for clinical practice was far more limited than previously thought (IOM, 2000). There was little objective basis for determining the resource requirements for care. Studies of resource use among populations that should have had similar burdens of illness revealed wide differences in resource use. The widespread lack of valid clinical guidelines for determining the resource needs for health care

meant that many of the costs of treatment were under the control of doctors and hospitals whose financial incentives created a severe problem of moral hazard (Starr, 1982).

The last reason for change has been the resistance of the insured to cost sharing. The common expectation of today's consumers has been to pay little or nothing for health care services. There has been a consistent trend for employers to provide more generous insurance coverage to their workers. Because health insurance premiums and benefits are free of taxation, employees have often found it more valuable to have their employers purchase more comprehensive health care coverage with pretax dollars than provide the same amount to them in taxable wages. Many of the improvements in coverage have included coverage for preventive and other relatively inexpensive services and substantial reductions in deductibles and copayments. This expectation has spread to the Medicare program, where about 80 percent of beneficiaries have supplemental coverage that helps pay for excluded services, deductibles, and copayments (IOM, 2000).

Today most insurance plans make direct payments to health care providers that usually constitute payment in full. These plans generally require providers to agree to participate in the plan. To limit costs, plans may set or negotiate fees and limits on the use of services and monitor the charges and behavior of providers, excluding from participation those who appear to abuse the plan or provide poor quality. This greater means of control over expenditures allows plans to offer not only payment in full but also fewer limitations on services covered, including preventive services (Starr, 1982).

Changes in the Medicare program have reflected this evolution. Instead of enrolling in Parts A and B, Medicare beneficiaries may enroll under Part C in comprehensive prepayment plans such as health maintenance organizations. Medicare Parts A and B today have most of the characteristics of other insurance plans. Nearly all providers who see Medicare patients do so under terms of participation. Payment amounts are regulated through fee schedules and prospective payment systems. Medicare has created Peer Review Organizations to monitor the utilization and quality of services (IOM, 1989). Cost sharing has been reduced—directly through elimination of copayments in areas such as laboratory services and indirectly through the proliferation of supplemental coverage.

The transformation of Medicare Parts A and B is also suggested by the extension of coverage to additional services, but these changes have occurred without a clear set of principles as to why and how extensions of coverage should be made. These issues were addressed in a previous IOM report, Extending Medicare Coverage for Preventive and Other Services (IOM, 2000). The section of that report that describes and analyzes Medicare coverage decisions is summarized in the next section, with particular attention to preventive services.

MEDICARE COVERAGE POLICY AND PREVENTIVE SERVICES

Medicare coverage decisions range from very broad-based decisions about whole categories of services to decisions about the general circumstances under which a specific service will be covered to very narrow decisions about whether a specific service will be covered for a specific individual. The entities that make these decisions have been, respectively,

Congress, making broad decisions about categories of coverage and coverage exclusions;

The Centers for Medicare and Medicaid Services (CMS), deciding whether a service qualifies for coverage under one of the approved categories and the circumstances under which that service will be covered; and

Private contractors that administer Medicare claims for the government, deciding whether specific services billed for a specific beneficiary are covered and establishing policies for services and circumstances for which CMS has no policy.

This delegation of responsibilities is a logical one. Congress must have the responsibility for determining the form and scope of the Medicare program and securing the financial resources to match those determinations. The operational policy required to implement congressional design is the responsibility of the executive agency, CMS. Contractors provide the actual services mandated by the program, the processing and payment of claims.

Congress has given CMS the responsibility to make specific determinations of what services are or are not covered within the broad coverage categories established in law. In carrying out this responsibility, CMS follows the provision of the law that authorizes payment for services only if they are "reasonable and necessary." At a minimum, it must be established that, in order to be covered, a service is safe and effective in achieving its purpose. All coverage decisions that CMS makes must follow federal rulemaking procedures and requirements. The decision-making process involves consultation with a Medicare Coverage Advisory Committee and takes advantage of the growth of the clinical evaluative sciences by obtaining systematic reviews of scientific evidence provided by sources such as the Food and Drug Administration, the National Institutes of Health, and the Evidence Based Practice Centers supported by the Agency for Healthcare Research and Quality.

The expansion of Medicare coverage to preventive services has been an exception to this established structure. Congress could have authorized the expansion of Medicare coverage to preventive services as a class and allowed the Health Care Financing Administration (the predecessor to CMS) or CMS to determine which preventive services were reasonable and necessary and, therefore, covered. The scientific tools and methods used to evaluate preventive services differ little from those used to evaluate diagnostic and treatment services. Instead of a systematic approach, individual services have been added on an ad

hoc basis through specific acts of Congress. This has resulted in an assortment of preventive services covered by Medicare that is substantially different from the group of services recognized as effective by the United States Preventive Services Task Force. The lack of a systematic approach also makes it difficult to make optimal decisions when services may be complementary, redundant, or obsolete. It may favor services for high-profile conditions and technologies that have strong lobbying groups but not necessarily a strong evidence base.

METHODS AND APPROACH

To develop this report, the Institute of Medicine of the National Academies created a nine-member committee with expertise in thyroidology, epidemiology, preventive medicine, primary care, clinical chemistry, economics, statistics, and health services research. The Committee on Medicare Coverage of Routine Thyroid Screening met three times between July 2002 and January 2003. In addition to the Committee's own knowledge and expertise, the Committee relied on three additional sources of information: (1) a systematic evidence review of the medical literature that was commissioned in conjunction with the United States Preventive Services Task Force; (2) a workshop with expert speakers invited to provide additional information in areas of interest and to participate in a roundtable discussion; and (3) an analysis of Medicare claims data to provide information on how TSH testing is currently used in the Medicare population and which beneficiaries potentially would be affected by coverage of a TSH screening benefit.

Chapter 2 turns the report from the general issue of Medicare and preventive services to the specific question of TSH testing. It is an orientation to thyroid disease, reviewing the physiology of the thyroid gland, the clinical approach to thyroid disease, and the role and efficacy of TSH testing in diagnosis and treatment.

Chapter 3 looks at the epidemiology and consequences of thyroid dysfunction. This chapter provides estimates of the population that screening could potentially identify and the burden of suffering that treatment could potentially relieve.

Chapter 4 assesses the scientific evidence for the benefits and harms of screening for thyroid disease using the TSH test. It introduces an analytic framework for the questions necessary to reach a conclusion and looks at how well the evidence answers those questions.

Chapter 5 looks at the financial implications of coverage. It examines the factors that may affect the use of TSH testing if coverage is provided, estimates the number of beneficiaries who would be candidates for screening, and calculates the costs and savings in the use of resources that would be affected by screening.

Chapter 6 provides the Committee's conclusions and recommendations.

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2

Pathophysiology and Diagnosis of Thyroid Disease

The thyroid is a butterfly-shaped gland located in the front of the neck just above the trachea. It weighs approximately 15 to 20 grams in the adult human. The thyroid produces and releases into the circulation at least two potent hormones, thyroxine (T_4) and triiodothyronine (T_3), which influence basal metabolic processes and/or enhance oxygen consumption in nearly all body tissues. Thyroid hormones also influence linear growth, brain function including intelligence and memory, neural development, dentition, and bone development (Larsen, 2003).

The thyroid gland produces T_4 and T_3 utilizing iodide obtained either from dietary sources or from the metabolism of thyroid hormones and other iodinated compounds. About 100 µg of iodide is required on a daily basis to generate sufficient quantities of thyroid hormone. Dietary ingestion of iodide in the United States ranges between 200 and 500 µg/day and varies geographically; ingestion is higher in the western part of the United States than in the eastern states. The specialized thyroid epithelial cells of the thyroid gland are equipped with a Na/I symporter that helps concentrate iodide 30 to 40 times the level in plasma to ensure adequate amounts for the synthesis of thyroid hormone. The iodide trapped by the thyroid gland is subsequently oxidized to iodine by the enzyme thyroid peroxidase. The iodine then undergoes a series of organic reactions within the thyroid gland to produce tetraiodothyronine or thyroxine (T_4) and triiodothyronine (T_3). T_3 is also produced in other tissues such as the pituitary, liver, and kidney by the removal of an iodine molecule from T_4. T_4 is considered to be more of a pro-hormone, while T_3 is the most potent thyroid hormone produced. T_4 and T_3 are both stored in the thyroglobulin protein of the thyroid gland and released into the circulation through the action of pituitary derived thyrotropin (thyroid stimu-

lating hormone or TSH). A normal individual produces from the thyroid gland approximately 90 to 100 µg of T_4 and 30 to 35 µg of T_3 on a daily basis. An estimated 80 percent of the T_3 produced daily in humans is derived from peripheral metabolism (5′-monodeiodination) of T_4, with only about 20 percent secreted directly from the thyroid gland itself. On a weight basis, T_3 is about 3 to 5 times more potent as a thyroid hormone than T_4 and is believed to be the biologically active form of the hormone.

TSH, secreted by thyrotroph cells located in the anterior pituitary gland, regulates thyroid gland function and hormone synthesis and release. The pituitary secretion of TSH in turn is influenced by the releasing factor, thyrotropin-releasing hormone (TRH) produced in the hypothalamus (see Figure 2-1). The secretion of both TSH and TRH is regulated by negative feedback from thyroid hormone, predominantly T_3, from the circulation and/or T_3 that is produced locally from intracellular conversion of T_4 to T_3. When circulating thyroid hormone levels are elevated, both the synthesis and secretion of serum TSH are blunted. In contrast, when circulating levels of T_4 and T_3 are low, serum TSH levels are increased in a compensatory fashion. The geometric mean level of serum TSH in normal individuals is approximately 1.5 µU/ml as recently reported in the NHANES III study (Hollowell et al., 2002). When hypothalamic pituitary function is intact,

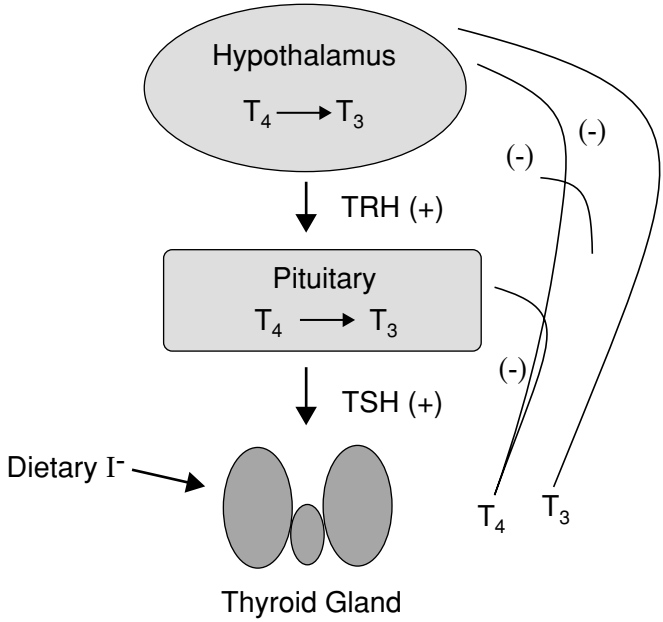

FIGURE 2-1

serum TSH levels are markedly suppressed (to <0.05 μU/ml) in patients with hyperthyroidism and elevated circulatory levels of serum thyroxine, while a marked increase in TSH (>5 μU/ml) occurs in patients with hypothyroidism and low blood levels of serum T_4. The mechanism through which TSH binds to and activates the thyroid gland is well understood. TSH binds to a specific membrane receptor located on the surface of the thyroid epithelial cell and activates the cell signaling mechanisms through the enzyme adenylate cyclase located in the plasma membrane. Activation of adenylate cyclase increases intracellular cyclic adenosine monophosphate (cAMP) levels, which in turn stimulate additional intracellular signaling events that lead to thyroid hormone formation and secretion.

T_4 and T_3 circulate bound primarily to carrier proteins. T_4 binds strongly to thyroxine binding globulin (TBG, ~ 75 percent) and weakly to thyroxine binding prealbumin (TBPA, transthyretin, ~ 20 percent) and albumin (~5 percent). T_3 binds tightly to TBG and weakly to albumin, with little binding to TBPA. The geometric mean for serum T_4 in normal individuals is approximately 8 μg/dl, while the mean serum T_3 level is approximately 130 ng/dl. Under normal protein binding conditions, all but 0.03 percent of serum T_4 and 0.3 percent of serum T_3 is protein bound. Only a small amount of unbound (or free) T_4 (approximately 2 ng/dl) and T_3 (approximately 0.3 ng/dl) circulates in a free state, and it is this free concentration that is considered responsible for the biological effects of the thyroid hormones. There are physiologic situations associated with a change in the serum concentration of these thyroid-binding proteins—such as pregnancy, non-thyroidal illness, or ingestion of drugs—that affect the level and/or affinity of these binding proteins. Under these circumstances, the serum concentrations of total T_4 and total T_3 change in parallel to the changes that occur in the thyroid hormone binding proteins, but the serum concentrations of free T_4 and free T_3 remain normal and the individual remains euthyroid. In contrast, the serum concentration of free T_4 and free T_3 are raised in hyperthyroidism and decreased in hypothyroidism.

THYROID FUNCTION TESTING

At the present time, serum-based tests available by immunoassay for measuring the concentration of thyroid hormones in the circulation include total (TT_4 and TT_3) and free (FT_4 and FT_3) hormone. In addition, direct measurements of thyroid hormone binding plasma proteins, thyroxine binding globulin (TBG), transthyretin (TTR)/prealbumin (TBPA), and albumin are also available. However, the thyroid test measurement that has the greatest utility for evaluating patients suspected of thyroid disease is the third-generation thyroid stimulating hormone (TSH, thyrotropin) assay. Most third-generation TSH assays today that can reliably detect differences of 0.02 μU/ml or better (interassay imprecision <20 percent) can easily distinguish both hyper- and hypothyroidism from euthyroidism (normal thyroid function) and may differentiate the patient suffering

from the "euthyroid sick syndrome" from true hyperthyroidism. Other methods in thyroid testing include the measurement of thyroid gland autoantibodies, including antithyroid peroxidase (TPOab), antithyroglobulin (Tgab), and antibodies against the TSH receptor (Trab). All of these thyroid test methods are routinely available on automated immunoassay instruments located in most hospital and reference laboratories with tight (<10 percent) method between run coefficients of variation.

TESTING FOR DIAGNOSIS AND MANAGEMENT OF THYROID DYSFUNCTION

The most sensitive test in an ambulatory population at risk for thyroid dysfunction is the serum TSH (Demers and Spencer, in press). Serum TSH assays today have sufficient sensitivity and specificity to identify individuals with all forms of thyroid dysfunction in the general population. However, among individuals with serious, acute illness, the serum TSH is less specific for thyroid disease because a serious illness alone can depress TSH secretion (to be discussed). TSH screening of the neonatal population to detect congenital hypothyroidism before it is clinically evident is mandated throughout the United States and in many other countries.

When an abnormal serum TSH value is obtained, the usual next step is to repeat the measurement of TSH and also measure a serum free T_4. The latter can be performed in several ways and among non-hospitalized individuals, most methods give results that are inversely correlated with the serum TSH result. The most common cause of discordance between the TSH and free T_4 result occurs in patients with subclinical thyroid dysfunction with high or low serum TSH values and a normal serum free T_4 result.

Serum TSH measurements may yield misleading results for individuals with changing levels of thyroid hormones. For example, a serum TSH level may remain high for weeks in hypothyroid patients treated with T_4. Similarly, serum TSH levels may remain low for weeks after the serum T_4 level falls to normal in patients treated for hyperthyroidism.

Reference Intervals for Thyroid Function Tests

Typical reference intervals for thyroid function tests in normal adults are shown in Table 2-1. The median serum concentration in U.S. subjects 12 years and older, as reported from 1988 to 1994 in the NHANES III study, was 1.49 μU/ml, a value that is considerably below the upper limit of normal (4.5 μU/ml) reported by most laboratories (Hollowell et al., 2002). This finding has led to the suggestion that a serum TSH value above 3 μU/ml may not be normal. In the same study, median serum TSH concentrations in subjects more than 50 years old were higher than in younger individuals: 1.60 μU/ml after age 50, 1.79 μU/ml after age 60,

TABLE 2-1 Serum TSH and Thyroid Hormone Reference Ranges in Adults

Hormone	Reference Range
TSH	0.4 – 4.5 μU/ml
Total thyroxine (total T_4)	4.0 – 12.0 μg/dl
Free thyroxine (free T_4)	0.7 – 1.8 ng/dl
Total triiodothyronine (total T_3)	100 – 200 ng/dl
Free triiodothyronine (free T_3)	208 – 596 pg/dl

1.98 μU/ml after age 70, and 2.08 μU/ml after age 80. Serum total and free T_4 levels do not change significantly with age, while serum total and free T_3 do show an age-related decline in concentration.

Thyroid Function Testing in the Elderly

The prevalence of both low and high serum TSH levels (with normal serum free T_4 results) is increased in elderly subjects compared with younger people. With respect to high serum TSH values, the increase is thought to represent an increased prevalence of autoimmune thyroiditis, especially in women, as will be discussed. The higher prevalence of low serum TSH values may be due to thyroid nodular disease or unrecognized non-thyroid illness.

Diagnosis of Hypothyroidism

Hypothyroidism is a hypometabolic state that results from a deficiency in T_4 and T_3. Its major clinical manifestations are fatigue, lethargy, cold intolerance, slowed speech and intellectual function, slowed reflexes, hair loss, dry skin, weight gain, and constipation. It is more prevalent in women than men. The most common cause of hypothyroidism is disease of the thyroid itself, primary hypothyroidism.

The most common cause of primary hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's disease), in which the thyroid is destroyed by antibodies or lymphocytes that attack the gland. Other causes are radioactive iodine and surgical therapy for hyperthyroidism or thyroid cancer, thyroid inflammatory disease, iodine deficiency, and several drugs that interfere with the synthesis or availability of thyroid hormone. Hypothyroidism may also occur rarely (<1 percent of cases) as a result of deficiency of TRH or impaired TSH secretion due to hypothalamic or pituitary disease, respectively. This is known as secondary or central hypothyroidism because of the negative feedback relationship between serum T_4 and T_3 levels and TSH secretion. As noted earlier and shown in Figure 2-1, people with primary hypothyroidism have high serum TSH levels. If

an individual has a high serum TSH value, serum free T_4 should be measured. The concomitant finding of a high serum TSH concentration and a low free T_4 level confirms the diagnosis of primary hypothyroidism. People with a high serum TSH concentration and a normal or low-normal serum free T_4 level have, by definition, subclinical hypothyroidism. The diagnosis of secondary hypothyroidism is based on the findings of a low serum free T_4 level and a serum TSH level that is normal or low. People with secondary hypothyroidism are unlikely to be detected by a screening program based on measurements of serum TSH, but the condition is much less common than primary hypothyroidism.

Diagnosis of Hyperthyroidism

Hyperthyroidism is a hypermetabolic state that results from excess production of T_4 and T_3. Its major clinical manifestations are nervousness, anxiety, heart palpitations, rapid pulse, fatigability, tremor, muscle weakness, weight loss with increased appetite, heat intolerance, frequent bowel movements, increased perspiration, and often thyroid gland enlargement (goiter). Most individuals with hyperthyroidism are women.

The most common cause of hyperthyroidism is Graves' disease, an autoimmune disease characterized by the production of antibodies that activate the TSH receptor, resulting in stimulation of T_4 and T_3 production and enlargement of the thyroid. Other caused of hyperthyroidism are a multinodular goiter, solitary thyroid adenoma, thyroiditis, iodide- or drug-induced hyperthyroidism, and, very rarely, a TSH secreting pituitary tumor.

The diagnosis of hyperthyroidism is based on the findings of a high serum free T_4 level and a low serum TSH concentration. Occasionally, people with hyperthyroidism have a normal serum free T_4 and high serum free T_3 concentrations. These patients have what is called T_3-hyperthyroidism. An increase in serum thyroid hormone binding protein will raise the serum total T_4 level but not free T_4 concentrations. In these patients the serum TSH remains normal. Patients with a low serum TSH concentration and normal serum free T_4 and free T_3 levels have, by definition, subclinical hyperthyroidism.

Effect of Medications on Thyroid Test Results

Several medications have in vivo or in vitro effects on thyroid function tests that can create misleading results. Medications, notably estrogens, that raise serum TBG levels result in an increase in serum total T_4, but no change in serum free T_4 levels and no change in serum TSH concentrations. High doses of glucocorticoids (adrenal hormones) can lower the serum T_3 concentration by inhibiting the peripheral conversion of T_4 to T_3 and lower serum T_4 (and T_3) by inhibiting TSH secretion. Iodide, contained in solutions used to sterilize the skin and in radiopaque contrast media used in coronary angiography and many other radiological

procedures, can cause either hyper- or hypothyroidism, depending on whether the individual has a nodular goiter or some unsuspected thyroid injury. The iodide-containing drug amiodarone, given to patients with cardiac arrhythmias, can also cause either hypothyroidism or hyperthyroidism in appropriately susceptible individuals.

Other drugs have effects that alter thyroid function test results directly. For example, the anticoagulant heparin can raise serum free T_4 concentrations by stimulating release of free fatty acids from triglycerides in serum. Thyroid test methods that use fluorescence detection may be sensitive to the presence of fluorophore-containing drugs or diagnostics agents used in radiology.

Thyroid Function Testing and Nonthyroidal Illness

Many people who are seriously ill have abnormal thyroid test results but no other evidence of thyroid dysfunction. These abnormalities occur in people with both acute and chronic illnesses and tend to be greater in those with more serious illnesses. Thus the laboratory diagnosis of thyroid disease can be extremely difficult to make in very sick people, especially those who need to be hospitalized. The effects of illness include decreased peripheral conversion of T_4 to T_3, decreases in serum concentrations of thyroid hormone binding proteins, and decreases in TSH secretion. These changes are reversible and do not seem to cause clinical manifestations of thyroid deficiency. Among healthier individuals, a few may have small changes in thyroid test results as a result of unrecognized nonthyroidal illness rather than thyroid dysfunction.

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3

Prevalence and Consequences of Thyroid Dysfunction

The prevalence of thyroid dysfunction in adults in the general population ranges from 1 to 10 percent, and is even higher in selected groups (Samuels, 1998; Vanderpump, 2000; Wang and Crapo, 1997). Reasons for the variation include the testing site (community, health fair, medical clinic), age and sex of people tested, and method of assessment. In addition, it is not always clear whether people with known thyroid disease, those taking thyroid hormone or antithyroid therapy, or those who had other disorders that might affect thyroid function were included or excluded from the study group.

Subclinical hypothyroidism is defined as a high serum thyroid stimulating hormone (TSH) concentration and a normal serum free T_4 concentration, and overt hypothyroidism as a high serum TSH concentration and a low serum free T_4 concentration. Subclinical hyperthyroidism is defined as a low serum TSH concentration and a normal serum free T_4 concentration, and overt hyperthyroidism as a low serum TSH concentration and a high serum free T_4 concentration. These definitions of "subclinical" and "overt" dysfunction are made purely by biochemical criteria. Persons with "subclinical" hyperthyroidism or hypothyroidism may display clear symptoms or signs of thyroid dysfunction while those with "overt" hyperthyroidism or hypothyroidism may show no other evidence of thyroid dysfunction. In all population surveys, most of the abnormal serum TSH concentrations are just outside the normal range, indicative of very mild thyroid dysfunction, and the frequency of more abnormal values is considerably lower.

Screening for thyroid dysfunction by measurement of serum TSH may yield several possible results (Figure 3-1). In the context of this volume, candidates for screening are people who have no recognized symptoms or signs of thyroid

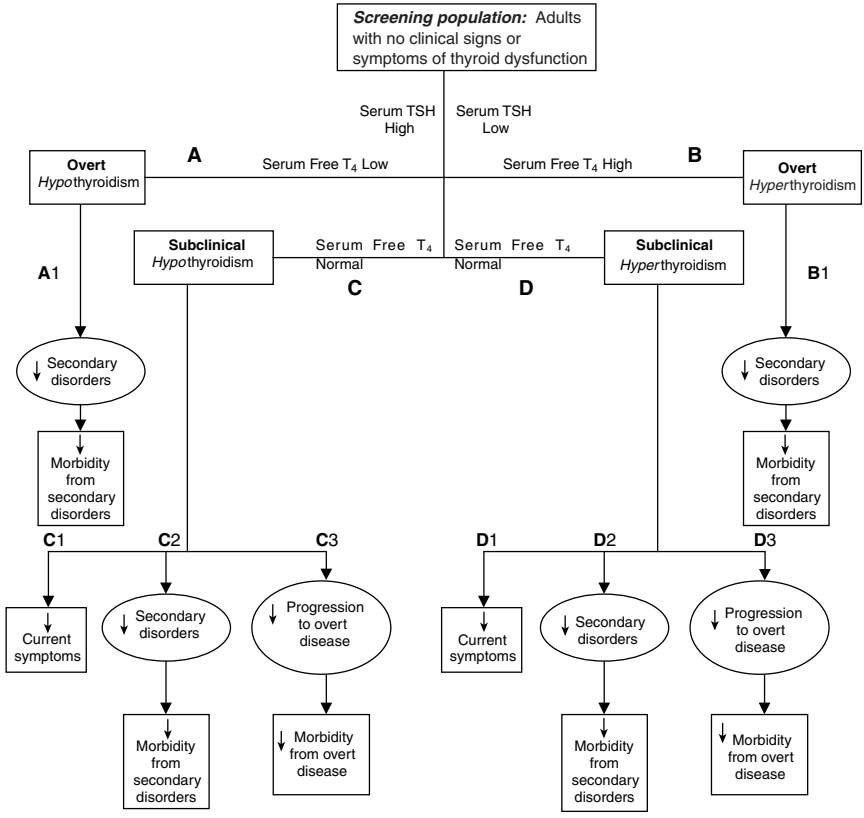

FIGURE 3-1 Possible benefits from screening for thyroid dysfunction

dysfunction. High serum TSH values indicate the presence of subclinical or overt hypothyroidism, and low serum TSH values indicate the presence of subclinical or overt hyperthyroidism. The distinction between subclinical and overt thyroid dysfunction is made on the basis of measurements of serum free T_4, as described in the preceding paragraph. Among people who are found by screening to have abnormal serum TSH concentrations, careful evaluation will often reveal symptoms or signs of thyroid dysfunction, as described in the preceding chapter. In general, those people whose screening tests indicate subclinical thyroid dysfunction more often have none or fewer of these symptoms and signs than do those people whose screening tests indicate overt thyroid dysfunction. However, there are no symptoms or signs that are unique to either group or that reliably distinguish persons with any of these forms of thyroid dysfunction from normal people.

In this chapter we summarize the results of studies using currently available tests done in people outside of hospitals, mostly in the United States. Prevalence rates have been rounded to the nearest 1 percent (unless <2 percent) for simplicity. The emphasis is on the results in older people. In making its assessments the committee relied to a much greater degree on information related to subclinical dysfunction than overt dysfunction because the population of screening positives much more resembles populations with subclinical dysfunction than populations with overt dysfunction. There are several reasons for this:

1. The vast majority (90%-95%) of persons with positive screening tests have subclinical dysfunction. The classification into overt and subclinical thyroid dysfunction is an arbitrary splitting of a continuum. The two groups are not necessarily distinct. Many subjects in the subclinical population will resemble subjects in the overt group.

2. The literature on patients with biochemically overt thyroid dysfunction is less relevant to the population of screened subjects who have biochemically overt dysfunction. Most of the information on biochemically overt dysfunction comes from patients who have marked symptoms or a long history of known thyroid disease. There is little information on patients with overt dysfunction who are discovered without prior suspicion. While not perfectly applicable, the literature on biochemically subclinical hypothyroidism is more relevant to the screening population; the subject became of interest over the question of whether an abnormal serum TSH level is significant in persons who have normal serum thyroxine levels.

3. The distinction between biochemically defined "subclinical" or "overt" thyroid dysfunction is less likely to be meaningful in terms of either burden of disease or potential to benefit from treatment in the screening population than in the entire population. In the overall population of persons with thyroid dysfunction defined by abnormal serum TSH concentrations, those who also have abnormal serum T_4 will be much more likely to have clinically recognizable morbidity and potential to benefit from treatment. The screening population, however, is a much more homogeneous group; subjects, by definition, lack recognized morbidity. This does not mean that there are not people with "overt" dysfunction in the screening population whose symptoms were grossly overlooked and/or who would benefit significantly from treatment; it just means that a similar problem exists among people with biochemically "subclinical" dysfunction.

PREVALENCE OF SUBCLINICAL AND OVERT HYPOTHYROIDISM

The largest community-based study of thyroid function in the United States was carried out as part of the National Health and Nutrition Examination Survey (NHANES III) in 1988 to 1994 (Hollowell et al., 2002). Among 13,444 people aged 12 years and older remaining after all subjects with either known thyroid disease, antithyroid antibodies, or abnormal levels of serum T_4 were excluded,

1.8 percent had a high serum TSH concentration. Exact percentages by age are not given, but based on extrapolation from a figure in the article, the prevalence of high serum TSH concentrations was 2 percent in people aged 60 to 69 years, 6 percent in those aged 70 to 79 years, and 10 percent in those aged 80 years and older. If only subjects with known thyroid disease are excluded from the NHANES sample, the prevalence of high serum TSH concentrations was 4.1 percent among 16,533 people. Extrapolated figures for the older population were 6.5 percent in people aged 60 to 69, 12 percent among ages 70 to 79, and 14 percent among subjects aged 80 years and older.

In the Colorado Thyroid Disease Prevalence Study, among 24,337 people (mean age 56 years) who attended a health fair, 2,067 (8 percent) had subclinical hypothyroidism and 103 (0.4 percent) had overt hypothyroidism (Canaris et al., 2000). Among those persons with high serum TSH concentrations, 74 percent had slightly high values (5.1 to 10 mU/L), and 26 percent had values >10 mU/L. The prevalence of high serum TSH values (independent of serum T_4 values) was 16 percent among women aged 65 to 74 years and 21 percent among women aged 75 years and older; the comparable rates for men were 11 percent and 16 percent, respectively.

The results of other, smaller studies focused on older people were similar. For example, among 2,139 people aged 60 years or older enrolled in the Framingham Heart Study, 8 percent had subclinical hypothyroidism (women, 14 percent; men, 6 percent) (Sawin et al., 1985). Among 283 people aged 60 years and older attending a primary care geriatrics clinic in Oklahoma, the prevalence of subclinical hypothyroidism was 15 percent and that of overt hypothyroidism was 1 percent in both women and men (Bemben et al., 1994). Among 968 people aged 55 years or older attending a health fair in Michigan, 7 percent had subclinical hypothyroidism (the prevalence was 9 percent among those aged 65 to 74 years, and 10 percent among those aged 75 years and older) (Bagchi et al., 1990). With respect to patients enrolled in the Medicare program, 111 of 719 people (15 percent) living in New Mexico had high serum TSH concentrations (Lindeman et al., 1999).

CONSEQUENCES OF SUBCLINICAL HYPOTHYROIDISM

The consequences of subclinical hypothyroidism are symptoms attributed to thyroid deficiency, the presence of biochemical or physiological abnormalities that might be a threat to the person's health and quality of life, and the risk of progression to more severe thyroid dysfunction. In the screening population, the consequences of biochemically overt hypothyroidism are similar, but presumably greater. We focus here on subclinical hypothyroidism because of its greater relevance to the screening population.

Symptoms and Signs of Subclinical Hypothyroidism

Patients with subclinical hypothyroidism may or may not have symptoms similar to those present in most patients with frank hypothyroidism. In the Colorado Thyroid Disease Prevalence Study, the frequency of several symptoms of hypothyroidism, such as dry skin, poor memory, and muscle weakness, was approximately 3 to 5 percent higher in those people with high serum TSH concentrations than in those with normal serum TSH concentrations, and those with a higher number of symptoms were more likely to have a high serum TSH concentration (Canaris et al., 2000). However, in the Oklahoma and New Mexico surveys cited earlier, there were few differences in symptoms or results of cognitive tests in the normal people and those with subclinical hypothyroidism (Bemben et al., 1994; Lindeman et al., 1999). Also, in the placebo-controlled studies of thyroid hormone treatment in patients with subclinical hypothyroidism, thyroid hormone treatment has proven little more effective than placebo in ameliorating any symptoms the patients might have had (summarized by Helfand in Appendix B).

Disorders Secondary to Subclinical Hypothyroidism

Patients with subclinical hypothyroidism may have slightly high serum total or low-density-lipoprotein (LDL) cholesterol concentrations, and therefore might be at increased risk for atherosclerosis. The frequency of high serum total and LDL cholesterol concentrations in people with subclinical hypothyroidism has varied substantially in different studies, from no increase to a definite increase. In general, people with higher serum TSH concentrations have higher serum cholesterol concentrations (Canaris et al., 2000). Given the multiple factors (diet, activity, smoking status, heredity) that affect serum cholesterol values, perhaps more relevant is the extent to which serum cholesterol values change with thyroid hormone treatment in patients with subclinical hypothyroidism. A systematic review of the effect of thyroid hormone therapy in these patients revealed a mean decrease in serum cholesterol concentration of 7.9 mg/dl (0.2 mmol/L) and a mean decrease in serum LDL cholesterol concentration of 10 mg/dl (0.3 mmol/L) (Danese et al., 2000).

There is little evidence that patients with subclinical hypothyroidism have an increased risk of cardiovascular disease (Vanderpump et al., 1996). Some have abnormalities in left ventricular function, such a decrease in ejection fraction or prolonged diastolic relaxation time, as assessed by echocardiography (Biondi, 2002), but whether these changes have clinical consequences is not known. With respect to mortality from cardiovascular disorders (and all-cause mortality), the annual mortality rates for years 1 to 5 and the 10-year mortality rates among 76 people aged 60 years and older with subclinical hypothyroidism (some of whom

later received thyroid hormone) followed in a general practice in England were similar to the rates in England and Wales as a whole (Parle et al., 2001).

Risk of Progression of Subclinical Hypothyroidism to Overt Hypothyroidism

The risk of progression of subclinical hypothyroidism to overt hypothyroidism ranges from 3 percent to nearly 20 percent per year (Samuels, 1998; Vanderpump, 2000). In the only study in which adults living in the community (Whickham, United Kingdom) who had subclinical hypothyroidism were followed for a prolonged period (20 years), the average rate of progression to a clinical diagnosis of hypothyroidism in women was 3 percent per year in those with high serum TSH concentrations and 4 percent per year in those with high serum TSH concentrations and high serum antithyroid peroxidase antibody concentrations (Vanderpump et al., 1995). The risk of progression was higher in men, but there were far fewer cases at base line. In a follow-up study done in people being followed in a general practice in England, 13 of 73 patients (18 percent) aged 60 years and older who had subclinical hypothyroidism at the time of initial testing had biochemically overt hypothyroidism one year later (6 percent had normal concentrations at the latter time) (Parle et al., 1991).

The variation in rate of progression in different studies can be explained at least in part by variations in the cause of subclinical hypothyroidism. Although chronic autoimmune thyroiditis is undoubtedly the most common cause of both subclinical and overt hypothyroidism, other important causes are previous radioactive iodine (^{131}I) or surgical treatment for hyperthyroidism; undertreatment of hypothyroidism; drugs, including lithium carbonate, iodine, and iodine-containing drugs; and the recovery phase of silent (painless) thyroiditis. The latter two situations are usually transient, as is chronic autoimmune thyroiditis occasionally. Treatment-related causes of hypothyroidism would not be relevant to screening except in cases where radioactive iodine was given years earlier and forgotten. There are no studies of people with subclinical hypothyroidism in which the causes were carefully investigated.

The degree of elevation in serum TSH concentration is an important determinant of progression. In the Whickham study cited earlier, the probability of clinically diagnosed hypothyroidism during the 20-year follow-up period was 0.3 percent per year among women with a baseline serum TSH concentration of 6 mU/L and 1 percent per year among those with a baseline serum TSH concentration of 12 mU/L (Vanderpump et al., 1995).

Thyroid hormone therapy prevents hypothyroidism but, based on the above rates of progression, many patients will never need therapy. This applies particularly to those people with only slightly high serum TSH concentrations, who constitute the largest subgroup of people at potential risk.

PREVALENCE OF SUBCLINICAL AND OVERT HYPERTHYROIDISM

The prevalence of hyperthyroidism is lower than that of hypothyroidism. In the NHANES III study, 1.6 percent of the 13,444 people aged 12 years and older had low serum TSH concentrations (Hollowell et al., 2002). Based on extrapolation from a figure in the article, the prevalence of low serum TSH concentrations was 1 percent in people aged 60 to 69 years and 70 to 79 years, and 3 percent in those aged 80 years and older. In the Colorado Thyroid Disease Prevalence Study, 219 of 24,337 people (0.9 percent) had subclinical hyperthyroidism and 22 (0.1 percent) had biochemically overt hyperthyroidism (Canaris et al., 2000). Among 2,007 people aged 60 years and older enrolled in the Framingham Heart Study, 248 (12 percent) had subclinical hyperthyroidism (Sawin et al., 1994), whereas among 968 people aged 55 years and older attending a health fair in Michigan, only 33 (3 percent) had subclinical hyperthyroidism (Bagchi et al., 1990).

CONSEQUENCES OF SUBCLINICAL HYPERTHYROIDISM

The burdens of subclinical hyperthyroidism are symptoms attributed to thyroid hormone excess, the presence of biochemical or physiological abnormalities that might be a threat to the person's health and quality of life, and the risk of progression to more severe disease. The burdens of overt hyperthyroidism detected by screening are similar, but presumably greater. We focus on subclinical hyperthyroidism because of greater relevance to the screening population.

Symptoms and Signs of Subclinical Hyperthyroidism

People with subclinical hyperthyroidism may or may not have the symptoms that are present in most patients with frank hyperthyroidism or some impairment in physical and mental activity (Biondi et al., 2000; Marqusee et al., 1998). In the only trial of antithyroid drug therapy of subclinical hyperthyroidism, in 20 people (age range, 24 to 48 years), symptoms of hyperthyroidism improved in the treated patients, but untreated patients did not receive a placebo and the observers were probably aware of treatment group assignment (Yonem, 2002).

Disorders Secondary to Subclinical Hyperthyroidism

In people with subclinical hyperthyroidism, the values for measurements of cardiovascular function such a pulse rate, cardiac ejection fraction, and ventricular contractility and mass are intermediate between the values in normal subjects and patients with overt hyperthyroidism (Biondi, 2002). Cardiovascular function becomes more normal in people with subclinical hyperthyroidism during antithyroid therapy (or a reduction in dose of thyroid hormone). The only defined

long-term cardiovascular risk of subclinical hyperthyroidism is an increase in risk of atrial fibrillation. Among 2,007 people aged 60 years or older followed for 10 years, 28 percent of those with serum TSH concentrations ≤0.1 mU/L at base line later had atrial fibrillation, as compared with 12 percent of those with serum TSH concentrations of >0.1 to 0.4 mU/L and 8 percent of those with normal serum TSH concentrations (>0.4 to 5 mU/L) (Sawin et al. 1994).

There is a tendency for a decrease in bone density in people with subclinical hyperthyroidism, especially in postmenopausal women (Greenspan and Greenspan, 1999). This decrease is minimal in those women with only slightly low serum TSH concentrations, and is more marked in those with lower concentrations. The clinical correlate of low bone density is fracture. In a prospective study of 686 white women aged 66 years and older followed for 6 years, those with serum TSH concentrations of ≤0.1 mU/L at baseline had a threefold increase in risk of hip fracture (hazard ratio 3.6). Those with serum TSH concentrations of >0.1 to <0.5 mU/L had a smaller increase (hazard ratio 1.9), as compared with women with normal serum TSH concentrations (0.5 to 5.5 mU/L) (Bauer et al., 2001). The women who had serum TSH concentrations of ≤0.1 mU/L also had an increase in vertebral fracture. A large majority (86 percent) of the women with low serum TSH concentrations at baseline in this cohort were taking thyroid hormone.

Mortality may be increased in people with subclinical hyperthyroidism in the first years after detection. Among 70 people aged 60 years and older with subclinical hyperthyroidism followed in a general practice in England, the 10-year cardiovascular and overall mortality rates were similar to the rates in England and Wales as a whole, but the numbers of deaths were higher than expected at 2, 3, 4, and 5 years of follow-up (standardized mortality ratios 1.7 to 2.2) (Parle et al., 2001).

Risk of Progression of Subclinical Hyperthyroidism to Overt Hyperthyroidism

The overall rate of progression of subclinical hyperthyroidism to overt hyperthyroidism ranges from 1 percent to 15 percent per year (summarized in Samuels, 1998, and Marqusee et al., 1998). The studies were all small (the largest was of 66 people), and the percentage of people who had normal serum TSH concentrations when retested varied, ranging from 14 percent to 61 percent (summarized in Marqusee et al., 1998). These wide variations undoubtedly reflect differences in the cause of the subclinical hyperthyroidism, and indeed the likelihood that in some people, the low serum TSH concentration was caused by transient nonthyroidal illness.

The causes of subclinical hyperthyroidism are the same as the causes of overt hyperthyroidism. They are Graves' disease (autoimmune hyperthyroidism), nodular goiter, silent (painless) thyroiditis, subacute (painful) thyroiditis, iodine- and

drug-induced hyperthyroidism, and thyroid hormone therapy. However, their relative frequency differs considerably. Among people with subclinical hyperthyroidism, the proportion taking thyroid hormone is high. For example, in the Colorado Thyroid Disease Prevalence Study, 316 of the 535 people with subclinical hyperthyroidism (59 percent) were taking thyroid hormone; in other studies the proportion ranged from 5 percent to 62 percent (summarized in Marqusee et al., 1998). These data are not relevant to screening, but they indicate that a high proportion of people with subclinical hyperthyroidism can be treated by a reduction in thyroid hormone dose. In the only study in which the cause of spontaneously occurring subclinical hyperthyroidism was carefully sought, 12 of 24 people (50 percent) had silent thyroiditis or iodine-induced hyperthyroidism, and presumably recovered soon thereafter (Charkes, 1996). These people were identified in the course of medical practice, not by screening or clinic survey. Nonetheless, the results would seem to make documentation of persistent subclinical hyperthyroidism mandatory before considering whether intervention is warranted.

CONCLUSION

Thyroid dysfunction is common, especially in elderly people. Most people found to have thyroid dysfunction in surveys have subclinical thyroid dysfunction, in particular subclinical hypothyroidism. Among people with subclinical thyroid dysfunction, most have very small increases or decreases in serum TSH concentrations. When asked, some of these people with subclinical thyroid dysfunction have symptoms that are compatible with, though not specific for, thyroid dysfunction or have another indication for testing for thyroid dysfunction. Some people have biochemical or physiological abnormalities that are ameliorated by thyroid hormone therapy, in the case of people with subclinical hypothyroidism, or antithyroid therapy, in the case of subclinical hyperthyroidism. Among people with thyroid dysfunction, therapy may have beneficial effects on intermediate outcomes, such as reduction in serum lipid concentrations and improvement of myocardial contractility. However, appropriate therapy has not been proven to alter long-term morbidity or mortality in people with subclinical thyroid dysfunction. Similarly, while it is accepted that treatment will benefit patients with biochemically overt thyroid dysfunction who present with significant symptoms or complications, the lack of well designed studies makes it difficult to determine whether treatment would provide significant net benefit in persons who have biochemically defined overt thyroid dysfunction but little evidence of illness; the potential for harms is similar but potential for benefit is less. These uncertainties contribute to the difficulty in assessing the value of a screening program for thyroid dysfunction.

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4

Screening for Thyroid Dysfunction

This chapter discusses the conceptual issues surrounding screening for thyroid dysfunction and evaluates the evidence base for the value of screening, using the basic methods of the United States Preventive Services Task Force. The chapter concludes with a recommendation on the value of screening in the Medicare population. We take advantage of the evidence review, which was conducted concurrently by Dr. Mark Helfand of the Oregon Health & Science University Evidence-based Practice Center for the Task Force; the review is contained in Appendix B of this volume.

PRINCIPLES OF DISEASE PREVENTION

The intent of preventive interventions is to eliminate totally or to defer as long as possible the clinical onset of overt disease or, if a disease has become clinically apparent in an individual, to defer the progression and secondary consequences of that disease. Preventive interventions, by conventional definitions, comprise three kinds of activities: primary, secondary, and tertiary prevention.

Types of Prevention

Primary prevention generally refers to interventions that avoid the biological onset of a disease or condition within an individual, either by avoiding exposure to disease-causing agents or situations or by protecting the individual from the harmful effects of those exposures. Examples include all immunization against infectious agents, pasteurization of milk and other foods, avoidance of alcohol

when operating a motor vehicle, and condom use to prevent sexually transmitted diseases. These interventions may not work perfectly, nor are they necessarily free of adverse effects: A vaccine may protect most but not all of those immunized and occasionally may cause a clinical illness itself. In general, society demands that primary preventive interventions have relatively few adverse effects because they are administered to healthy individuals with varying levels of disease risk.

Secondary prevention refers to the early and asymptomatic detection of existing but subclinical diseases in individuals; this is usually referred to as *disease screening*. The term "subclinical" is paramount here because it indicates that the disease shows no apparent manifestations that are identifiable either to the individual or to the health professional. Examples of screening tests include cervical cytology (the "Pap smear") for early detection of cervical cancer; a blood cholesterol test to detect blood lipid abnormalities that may put someone at risk of heart attack, stroke, and other conditions; and mammography, which may detect early breast cancers that are more curable than when they become palpable to the patient or the professional. As a rule, society may tolerate less than perfect accuracy in a screening test and, if unavoidable, a higher level of adverse effects due to the screening test or its later clinical consequences than in primary prevention because of the high likelihood of emerging disease being present.

It is important to note that tests that are used for screening purposes usually have different characteristics from tests used for diagnostic purposes. Usually, a positive screening test only indicates that a disease or condition has a higher likelihood of being present; additional definitive diagnostic testing is indicated to confirm that likelihood. Screening tests emphasize sensitivity over specificity. In order to achieve their purpose, they generally produce a large proportion of false-positive results. Thus, a positive screening test usually leads to further diagnostic testing before the condition is assumed to be present. In fact, for some conditions, various levels of staged screening tests may be applied. Like screening tests, diagnostic tests may not always be perfectly accurate; thus persons being screened for a condition should be counseled about the levels of accuracy of both types of tests and the possibility that a negative screening test does not always guarantee that disease is not present or will not occur in the future. As will be discussed, this is directly relevant to the issue of screening for thyroid dysfunction.

Screening tests are generally only applied if they meet a set of standard criteria (Cuckle and Wald, 1984), which are briefly summarized here:

- The natural history of the condition being screened must be understood, so that there is good evidence that the disease outcome will be favorably influenced by further diagnosis and treatment.
- The screening test must be suitably reliable and valid so that most of those tested are accurately classified as to the current presence or absence of the disease in question.

- The screening test must be acceptable when applied to most persons for whom it is indicated. If not, the test will not effectively reach its intended target population and will fail as a disease prevention measure.
- If a screening test indicates the possibility of a disease being present, there must be suitable, definitive tests to make a formal diagnosis of that condition.
- Suitable professional resources should be available to explain the results of the screening test to those with both negative and positive findings.
- Proven, effective treatments must exist for the conditions screened for and diagnosed—treatments that lead to increased survival, function, and quality of life. It is important that these treatments be widely available and accessible, both geographically and fiscally. Raising patient concern may have little value if the requisite medical care cannot be delivered.
- Early intervention must have value. Diagnosis as a result of screening must either provide a better chance of cure, less disability, a reduction in the development of pain or other significant symptoms, or enable treatment that is less arduous or expensive. If early diagnosis only extends the period of treatment of chronic illness or results in expenditures for expensive treatment occurring sooner rather than later, it may only increase costs without commensurate benefit.

Tertiary prevention usually refers to the prevention of the secondary adverse consequences of existing diseases and conditions. Examples include the administration of physical therapy to prevent freezing of arthritic joints or the use of medications that prevent rhythm disorders of the heart in those who have had a heart attack. Thus, tertiary prevention merges with the normal medical management of diseases, an activity by and large covered by Medicare as "reasonable and necessary for the diagnosis or treatment of illness," and therefore not considered to be a preventive service excluded by Section 1862(a)(1)(A) of Title XVIII of the Social Security Act.

Issues in Screening for Thyroid Dysfunction

When considering screening for thyroid dysfunction, several issues concerning the application of the screening principles require discussion. First, as noted elsewhere in this volume, thyroid dysfunction is more than one condition. Thus, screening applications and outcomes may be different for hypothyroidism than for hyperthyroidism, and this issue will be discussed. This is true of other screening applications. For example, mammography screens for several types of histologically distinct breast tumors, some with varied natural histories and clinical trajectories.

Second, there is the issue of whether persons whose thyroid dysfunction is identified by screening are truly asymptomatic. In general, among diseases for which screening is known to be effective, a symptomatic patient with that condition, *ceteris paribus,* is likely to be in a more advanced stage than an individual

without symptoms. When this is the case, the impact and improved outcomes from screening may be lessened or eliminated. As noted in Chapter 3, the Committee discussed the definition of subclinical thyroid dysfunction and concluded that it was not possible to conclude that an individual with the biochemical diagnosis was or was not truly free of symptoms because the symptoms are general, common, and have a high background occurrence in biochemically normal persons. Thus, the Committee concluded that screening would be considered when thyroid dysfunction-compatible symptoms, if present, are *unrecognized* by the patient or the health professional. Otherwise, if a clinician has a strong suspicion that clinically manifest thyroid dysfunction is present, then any testing is a diagnostic process already covered by Medicare. This is the position that Helfand (Appendix B) takes on this matter. This situation is made more complex by the fact that many older persons have substantial co-morbidity (Kaplan et al., 1999). Thus, many thyroid dysfunction-compatible symptoms (e.g., fatigue) may in fact be related to other conditions.

Helfand (Appendix B) also points out that the scientific literature usually applies the term "subclinical hypothyroidism" on purely biochemical terms as an elevated serum thyroid stimulating hormone (TSH) level coincident with a normal serum free T_4. This definition would apply to many persons who are not candidates for screening: Because they are known to or are likely to have thyroid disease by their history, they have abnormal results stemming from the consumption of an incorrect amount of levothyroxine in the treatment of hypothyroidism, they have thyroid failure after treatment of hyperthyroidism; or they have thyroid failure already recognized by its symptoms. There is also the clinical situation in which a patient is tested for thyroid dysfunction because it is a known cause or aggravating factor for some other condition, such as atrial fibrillation or hyperlipidemia. For the purposes of this Committee's analysis anyone with recognized symptoms or a history of any kind of thyroid disease or exposure to an agent known to be thyrotoxic will not be considered a potential screening subject, and the search for thyroid dysfunction as a cause or complicating factor in patients with other conditions will not be considered a screening procedure.

Third, as for many other disorders that are first diagnosed biochemically, thyroid dysfunction is characterized by blood measures that possess continuous distributions, as are blood total cholesterol and hemoglobin levels. In this instance, assigning clinical or biochemical cut-points is in many ways arbitrary, if necessary; a particular categorical definition may lead to a certain amount of misclassification of disease occurrence or future risk of disease. Thus, not everyone assigned by biochemical criteria to have or not have a particular condition will be classified correctly on measurement grounds alone. In the case of subclinical thyroid dysfunction, there are conceptual arguments as to whether biochemical criteria reflect physiological abnormalities; for the same reasons of measurement error and miscategorization, the likelihood that a biochemical abnormality indi-

cates an abnormal clinical or functional state may depend on the degree of that abnormality.

A similar difficulty occurs with the division of thyroid dysfunction into "subclinical" or "overt" on the basis of serum T_4 measurements. In the entire population of persons with thyroid dysfunction defined by abnormal serum TSH concentrations, those who also have abnormal serum T_4 will be much more likely to have clinically recognizable morbidity and potential to benefit from treatment. The screening population, however, is a much more homogeneous group; subjects, by definition, lack recognized morbidity. The distinction between biochemically defined "subclinical" or "overt" thyroid dysfunction in the screening population is less likely to be meaningful in terms of either burden of disease or potential to benefit from treatment.

EVIDENCE OF EFFICACY OF SCREENING FOR THYROID DYSFUNCTION

The Committee considered the evidence concerning the efficacy of biochemical screening for thyroid dysfunction using serum TSH levels in several ways: (1) reviewing and considering the evidence summarized in the systematic evidence review by Helfand (Appendix B); this was prepared for the Task Force, which has presented screening recommendations for thyroid conditions in the past (United States Preventive Services Task Force, 1996); (2) reviewing other peer-reviewed literature relevant to the Committee's mission; and (3) conducting a workshop on thyroid function screening, held in Irvine, CA, in October 2002. See Appendix A for the workshop agenda.

Analytical Framework for Interpretation of the Evidence

Although the paper (Appendix B) by Helfand contains an analytical framework for evaluating the evidence on thyroid dysfunction screening, the Committee chose to create its own framework, shown in Figure 4-1. This framework is similar to the Helfand approach in several ways but differs in certain areas of organization and complexity. The Committee's framework portrays the *theoretical* benefits to health from TSH screening and looks for evidence to confirm or reject the theory. This approach begins with TSH screening of an adult population with no recognized symptoms related to thyroid dysfunction (see earlier discussion). While not noted, a repeat TSH level may be performed at this point for confirmatory reasons. If an abnormal TSH value is found, a free thyroxine (free T_4) level is determined (Paths A-D). If the TSH is high and the free T_4 is low, then a biochemical diagnosis of *overt* hypothyroidism is made (Path A). Effective treatment could then reduce the risk of this condition's secondary disorders and metabolic consequences (Effect A1), which in turn could reduce the morbidity from these consequences. In an analogous manner, if the TSH level is low, and

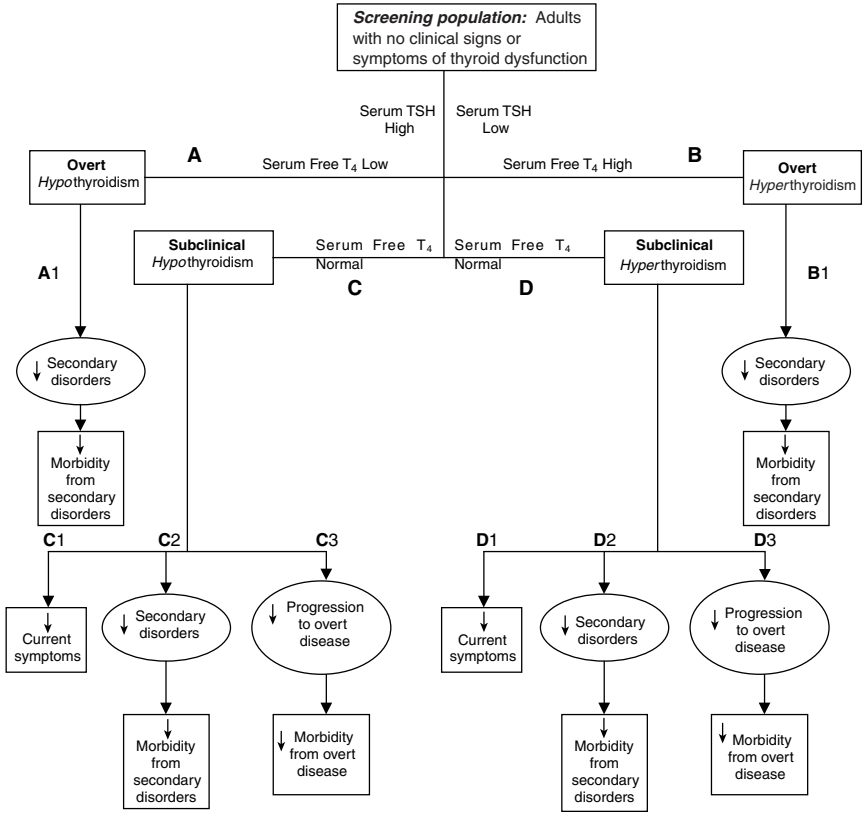

FIGURE 4-1 Theoretical benefits to health from screening for thyroid dysfunction

the free T_4 level is elevated (Path B), a diagnosis of biochemical *overt* hyperthyroidism is made, and with effective treatment could lead to amelioration of the consequent secondary disorders (Effect B1) and morbid outcomes.

If the TSH level is high, but the free T_4 level is normal (Path C), then biochemical *subclinical* hypothyroidism is designated. This condition, in turn, may be treated leading in the short or long term to fewer current if unrecognized symptoms (Effect C1), a decrease in secondary disorders and consequent morbidity (Effect C2), or prevention of progression to overt hypothyroidism, with any associated morbid consequences (Effect C3). If the screening TSH level, however, is abnormally low and the free T_4 is normal, then a designation of subclinical hyperthyroidism is made (Path D). Effective treatment could theoretically lead to fewer symptoms if present (Effect D1), the management of secondary

disorders and their morbid consequences (Effect D2), or the prevention of progression to overt hyperthyroidism, with its morbid consequences (Effect D3).

However, as emphasized, the evidence for effective screening and treatment may not be fully present; and, using this framework for discussion, the following addresses the evidence related to each of these pathways. It should be noted at the outset that the Committee could find no randomized trial of thyroid dysfunction screening among adults with unrecognized thyroid disease and symptoms potentially related to thyroid dysfunction in which long-term clinical morbid outcomes were determined or compared.

Clinical Consequences of Subclinical Thyroid Dysfunction

Overt hypothyroidism and hyperthyroidism, when identified in a clinical as opposed to a screening context, are well-described clinical syndromes and will not be recounted further here. As was explained in the previous chapter and earlier in this chapter, subjects with biochemically overt thyroid dysfunction discovered in a screening context should more closely resemble persons with subclinical dysfunction than persons whose overt thyroid dysfunction is diagnosed on the basis of clinical suspicion. This discussion is based on the evidence-based review by Helfand (Appendix B), which will be cited by name and not further referenced. All paths noted refer to Figure 4-1 unless otherwise noted.

Evidence of the Clinical Consequences of Subclinical Hyperthyroidism

Symptoms Important to understanding the value of screening for subclinical thyroid dysfunction is the determination of concurrent symptoms that may be relieved and subsequent morbidity and mortality that could be prevented through diagnosis and treatment. As Helfand notes, subclinical hyperthyroidism has been associated with cognitive abnormalities, and in several studies with abnormal myocardial contractility, sometimes associated with exercise intolerance. However, the frequency of these cardiac abnormalities in screening of persons with unrecognized symptoms is not well studied, and no study has linked these physiological abnormalities to a greater risk of developing overt congestive heart failure (Effect D1).

Morbidity With respect to subclinical hyperthyroidism in persons not known to have thyroid disease, Helfand found one good-quality observational study showing that a low TSH level was associated with a substantially increased risk of atrial fibrillation. Although the clinical consequences of atrial fibrillation in such patients have not been studied longitudinally, this condition is generally associated with increased risk of stroke and other conditions and with a higher risk of death (Effect D2).

In one prospective cohort study of older persons from the Netherlands, low TSH levels were associated with an increased risk of dementia after 2 years of

follow-up, after adjusting for age and sex. With respect to osteoporosis, Helfand found one good-quality study suggesting there were similar amounts of age-related bone loss among women with normal, low, or undetectable serum TSH levels. In that same cohort, there was an increased rate of hip fracture among those being treated for hyperthyroidism. Other studies on the risk of osteoporosis were in small numbers of patients with nodular thyroid disease or Graves' disease.

Mortality With regard to the impact of subclinical hyperthyroidism on total mortality associated with subclinical hyperthyroidism, Helfand found one study where mortality was higher among those with low serum TSH levels. However, there was no adjustment for co-morbidity, which, as noted in Chapter 2, may cause low TSH levels in the absence of thyroid dysfunction and therefore create an association between low TSH levels and mortality that would be neither causal nor related to thyroid disease.

Evidence of the Clinical Consequences of Subclinical Hypothyroidism

As documented in Chapter 3, the incidence and prevalence of subclinical hypothyroidism is substantially greater than of subclinical hyperthyroidism, and thus the former is in some dimensions more thoroughly studied. Particular attention has been paid to symptoms and well-being, blood lipid abnormalities, and atherosclerotic cardiovascular disease. Issues of thyroid disease in pregnancy will not be considered here.

Symptoms and quality of life As Helfand notes, a 1998 review by the American College of Physicians concluded there were no clear differences in prevalence and severity of symptoms or quality of life between euthyroid individuals in the general population and those with untreated subclinical hypothyroidism. Two more recent cross-sectional studies came to the same conclusion, although one found a higher prevalence of "changed" symptoms in those with subclinical dysfunction. Thus, overall, it appears there is little evidence that the subclinical condition is associated with a higher prevalence of symptoms in a population naïve for thyroid disease (Effect C1).

Hyperlipidemia Overt hypothyroidism has long been known to be associated with elevated levels of blood total cholesterol and LDL cholesterol. Most of these studies were performed in patients with severe hypothyroidism. As Helfand notes, studies of blood lipid abnormalities in subclinical hypothyroidism have yielded inconsistent results; they have been mostly in women, with sparse and inconsistent data in men (Effect C2). Most but not all studies, generally cross-sectional in nature, do not find significantly altered blood cholesterol or other lipid levels associated with subclinical hypothyroidism; there are exceptions where increased levels of 2-15 mg/dl are found. Some of the studies, both with null and positive findings, do not always adequately control for possible confounders such as co-morbidity, socioeconomic status, diet, other drugs that may

alter lipid levels such as estrogens, or history of known thyroid disease, with or without treatment.

Atherosclerosis Helfand states the relation between subclinical hypothyroidism and clinical atherosclerotic conditions is likewise unclear (Effect C2). In an English cohort (the Whickham study), no relation was found. However, in a Dutch cohort (the Rotterdam study) using mainly a cross-sectional analysis, myocardial infarction and abdominal atherosclerosis rates were significantly elevated among women with subclinical hypothyroidism, even after adjusting for major cardiovascular risk factors, including blood cholesterol levels. Helfand reviewed other cross-sectional studies and concluded that the causal direction was uncertain and that few adequately controlled for the range of cardiovascular risk factors.

EVIDENCE OF EFFICACY OF TREATMENT FOR THYROID DYSFUNCTION

This section draws on the work of Helfand in considering the evidence that treatment of thyroid dysfunction affects the long-term clinical outcomes of individuals with these conditions. Details of the strategy for literature search, inclusion criteria for studies and the grading of study quality, are detailed within the Helfand report. (Appendix B)

Evidence of Efficacy of Treatment of Overt Thyroid Dysfunction

While it has been accepted without randomized trials that treatment will benefit patients with overt thyroid dysfunction who present with significant symptoms or complications, there cannot be as much confidence of net long-term benefit for treatment of persons with biochemically overt thyroid dysfunction who are detected by screening. The latter group has a lower burden of disease, on average (the more symptomatic patients are more likely to be discovered without screening), but is subject to the same degree of adverse effects from treatment. No studies were found that examined the benefits of treating overt thyroid dysfunction identified by screening. Some patients found by screening to have overt hypothyroidism had symptoms of which the treating physicians were unaware, and in uncontrolled "pre/post" studies, reductions in high blood cholesterol levels were reported.

Evidence of Efficacy of Treatment for Subclinical Hyperthyroidism

Helfand found no controlled trials of the treatment for subclinical hyperthyroidism. Small observational treatment studies of patients with thyroid nodular disease reported improvements in bone metabolism and hemodynamic measures.

Evidence of Efficacy of Treatment for Subclinical Hypothyroidism

Helfand found no clinical trials of treatment of persons who were ascertained as having subclinical hypothyroidism through TSH screening. However, 15 randomized clinical trials of treatment with levothyroxine were found. Seven of these were excluded from analysis for a variety of reasons, such as not reporting clinical outcomes, including patients with overt disease, or being conducted to test alternative thyroxine preparations. The remaining eight trials are discussed at length and presented in Helfand's Tables B-3 and B-4.

Six of the eight trials were deemed to have several important methodological or conceptual problems, including small numbers of subjects; treatment of persons with previous hyperthyroidism, with or without Graves' disease; lack of reports on important methodological details; follow-up durations too short to assess long-term benefits or adverse effects on morbidity or mortality; and absence of blinding. Only one of the studies was rated as high as "good" quality. Where symptomatic outcomes were evaluated, the evidence was decidedly mixed, with more studies showing no improvement than showing benefit. However, the methods of evaluating symptoms and outcomes were diverse. Many of the patients in these treatment trials were below the usual age of Medicare beneficiaries.

Patients in the remaining two trials began TSH levels in the normal range and thus were deemed not relevant to questions at issue here. In one, blood LDL cholesterol levels, which were elevated at baseline, were modestly decreased by treatment. In the other, patients with symptoms of hypothyroidism (but normal blood parameters) found a decrement in vitality associated with the active drug. Most of the observational studies of levothyroxine treatment were primarily to evaluate blood lipid-lowering effects. In general, small effects were seen in some studies, but not in others.

Adverse Effects of Levothyroxine Treatment

A clear description of the adverse effects of levothyroxine is available in textbooks and the drug package insert (Bartalena et al., 1996). These include nervousness, palpitations, atrial fibrillation, and exacerbation of angina pectoris. The randomized trials reviewed by Helfand did not systematically report adverse events, but some were reported incidentally and were of the types noted earlier. A systematic review of *observational* studies published from 1966 to 1997 found that replacement doses of levothyroxine were not associated with osteoporosis or any other long-term adverse effects. However, Helfand notes that suppressive therapy for thyroid cancer, goiter, or nodules has been reported to be associated with increased osteoporosis risk. Helfand also notes that "overtreatment" with levothyroxine is a potential problem, as about one-fourth of patients on replacement therapy have been reported to be on doses sufficient to suppress the serum TSH level to below normal. Observational data from the Framingham study

suggest that replacement therapy can increase the risk of atrial fibrillation in those with suppressed TSH levels. In the observational Study of Osteoporotic Fractures, low TSH levels in subjects taking levothyroxine were associated with increased osteoporotic fracture risk.

SUMMARY AND CONCLUSIONS

In assessing the balance of benefits and harms for both hyperthyroidism and hypothyroidism, the key uncertainties are the following questions: (1) Without screening, how long would thyroid dysfunction be undetected? (2) How much morbidity would undiagnosed thyroid dysfunction cause while undetected? (3) What are the harms of treatment in those who do not progress?

Based on the review by Helfand of the evidence base for screening for thyroid dysfunction, the Committee reached the following conclusions.

1. There is suitable evidence that individuals in the community with no history of thyroid disease can be identified through serum TSH screening and systematic medical evaluation with hypothyroidism and hyperthyroidism as defined biochemically. The prevalence of thyroid dysfunction is higher in persons over age 65 years than among younger adults.

2. Individuals with subclinical hyperthyroidism appear to be at greater risk of atrial fibrillation and possibly to its downstream consequences, such as stroke. Also, individuals with subclinical hypothyroidism are more likely to have functional abnormalities in cardiac contraction, although whether this translates into long-term risk of congestive heart failure or other cardiac conditions is uncertain. The evidence that persons with subclinical hypothyroidism are clinically different from persons who have biochemically normal thyroid function—either with respect to symptoms or blood lipid levels—is inconclusive.

3. No randomized trials examining the treatment of overt or subclinical hyperthyroidism (Figure 1, Effects B1 and D1-D3) could be identified. As noted in Chapter 3, subclinical hyperthyroidism will frequently resolve spontaneously. While treatment of subclinical hyperthyroidism effectively eliminates the biochemical condition, it usually leads to a hypothyroid state and to other adverse effects. Properly designed clinical studies are needed to determine whether treatment reduces the risks associated with hyperthyroidism, such as atrial fibrillation, and whether benefits outweigh adverse effects.

4. There are no trials of the treatment of subclinical or overt hypothyroidism in patients who were identified by serum TSH screening programs. Although thyroxine treatment manifestly eliminates the biochemical characteristics of subclinical hypothyroidism, evidence from controlled trials suggests that overall short-term (i.e., 6-24 months) treatment does not lead to any important clinical improvements. No long-term controlled trials of thyroid hormone replacement have been published; the long-term clinical benefits and adverse effects are un-

known. There is evidence that about one-fourth of patients on levothyroxine are overtreated, and these patients may be at increased risk of cardiac complications and osteoporotic fractures.

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5

The Cost of Coverage

The Committee was asked to consider, in addition to the possible benefits, the cost to the Medicare program of coverage of thyroid stimulating hormone (TSH) screening. This cost is dependent on the number of people screened and changes in the use of resources that result from screening. This chapter begins with an examination of the effect that Medicare coverage has had on the use of other preventive services and identifies factors from that experience that may be relevant to screening with TSH for thyroid dysfunction. The impact of these factors is assessed in conjunction with additional data from a study of thyroid disease among Medicare beneficiaries and an analysis of Medicare claims data to provide estimates of the number of beneficiaries who would be screened. Finally, an economic model is used to estimate costs per beneficiary screened.

COVERAGE AND USE OF PREVENTIVE SERVICES

There are limited historical data that can be used to ascertain how much of an effect Medicare coverage of various preventive services has had on the use of those services. The Centers for Disease Control and Prevention tracks use of preventive services through its Behavioral Risk Factor Surveillance System (BRFSS) (Centers for Disease Control and Prevention, 2002). After these services are covered, their use also can be tracked through the use of Medicare claims data (McBean, 2002). Tables 5-1A through 5-1C show the BRFSS data for influenza and pneumonia immunizations, mammography, and Pap smears, the only preventive services covered by Medicare for which BRFSS data are available.

TABLE 5-1A Use of Preventive Services Covered by Medicare: Pneumonia and Influenza Immunizations

Year	Pneumonia Shot Ever (Age 65+)[a]	Flu Shot Within 12 Months (Age 65+)[b]
1993	27.8%	50.9%
1995	38.4%	60.0%
1997	45.7%	65.9%
1999	54.9%	67.4%
2001	61.3%	66.2%

[a]First year of Medicare coverage -1981
[b]First year of Medicare coverage -1993
SOURCE: Centers for Disease Control and Prevention, 2001

TABLE 5-1B Use of Preventive Services Covered by Medicare: Mammography and Breast Examination

	Mammogram & Breast Exam Ever		Within 2 Years	
Year	Age 50-64	Age 65+	Age 50-64	Age 65+
1990	70.4%	58.9%	63.8%	54.3%
1991[a]	74.2%	64.8%	67.0%	58.0%
1992	75.0%	66.2%	67.7%	60.7%
1993	78.8%	71.0%	70.6%	64.5%
1994	79.5%	71.3%	71.9%	65.4%
1995	82.6%	72.6%	74.5%	65.8%
1996	83.9%	75.3%	76.1%	67.2%
1997	85.0%	76.8%	76.9%	70.0%
1998[b]	85.2%	75.6%	77.6%	72.4%
1999	86.1%	78.6%	79.1%	73.3%
2000	87.8%	79.3%	81.2%	77.1%

[a]First year of Medicare coverage
[b]Annual mammography covered
SOURCE: Centers for Disease Control and Prevention, 2001

Coverage for preventive services has been accompanied by only gradual increases in the use of those services. In the case of pneumococcal vaccine, for example, by 1993 only 27.8 percent of the population age 65 and older reported that they had ever been immunized even though Medicare has covered the service since 1981. This proportion then nearly doubled between 1993 and 1999 and has continued to increase. The U.S. General Accounting Office (GAO) has found that Medicare coverage by itself has not been enough to promote use of preventive services by most beneficiaries, and additional efforts—working to increase demand or remove other barriers to access to services—are necessary to increase their use (GAO, 2002). A large body of work on theories and behavioral models

TABLE 5-1C Use of Preventive Services Covered by Medicare: Pap Smears

	Pap Smear Within 3 Years	
Year [a]	Age 50-64	Age 65+
1992	82.6%	67.6%
1993	81.9%	70.1%
1994	82.4%	69.9%
1995	83.1%	70.1%
1996	84.6%	69.3%
1997	84.9%	71.2%
1998[b]	84.6%	68.9%
1999	85.3%	72.3%
2000	87.5%	74.5%

[a]First year of Medicare coverage - 1990
[b]Pelvic Examinations covered
SOURCE: Centers for Disease Control and Prevention, 2001

has addressed the question of determinants of utilization of clinical preventive interventions in primary care (Elder et al., 1999).

Demand is a key factor in service use. If there is little interest in or awareness of the service by the patient (or the patient's physician), coverage will make little difference. This appears to have been the case for pneumococcal vaccine—significant educational and outreach programs were used to increase immunization rates (GAO, 2002). The close correlation between the usage of services in the population over age 65 and in younger age ranges suggests that demand for preventive services by Medicare beneficiaries parallels more general trends in society.

Medicare coverage may be an important factor in the use of a service, but the effect is indirect. Strictly speaking, Medicare coverage policy only assures that Medicare payment for a particular service is available. A cost barrier is removed for those Medicare beneficiaries for whom the cost of the test would be a barrier to its use. If these beneficiaries encounter barriers in addition to the cost of the service, payment will not enable them to make use of the service unless those barriers are also overcome. The primary economic barrier to the use of preventive services may not be the cost of the service but the costs of other activities related to obtaining the service.

Access to health care services is also heavily influenced by factors that are not related or only indirectly related to payment for services. For example, significant differences exist in the use of Medicare-covered preventive services among racial and ethnic groups (GAO, 2002); these differences are partially

related to the degree of trust held in providers and the health care system (IOM, 2002). In some states, the lack of easily available Medicare providers has limited the use of preventive services (GAO, 2002). The problem of availability of providers may be geographical remoteness in rural areas or may be a reflection of the lack of material resources in communities too poor to provide adequate health care facilities. Factors with important positive influence on access to care include social support networks that encourage patients to seek care and support; the ability of patients to leave home or work to obtain care; well-developed transportation systems; low crime rates; high literacy rates; providers with compatible language and culture; and a regular provider and site of care (IOM, 2002). Even when patients have good access to health care services, the delivery system may need to be changed so that preventive services can be easily offered, accepted, and delivered within the usual patterns of care (GAO, 2002).

Finally, coverage may not have a significant impact on the use of a service if the service is easily available without coverage. If it is not expensive, a patient may pay for the service himself. A number of "Medigap" supplemental insurance plans cover preventive services. Providers are often motivated to offer free screening as a means of identifying new patients in need of services for which the providers would be paid. Some screening tests are also used for diagnostic purposes, and the line between screening and diagnosis can often be blurred (McBean, 2002). If good alternative means exist for obtaining the service, a beneficiary may not take advantage of coverage or may substitute for the alternative by obtaining the service through Medicare coverage.

ESTIMATING DEMAND FOR TSH SCREENING

There is no direct evidence, such as surveys or pilot programs, of the level of interest or demand for serum TSH screening among Medicare beneficiaries or health care practitioners. Statements of expert opinion have been made on screening for thyroid disease, and a number of groups have published recommendations on the subject (Arbelle and Porath, 1999; United States Preventive Services Task Force, 1996), but their conclusions have differed. Even without such disagreements, the acceptance of recommendations into common practice is a long and complex process (IOM, 1990).

To estimate the use of serum TSH screening with Medicare coverage, the Committee needed two types of information: the size of the population covered and the proportion of the potential screening population likely to be tested. Creation of a preventive services benefit for TSH screening should only affect directly those Medicare beneficiaries who do not already have an indication for testing. To estimate the size of the potential screening population, it is necessary to count only those beneficiaries who would not already be covered for serum TSH testing under current Medicare coverage policy. That group would include not just beneficiaries with known thyroid disease but also those with conditions

believed to be affected by thyroid disease. The proportion of beneficiaries who receive serum TSH tests among those who are without known thyroid disease but currently covered for serum TSH testing could provide a plausible estimate of the proportion tested out of the potential screening population.

Current Medicare Coverage Policy

On November 23, 2001, the *Federal Register* published a Medicare National Coverage Decision for thyroid testing (Centers for Medicare and Medicaid Services, 2001). According to this document (page 58853);

> Thyroid function tests are used to define hyperfunction, euthyroidism, or hypofunction of thyroid disease. Thyroid testing may be reasonable and necessary to:
>
> - Distinguish between primary and secondary hypothyroidism;
> - Confirm or rule out primary hypothyroidism;
> - Monitor thyroid hormone levels (for example, patients with goiter, thyroid nodules, or thyroid cancer);
> - Monitor drug therapy in patients with primary hypothyroidism;
> - Confirm or rule out primary hyperthyroidism; and
> - Monitor therapy in patients with hyperthyroidism.
>
> Thyroid function testing may be medically necessary in patients with disease or neoplasm of the thyroid and other endocrine glands. Thyroid function testing may also be medically necessary in patients with metabolic disorders; malnutrition; hyperlipidemia; certain types of anemia; psychosis and nonpsychotic personality disorders; unexplained depression; ophthalmologic disorders; various cardiac arrhythmias; disorders of menstruation; skin conditions; myalgias; and a wide array of signs and symptoms, including alterations in consciousness; malaise; hypothermia; symptoms of the nervous and musculoskeletal system; skin and integumentary system; nutrition and metabolism; cardiovascular; and gastrointestinal system. It may be medically necessary to do follow-up thyroid testing in patients with a personal history of malignant neoplasm of the endocrine system and in patients on long-term thyroid drug therapy.

This is a very broad range of clinical conditions. The document lists approximately 200 ICD-9-CM codes for diagnoses that would establish medical necessity for TSH testing. (These are listed in Appendix C.) Although many of these diagnoses are obscure, a large number describe conditions that are common in the Medicare population, including diabetes, hypertension, hyperlipidemia, anemia, dementia, cardiac arrhythmias, palpitations, insomnia, fatigue, weight change, and constipation. This would indicate that many Medicare beneficiaries already have an indication for TSH testing and, therefore, should be unaffected by coverage of TSH screening as a preventive services benefit.

Identifying the Target Population

The Committee used two sources of data to identify which Medicare beneficiaries in the population do not already have an indication for TSH testing. The first was the New Mexico Elder Health Survey, a population-based sample of Medicare beneficiaries in Bernalillo County (Albuquerque), New Mexico (Lindeman et al., 1999). The second was an analysis of Medicare claims data.

The New Mexico Elder Study

The New Mexico Elder Study used Medicare enrollment data to select and recruit 883 Medicare beneficiaries for an interview and examination, including TSH and other diagnostic tests. Nearly half of this group was Hispanic, a proportion much larger than the national Medicare population, which is less than 3 percent Hispanic (U.S. Department of Health and Human Services, 1998); none were African American. Because the prevalence of some common conditions that are indications for TSH testing, particularly diabetes, is significantly different in the Hispanic population than in the general Medicare population, we analyzed the 469 non-Hispanic subjects (non-Hispanic whites are about 85 percent of the national Medicare population) (U.S. Department of Health and Human Services, 1998) separately from the 414 Hispanic subjects.

We estimated the number of subjects who did not have an indication for TSH testing under current Medicare coverage policy by removing from the sample those who appeared to have an indication for testing:

- Known thyroid disease: A history of thyroid disease or current thyroid medication use
- Hypertension: Systolic blood pressure above 160 mmHg, self-reported hypertension, or current antihypertension medication
- Current fatigue
- Weight gain or loss of more than 10 pounds in the past 6 months
- Hyperlipidemia: Serum cholesterol greater than 240mg/dl
- Insomnia
- Current hoarseness
- Arrhythmia on electrocardiogram or physical examination
- History of depression
- Anemia: Men with a hematocrit below 40,women with a hematocrit below 35
- Diabetes: Current diabetes medication or history of diabetes
- Current neurological problem
- Current chronic constipation
- Current tranquilizer use as evidence of anxiety or insomnia

After these subjects were removed from the sample, only 51 (11 percent) of the non-Hispanic subjects remained, having none of the above indications for TSH testing. Of the 51, 14 had not seen a physician in the preceding 6 months, making it less likely that they would be available for screening even if the benefit were available. We concluded that 8 percent (37 of 469) of the non-Hispanic white Medicare beneficiaries in the sample would be eligible and available for TSH screening. The subjects identified as likely candidates for screening were, on average, 2 years younger than the entire study population and more than twice as likely to be men. Because increasing age and being female are major risk factors for thyroid disease, the screening candidates should be at relatively low risk for thyroid disease.

Among Hispanic subjects, 46 (11 percent) remained, having none of the indications listed for TSH testing. Of the 46, 18 had not seen a physician in the preceding 6 months. We concluded that 7 percent (28 of 414) of the Hispanic Medicare beneficiaries in the sample would be eligible and available for TSH screening. The subjects identified as likely candidates for screening were also, on average, 2 years younger than the entire study population, but not significantly more likely to be men (57 percent versus 51 percent).

Medicare Claims

Analyzing Medicare claims data was the second method the Committee used to estimate the number of Medicare beneficiaries who would become eligible for TSH testing with the establishment of a preventive services benefit. A claim to Medicare for payment is generally required to present documentation that the service provided is medically necessary. This is usually done by submitting a diagnosis (and associated ICD-9-CM code) with the claim. When there is a coverage policy for the service, the diagnosis must be one accepted by the policy in order for the service to be covered and payment to be made.

We attempted to define the screening population by asking, "How many Medicare patients who have never submitted a claim containing a diagnosis with an indication for TSH testing see a physician in a given year?" Answering this question involved some cautions and complications in analysis. The answer could exaggerate the number of potential screening candidates because not all patient diagnoses are entered on claims. A further complication came from the need to limit the time period in which to search for relevant claims. Too short a period of looking back from the reference year would make it more likely that diagnoses will be missed. Too long an observation period will exclude too many beneficiaries who entered the program during the period for which claims are examined. There was also a question of how to approach a patient who had an indication for testing in the past that was transient. For example, a patient who reported constipation 2 years earlier may no longer have this problem in the reference year; testing in the reference year, assuming there were no other indications, would be

considered screening. However, if the patient received TSH testing as part of the evaluation of his constipation, the patient would not be a candidate for screening if the interval approved for screening was greater than the time since the last TSH test.

To perform this analysis, we created a cohort consisting of 5 percent of Medicare beneficiaries enrolled on January 1, 1997. Using physician and outpatient claims files for 1997, we then examined their submitted claims for diagnoses that are approved for TSH testing under current policy. We divided the diagnoses listed in Appendix C into three groups: (1) diagnoses of thyroid disease, (2) diagnoses of chronic or permanent conditions that would be persistent indications for testing, and (3) diagnoses of possibly transient conditions that would be short-term indications for testing. A patient was considered a candidate for screening in 1997 if he did not submit a claim containing one of the indications for testing and saw a physician whose specialty was general practice, family practice, or internal medicine (including subspecialties) that year; we considered these specialties to be the most likely to do testing for thyroid disease. This would be the potential population size for screening on an annual basis. To look at longer periods, we removed from the cohort all of the subjects in the first and second categories along with those in the third category who actually received a TSH test. We then looked at the claims data for the remaining subjects for 1998, applying the same criteria for potential screening candidates (this time with a 2-year testing interval) and removal from the cohort. This process was repeated for a total of 5 years.

Results from the claims data study are given in Table 5-2. Even when evaluated on the most liberal criteria—no indications for testing listed on claims for 1997 only—just 7.7 percent of beneficiaries would have been available for screening in that year. As was found in the New Mexico study, the potential screening population is younger and more heavily male, hence at lower risk for thyroid dysfunction. As the criteria for screening become stricter by looking for testing indications over a longer period and allowing more subjects to develop indications for testing over a longer screening interval, the potential screening population becomes even smaller, younger, and more likely to be male. With a 5-year

TABLE 5-2 Potential Candidates for Screening Identified by Claims Data

Reference Year	Interval (Years)	% of Medicare Beneficiaries	Average Age in 1997	% Male
1997	1	7.7%	68.3	48.4%
1998	2	4.3%	66.3	51.4%
1999	3	2.7%	65.0	53.3%
2000	4	1.8%	64.1	54.5%
2001	5	1.3%	63.5	55.3%
Total population			71.3	42.5%

testing interval, looking in 2001 for all claims from 1997 to 2001, candidates for screening make up only 1.3 percent of the Medicare population; they are 55.3 percent male (compared to 42.5 percent male in the total Medicare population) and are, on average, 7.8 years younger than the average Medicare beneficiary. Fewer than 10 percent of these candidates for screening received testing for diabetes or cholesterol; if the remainder of this group were screened for these other conditions instead of being screened for thyroid disease, those who tested positive would have an indication for testing and no longer be considered candidates for screening. For the purposes of our estimates, we have taken the middle figure from Table 5-2, 2.7 percent, as the proportion of Medicare beneficiaries who will be available and newly eligible for serum TSH testing because of the implementation of a screening benefit.

To estimate the proportion of candidates of screening who would be tested, we looked at the population of beneficiaries enrolled in the Medicare program on January 1, 2001. From this group we identified those beneficiaries who (1) did not submit a claim in 2001 with a thyroid disease diagnosis, (2) had a physician visit with one of the specialties most likely to test for thyroid disease, and (3) submitted a claim in 2001 with a diagnosis recognized by current Medicare coverage policy as an indication for serum TSH testing. Of this group, 21 percent received serum TSH testing.

Combining these figures, we estimate that 0.6 percent (21 percent of 2.7 percent) of Medicare beneficiaries, 250,000 at the current population, would be screened if coverage were implemented. This is an imprecise estimate that is dependent on many factors. A short interval between screenings (1 to 2 years) would likely increase the number screened because fewer subjects would develop indications for diagnostic testing; a longer interval would have the opposite effect.

The estimate does not consider the effect of efforts to encourage serum TSH testing that may occur in conjunction with coverage for screening. Such efforts could also lead to "screening" among patients who already have indications for testing. We did not include any increases in testing among this group as being due to coverage for screening because such an effect is not specific to the change in coverage; it could occur in the absence of a change in coverage and as a result of any phenomenon that would encourage testing, such as higher payments or promotion of testing by advocacy groups.

In the absence of efforts to encourage testing, the figure of 21 percent of screening-eligible beneficiaries who see physicians being tested may be too high. This figure did not include patients who may have had indications for TSH testing that were not listed on claims and physicians may have a lower inclination to screen than they do to test patients with indications for diagnostic testing. Using a range of possibilities, 1.3 percent to 7.7 percent available for testing and testing 10 percent to 80 percent of those available, the percentage of Medicare beneficiaries tested could be as low as 0.1 percent or as many as 6.2 percent.

ESTIMATED COSTS OF SCREENING

Calculating the net costs of a serum TSH screening program entails comparing the incremental medical costs likely to be incurred from screening a population for thyroid dysfunction versus the diagnosis and treatment of thyroid dysfunction that now occurs in usual care. Under usual care, people receive treatment for thyroid dysfunction if their clinicians diagnose it, but there is no systematic screening program. The net costs of a screening program consist of the following components:

1. Costs of the screening program, including (a) serum TSH tests and (b) evaluation of any positive test results to distinguish people who do not have thyroid dysfunction (false positives) from those who do (true positives);
2. Net costs of treating thyroid dysfunction, calculated as the difference between (a) the cost of treating thyroid dysfunction detected by the screening program and (b) the cost of treating thyroid dysfunction diagnosed under usual care; and
3. Any net savings in treatment costs from preventing mortality and morbidity associated with thyroid dysfunction and secondary disorders in (a) people detected by the screening program compared with (b) people under usual care.

Tables 5-3A through 5-3C list the specific medical services that may be involved in screening and treating thyroid dysfunction. Under the screening program (Part A), all people screened would initially receive a serum TSH test, and those with positive test results would receive an office visit, a repeat serum TSH test, and a serum free T_4 test to confirm the abnormal results and rule out false positives. Those with high serum TSH results indicating subclinical or overt hypothyroidism (Part B) and those with low serum TSH results indicating subclinical or overt hyperthyroidism (Part C) would subsequently receive additional tests, consultations, visits, and therapies to evaluate and then treat the condition. If treatment for the thyroid dysfunction was effective, it might ameliorate the condition, reduce services associated with unrecognized symptoms of the condition, or reduce services associated with secondary disorders and thereby achieve savings in costs.

TABLE 5-3A Components of a Cost Analysis of Screening for TSH: Screening Program

Detection of dysfunction	Evaluation of positive screening test results
Serum TSH test	Office visit Serum TSH test Serum free T_4 test

TABLE 5-3B Components of a Cost Analysis of Screening for TSH: Evaluation and Treatment of Subclinical and Overt Hypothyroidism

Potential Costs		Potential Savings
Evaluation for treatment of hypothyroidism detected by screening	Treatment of hypothyroidism detected by screening	Amelioration of hypothyroidism detected by screening
Serum antithyroid antibody tests Endocrine consultation Serum lipid tests	Office visits for follow-up Serum TSH tests Thyroid hormone for therapy Monitoring or treatment for effects of excess thyroid hormone therapy	Reduction in consultations and tests for unrecognized symptoms of hypothyroidism (e.g., depression, constipation, dry skin) Reduction in treatment, morbidity, or mortality due to secondary disorders or to progression to more severe hypothyroidism (e.g., hyperlipidemia, cardiovascular disease, depression)

TABLE 5-3C Components of a Cost Analysis of Screening for TSH: Evaluation and Treatment of Subclinical and Overt Hyperthyroidism

Potential Costs		Potential Savings
Evaluation for treatment of hyperthyroidism detected by screening	Treatment for hyperthyroidism detected by screening	Amelioration of hyperthyroidism detected by screening
Serum triiodothyronine tests Serum antithyroid antibody tests Radioiodine tests Endocrine consultations	Office visits for follow-up Serum free T_4 tests Serum TSH tests Antithyroid drug or radioactive iodine treatment Blood counts, liver function tests Thyroid hormone therapy for hypothyroidism caused by radioactive iodine treatment	Reduction in consultations and tests for unrecognized symptoms of hyperthyroidism (e.g. anxiety, weight loss, cardiac arrhythmia) Reduction in treatment, morbidity, or mortality due to secondary disorders or to progression to more severe hyperthyroidism (e.g. atrial fibrillation, heart failure, osteoporosis and fracture)

The dearth of current evidence on the effectiveness of thyroid screening restricts the calculation of the full range of net costs associated with a screening program. Because evidence is lacking on the likely health benefits of screening, there is no reasonable basis for estimating whether a screening program would detect thyroid dysfunction more effectively than usual care and, hence, how the costs of treating thyroid dysfunction under the alternative strategies would compare. On the one hand, if screening only reduced the lead time to identify and treat people with thyroid dysfunction, the incremental costs of treatment might be quite small; most of the same costs would be incurred without screening, only later in time. In this regard, we know that the overall rate of progression of subclinical hypothyroidism to overt hypothyroidism is low, a few percentage points per year, but higher in those people with higher serum TSH concentrations or high serum anti-thyroid antibody concentrations (see Chapter 3). In a few people, however, serum TSH concentrations return to normal with time.

On the other hand, if screening identified people who otherwise would not be diagnosed and treated under usual care, the incremental costs of screening would be closer to the full amount of the costs of treating those people identified by screening. Without evidence on the effectiveness of screening, we have no basis for estimating where in that range incremental treatment costs are likely to fall; nor is there a reasonable basis for estimating the extent to which treatment of cases detected through screening would prevent the use of services, morbidity, or mortality associated with thyroid dysfunction and secondary disorders. Therefore, we lack an adequate basis for estimating whether any net savings in the costs of treating these sequelae would occur.

In the absence of sufficient evidence to estimate these health benefits and their associated medical costs, we have estimated the components of a cost analysis that do not incorporate an assessment of the effectiveness of screening: the costs of the screening program and the costs of treating cases detected by screening. For a cohort of 1 million Medicare beneficiaries 65 years or older who were screened, Tables 5-4A and 5-4B provide estimates of the prevalence of thyroid dysfunction that would be detected and the services that would be used to further evaluate and treat those people found to have thyroid dysfunction. Data are available that allow an estimate of the prevalence of abnormal screening serum TSH values (see the references accompanying Tables 5-4A and 5-4B), but it should be noted that some of these data are not from studies of screening. Nor are they from studies of people age 65 and older. No data are available on how people with subclinical thyroid dysfunction are evaluated or the proportion that is treated, so the estimates are drawn from the expert opinions of the Committee members. We have not attempted to estimate potential savings because of the complete absence of relevant data.

The estimates of how many people with abnormal screening serum TSH values would be further evaluated and treated are based on the following considerations. The base case contains the most reasonable estimate of each variable,

TABLE 5-4A Estimates of Medical Services to Screen, Evaluate, and Treat Thyroid Dysfunction, per 1 Million People Screened: Subclinical and Overt Hypothyroidism

Screening serum TSH value high (6% of people screened)[a] Follow-up	Base case	Lowest case	Highest case
Office visit	60,000		
Repeat serum TSH test	60,000		
Serum free T_4 test	60,000		
Serum antithyroid antibody test	30,000	10,000	50,000
Outcome 1: Normal – Repeat serum TSH value normal[b]			
3,000 (5% of people with high screening value)			
Years 2-5: Follow-up serum TSH test	2,500	1,000	2,800
Outcome 2: Subclinical hypothyroidism[b] *– serum TSH high & free T_4 normal*			
54,000 (90% of people with high screening value)			
Endocrine consultation	13,500	5,400	24,300
T_4 treatment	27,000	10,800	48,600
Outcome 3: Overt hypothyroidism[b] *– serum TSH high & free T_4 low*			
3,000 (5% of people with high screening value)			
Endocrine consultation	1,425	1,200	1,500
T_4 treatment	2,850	2,400	3,000
Follow-up after treatment			
(people with either subclinical or overt hypothyroidism)	29,850	13,200	51,600
Year 1, after treatment started			
Follow-up office visits, 2	29,850	13,200	51,600
Follow-up serum TSH tests, 2	29,850	13,200	51,600
Years 2 and beyond			
Lifelong T_4 treatment	29,850	13,200	51,600
Follow-up office visits, 2/year	29,850	13,200	51,600
Follow-up serum TSH tests, 2/year	29,850	13,200	51,600

[a]Prevalence data for high and low serum TSH concentrations extrapolated from Hollowell et al. (2002).

[b]Distribution of people among overt and subclinical subgroups (and normal repeat serum TSH subgroups) estimated from Canaris et al. (2000), Vanderpump et al. (1995), and Parle et al. (1991).

TABLE 5-4B Estimates of Medical Services to Screen, Evaluate, and Treat Thyroid Dysfunction, per 1 Million People Screened: Subclinical and Overt Hyperthyroidism

Screening serum TSH value low[a] (1% of all people screened) Follow-up	Base case	Lowest case	Highest case
Office visit	10,000		
Repeat serum TSH test	10,000		
Serum free T_4 test	10,000		
Outcome 1: Normal – Repeat serum TSH value normal[b]			
1,000 (10% of people with low screening value)			
Years 2-5: Follow-up serum TSH	800	200	900
Outcome 2: Subclinical hyperthyroidism[b]*– serum TSH low & free T_4 normal*			
8,500 (85% of people with low screening value)			
Serum triiodothyronine test	4,250	1,700	6,800
Serum antithyroid antibody test	2,550	425	5,100
Radioiodine tests	2,550	850	5,100
Endocrine consultation	4,250	1,700	6,800
Antithyroid treatment	2,550	850	5,950
Radioactive iodine[c]	1,275	425	2,975
Antithyroid drug treatment[d]	1,275	425	2,975
Outcome 3: Overt hyperthyroidism[b] *- serum TSH low & free T_4 normal*			
500 (5% of people with low screening value)			
Serum triiodothyronine test	150	25	300
Serum antithyroid antibody tests	250	50	400
Radioiodine tests	250	100	400
Endocrine consultation	400	300	500
Antithyroid treatment	450	350	500
Radioactive iodine[c]	225	175	250
Antithyroid drug treatment[d]	225	175	250
Follow-up after any treatment started (people with either subclinical or overt hyperthyroidism)			
Year 1, after treatment started (all treated people)			
Follow-up office visits, 3	3,000	1,200	6,450
Serum free T_4 tests, 3	3,000	1,200	6,450
Serum TSH tests, 3	3,000	1,200	6,450
Hypothyroidism after radioactive iodine treatment (all treated with T_4)	750	300	1,612
Years 2 and beyond			
Follow-up of group with hypothyroidism after radioactive iodine treatment			
Lifelong T_4 treatment	750	300	1,612
Follow-up office visits, 2/year	750	300	1,612

[a]Prevalence data for high and low serum TSH concentrations extrapolated from Hollowell et al. (2002).
[b]Distribution of people among overt and subclinical subgroups (and normal repeat serum TSH subgroups) estimated from Canaris et al. (2000), Vanderpump et al. (1995), and Parle et al. (1991).
[c]Some people given an antithyroid drug initially would probably be given radioactive iodine in year 2 or later, but it is very uncertain what that percentage would be.
[d]About 75 percent of the people given an antithyroid drug may receive it in year 2 and later as well. It may be discontinued with relapse of hyperthyroidism in some people, and others would be given radioactive iodine; the percentages are very uncertain.

and the lowest and highest cases contain the range of values that would be associated with the lowest and highest estimates of costs, respectively:

- All people with an abnormal screening serum TSH value would have at least an office visit, a repeat serum TSH test, and a serum free T_4 test. This is the ideal response to abnormality detected by screening, and the actual proportion having this further evaluation is likely to be lower.
- There are no recent data (<10 years old) indicating how physicians would evaluate people with overt thyroid disease and no data at all indicating how they would evaluate people with subclinical thyroid disease; nor are there data indicating what proportion of people with either subclinical hypothyroidism or subclinical hyperthyroidism would be treated. The estimates given are based on the best estimates of the Committee.
- In regard to treatment of subclinical hypothyroidism and subclinical hyperthyroidism, it is important to note that most people with either condition have serum TSH concentrations that are close to the limits of normal. This is one reason why the value for the base case is relatively low. The lowest and highest cases are set far apart because of the uncertainty about the proportions likely to be treated. Nearly all people with overt thyroid disease would be treated.
- We assumed that all patients who were treated for either subclinical or overt hypothyroidism would have the specified numbers of follow-up visits and tests. Therefore, the numbers of people listed at the bottom of Table 5-4A, are the combined numbers for the subclinical and overt groups.
- The causes of both subclinical and overt hyperthyroidism were assumed to be Graves' disease (50 percent), nodular goiter (30 percent), and thyroiditis and other causes (20 percent). (There are no published data concerning the causes of subclinical hyperthyroidism as detected by screening.) We assumed that considerably fewer patients with subclinical hyperthyroidism would be treated (base case, 30 percent versus 90 percent for overt hyperthyroidism) because many of the former have only very slightly high serum TSH concentrations (and some would have thyroiditis and need no treatment). We assumed that 50 percent of people with subclinical hyperthyroidism and 50 percent of those with overt hyperthyroidism who were treated would be given radioactive iodine, and the other 50 percent would receive an anti-thyroid drug.
- For both subclinical and overt hyperthyroidism, we assumed that all people who were treated would receive three office visits and sets of tests in the first year of treatment and that the number of visits and tests would be independent of the type of treatment.
- Some people (estimated as 50 percent because people with both Graves' disease and nodular goiter are included) treated for hyperthyroidism with radioactive iodine would develop hypothyroidism. (We assumed this would occur during year 1.) Therefore, in year 2 and thereafter, they would be followed according to the schedule for people with hypothyroidism in Table 5-4A. We

recognize that this treatment is more likely to cause hypothyroidism in people with Graves' disease than in those with nodular goiter and consider the estimate of 50 percent to be very crude. Moreover, a few people treated with radioactive iodine would probably develop hypothyroidism later.

- For years 2 and thereafter, the remaining people with hyperthyroidism who were treated would be followed as indicated at the bottom of Table 5-4B. Some of these people might be treated with radioactive iodine and others, particularly those with Graves' disease, might have a remission of their disease and need no antithyroid drug treatment and less frequent testing.
- There are no published data that address the question of optimal follow-up for people with either hypothyroidism or hyperthyroidism.

Many more branches or steps could be added to this table. For example, the types of diagnostic studies were limited. As we have noted, we assumed that all people who were treated for hypothyroidism or hyperthyroidism would have the specified follow-up visits and tests, an unlikely outcome in clinical practice. The combining of visits and tests during and after treatment for hyperthyroidism independent of the particular treatment given is certainly an oversimplification. We have made no provision for the side effects of antithyroid drug or radioactive iodine therapy, except for radioactive iodine-induced hypothyroidism.

The unit costs for each visit, test, and treatment are shown in Tables 5-5A and 5-5B. Price information for all services except prescription drugs were obtained from the Medicare program's published Fee Schedules for 2003 (Centers for Medicare and Medicaid Services, 2003). Where fee schedule amounts differed among localities, the median figure was used. Prescription drug prices were obtained from an Internet prescription drug price search engine (DestinationRx, Inc., 2003) that compares prices from major national retail sources, including shipping costs. The prices selected for methimazole and propylthiouracil represent the mid-point between the highest and lowest prices quoted for 100 pills. The price chosen for levothyroxine was the lowest quoted price for 100 tablets of the leading brand name.

Tables 5-6A through 5-6C show our cost estimates for each 1 million Medicare beneficiaries screened. A large proportion of the cost comes from lifetime monitoring and drug treatment. Because the portion of the Medicare population affected by screening would be younger and healthier than average, we estimated the average life expectancy of beneficiaries who screen positively and are treated to be 17 years, the average life expectancy for individuals ages 66 and 67 (National Center for Health Statistics, 2002). As Table 5-6A shows, our base case cost estimate for the screening test itself is $23.5 million, all of which would be paid by the Medicare program. The lifetime cost estimate of treatment and follow-up for those patients whose initial test results indicated hypothyroidism (Table 5-6B) was $98.8 million per million subjects screened; $46.6 million would be paid by Medicare and $52.2 million would paid by Medicare beneficia-

TABLE 5-5A Prices of Services Required for Follow-up and Treatment After Abnormal Results of Thyroid Screening: Subclinical and Overt Hypothyroidism

	CPT© Code[a]	Cost[b]
Screening serum TSH value high		
Follow-up		
Office visit[c]	99213	$47.18
Repeat serum TSH test	84443	$23.47
Serum free T_4 test	84439	$12.60
Serum antithyroid antibody test[d]	86376	$20.33
Outcome 1: Normal		
Repeat serum TSH value normal		
Years 2-5:		
Follow-up serum TSH tests	84443	$23.47
Outcome 2: Subclinical hypothyroidism		
Year 1		
Endocrine consultation	99241	$43.83
Levothyroxine treatment, 0.1 mg/day		$0.315/day
Outcome 3: Overt hypothyroidism		
Year 1		
Endocrine consultation	99242	$81.70
Levothyroxine treatment, 0.1 mg/day		$0.315/day
Follow-up after treatment (either subclinical or overt hypothyroidism)		
Year 1, after treatment started		
Follow-up office visits,[c] 2	99212	$33.57
Follow-up serum TSH tests, 2	84443	$23.47
Years 2 and beyond		
Lifelong levothyroxine treatment		$0.315/day
Follow-up office visits,[c] 2/year	99212	$33.57
Follow-up serum TSH tests, 2/year	84443	$23.47

[a]Common Procedural Terminology codes, copyright 2003, American Medical Association.
[b]All prices except for prescription drugs (levothyroxine, methimazole, and propylthiouracil) are from 2003 Medicare Fee Schedules (Centers for Medicare & Medicaid Services, 2003). Prescription drug prices were obtained from the DestinationRx website (DestinationRx, 2003).
[c]Initial office visits after a screening test is found to be positive in all groups is estimated as requiring more than minimum time
[d]Measurement of serum antithyroid peroxidase (microsomal) antibody.

TABLE 5-5B Prices of Services Required for Follow-up and Treatment After Abnormal Results of Thyroid Screening: Subclinical and Overt Hyperthyroidism

	CPT© Code[a]	Cost[b]
Screening serum TSH value low		
Follow-up		
Office visit[c]	99213	$47.18
Repeat serum TSH test	84443	$23.47
Serum free T_4 test	84439	$12.60
Outcome 1: Normal (repeat serum TSH value normal)		
Years 2-5:		
Follow-up serum TSH tests	84443	$23.47
Outcomes 2:and 3: Hyperthyroidism		
Year 1		
Serum triiodothyronine test	84480	$19.81
Serum antithyroid antibody test[d]	86376	$20.33
Radioiodine test	78000	$43.64
Endocrine consultation[e]	99242	$81.70
Antithyroid treatment		
Radioactive iodine		
Radiopharmaceutical therapy[f]	79000	$177.41
Radioactive iodine[g]		$87.50
Antithyroid drug treatment		
Methimazole 10 mg/day		$0.685/day
Propylthiouracil 300 mg/day		$1.20/day
Follow-up after any treatment started (either subclinical or overt hyperthyroidism)		
Year 1		
Follow-up office visits,[c] 3	99212	$33.57
Serum free T_4 tests, 3	84439	$12.60
Serum TSH tests, 3	84443	$23.47
Hypothyroidism after radioactive iodine treatment (all treated with T_4)		
Years 2 and beyond		
Follow-up of group with hypothyroidism after radioactive iodine treatment in year 1		
Lifelong levothyroxine treatment		$0.315/day
Follow-up office visits,[c] 2/year	99212	$33.57
Follow-up serum TSH tests, 2/year	84443	$23.47
Follow-up of all other groups		
(euthyroid after radioactive iodine and antithyroid drug treatment)		
Follow-up office visits,[c] 3/year	99212	$33.57
Follow-up serum TSH tests, 3/year	84443	$23.47
Follow-up serum free T_4 tests, 3/year	84439	$12.60

[a]Common Procedural Terminology codes, copyright 2003, American Medical Association.
[b]All prices except for prescription drugs (levothyroxine, methimazole, and propylthiouracil) are from 2003 Medicare Fee Schedules (Centers for Medicare & Medicaid Services, 2003). Prescription drug prices were obtained from the DestinationRx Web site (DestinationRx, 2003).
[c]Initial office visits after a screening test is found to be positive in all groups is estimated as requiring more than minimum time, whereas later visits are minimum-time visits.
[d]Measurement of serum antithyroid peroxidase (microsomal) antibody.
[e]Office endocrine consultation visits are categorized as requiring 30 minutes for both subclinical and overt thyroid dysfunction.
[f]Office consultation with nuclear medicine physician for radioiodine treatment.
[g]I-131 capsules, 15mCi dose

TABLE 5-6A Cost Estimates for Thyroid Screening, per 1 Million Medicare Beneficiaries—Initial Screening

	Base Cost		
Screening	Total	Medicare	Other Payer
Serum TSH Tests	*$23,470,000*	*$23,470,000*	

TABLE 5-6B Cost Estimates for Thyroid Screening, per 1 Million Medicare Beneficiaries—Subclinical and Overt Hypothyroidism

	Base Cost		
	Total	Medicare	Other Payer
Follow-up - screening TSH value high			
Office visit	$2,830,800	$2,264,640	$566,160
Repeat serum TSH test	$1,408,200	$1,408,200	
Serum free T_4 test	$756,000	$756,000	
Serum antithyroid antibody test	$609,900	$609,900	
Outcome 1: Repeat test normal			
Years 2-5 Follow-up TSH tests	$218,101	$218,101	
Outcome 2: Subclinical hypothyroidism			
Year 1			
Endocrine consultation	$591,705	$473,364	$118,341
T_4 treatment	$3,071,935		$3,071,935
Outcome 3: Overt hypothyroidism			
Year 1			
Endocrine consultation	$116,423	$93,138	$23,285
T_4 treatment	$324,260		$324,260
Follow-up after treatment (subclinical or overt hypothyroidism)			
Year 1, after treatment started			
Follow-up office visits, 2	$2,004,129	$1,603,303	$400,826
Follow-up serum TSH tests, 2	$1,401,159	$1,401,159	
Subsequent years			
Lifelong Levothyroxine	$42,659,951		$42,659,951
Follow-up office visits, 2/year	$25,174,069	$20,139,255	$5,034,814
Follow-up serum TSH tests, 2/year	$17,600,101	$17,600,101	
Total Cost – Hypothyroidism	*$98,766,732*	*$46,567,161*	*$52,199,571*

NOTE: Costs after the first year are discounted at 3% per year in the base and lowest cost estimates. No discounting is used in the highest cost estimate

Highest Cost			Lowest Cost		
Total	Medicare	Other Payer	Total	Medicare	Other Payer
$23,470,000	*$23,470,000*		*$23,470,000*	*$23,470,000*	

Highest Cost			Lowest Cost		
Total	Medicare	Other Payer	Total	Medicare	Other Payer
$2,830,800	$2,264,640	$566,160	$2,830,800	$2,264,640	$566,160
$1,408,200	$1,408,200		$1,408,200	$1,408,200	
$756,000	$756,000		$756,000	$756,000	
$1,016,500	$1,016,500		$203,300	$203,300	
$328,580	$328,580		$87,240	$87,240	
$1,065,069	$852,055	$213,014	$236,682	$189,346	$47,336
$5,529,483		$5,529,483	$1,228,774		$1,228,774
$122,550	$98,040	$24,510	$98,040	$78,432	$19,608
$341,326		$341,326	$273,061		$273,061
$3,464,424	$2,771,539	$692,885	$886,248	$708,998	$177,250
$1,401,159	$1,401,159		$1,401,159	$1,401,159	
$93,932,950		$93,932,950	$18,864,702		$18,864,702
$55,430,784	$44,344,627	$11,086,157	$11,132,252	$8,905,801	$2,226,450
$38,753,664	$38,753,664		$7,782,959	$7,782,959	
$206,381,489	*$93,995,005*	*$112,386,484*	*$47,189,417*	*$23,786,076*	*$23,403,341*

TABLE 5-6C Cost Estimates for Thyroid Screening, per 1 Million Medicare Beneficiaries—Subclinical and Overt Hyperthyroidism

	Base Cost		
	Total	Medicare	Other Payer
Follow-up - screening serum TSH value low			
Office visit	$471,800	$377,440	$94,360
Repeat serum TSH test	$234,700	$234,700	
Serum free T_4 test	$126,000	$126,000	
Outcome 1: Normal - Repeat serum TSH value normal			
Years 2-5 Follow-up TSH tests	$69,792	$69,792	
Outcome 2: Subclinical hyperthyroidism			
Serum triiodothyronine test	$84,193	$84,193	
Serum antithyroid antibody test	$51,842	$51,842	
Radioiodine tests	$111,282	$89,026	$22,256
Endocrine consultation	$347,225	$277,780	$69,445
Antithyroid treatment			
Radioactive iodine	$337,760	$278,687	$59,073
Antithyroid drug treatment	$390,950		$390,950
Outcome 3: Overt hyperthyroidism			
Serum triiodothyronine test	$2,972	$2,972	
Serum antithyroid antibody	$5,083	$5,083	
Radioiodine tests	$10,910	$8,728	$2,182
Endocrine consultation	$32,680	$26,144	$6,536
Antithyroid treatment			
Radioactive iodine	$59,605	$49,180	$10,425
Antithyroid drug treatment	$68,991		$68,991
Year 1 Follow-up after treatment started (all treated people)			
Follow-up office visits, 3	$302,130	$241,704	$60,426
Serum free T_4 tests, 3	$113,400	$113,400	
Serum TSH tests, 3	$211,230	$211,230	
Follow-up hypothyroidism after radioactive iodine treatment			
Lifelong T_4 treatment	$1,071,858		$1,071,858
Follow-up office visits, 2/year	$632,514	$506,011	$126,503
Follow-up TSH tests, 2/year	$442,214	$442,214	
Follow-up of euthyroid after either radioactive iodine or antithyroid drug treatment			
Follow-up office visits, 3/year	$2,846,314	$2,277,051	$569,263
Follow-up TSH tests, 3/year	$1,989,961	$1,989,961	
Follow-up free T_4 tests, 3/year	$1,068,322	$1,068,322	
Total Cost – Hyperthyroidism	*$11,083,726*	*$8,531,458*	*$2,552,268*

NOTE: Costs after the first year are discounted at 3% per year in the base and lowest cost estimates. No discounting is used in the highest cost estimate

Highest Cost			Lowest Cost		
Total	Medicare	Other Payer	Total	Medicare	Other Payer
$471,800	$377,440	$94,360	$471,800	$377,440	$94,360
$234,700	$234,700		$234,700	$234,700	
$126,000	$126,000		$126,000	$126,000	
$105,615	$105,615		$17,448	$17,448	
$134,708	$134,708		$33,677	$33,677	
$103,683	$103,683		$8,640	$8,640	
$222,564	$178,051	$44,513	$37,094	$29,675	$7,419
$555,560	$444,448	$111,112	$138,890	$111,112	$27,778
$788,107	$650,270	$137,838	$112,587	$92,896	$19,691
$912,216		$912,216	$130,317		$130,317
$5,943	$5,943		$495	$495	
$8,132	$8,132		$1,017	$1,017	
$17,456	$13,965	$3,491	$4,364	$3,491	$873
$40,850	$32,680	$8,170	$24,510	$19,608	$4,902
$66,228	$54,645	$11,583	$46,359	$38,251	$8,108
$76,657		$76,657	$53,660		$53,660
$649,580	$519,664	$129,916	$120,852	$96,682	$24,170
$243,810	$243,810		$45,360	$45,360	
$454,145	$454,145		$84,492	$84,492	
$2,934,494		$2,934,494	$428,743		$428,743
$1,731,675	$1,385,340	$346,335	$253,006	$202,405	$50,601
$1,210,676	$1,210,676		$176,885	$176,885	
$7,795,760	$6,236,608	$1,559,152	$1,138,526	$910,821	$227,705
$5,450,297	$5,450,297		$795,984	$795,984	
$2,926,022	$2,926,022		$427,329	$427,329	
$27,266,678	*$20,896,841*	*$6,369,837*	*$4,912,735*	*$3,834,408*	*$1,078,327*

ries or supplementary insurance. Most of the cost not paid by Medicare, $42.7 million, is for prescription drugs. The lifetime cost estimate of treatment and follow-up for those patients whose initial test results indicated hyperthyroidism (Table 5-6C) was $11.1 million per million subjects screened; $8.5 million would be paid by Medicare and $2.6 million would paid by Medicare beneficiaries or supplementary insurance. Again, most of the cost not paid by Medicare, $1.5 million, is for prescription drugs. These estimates are very sensitive to the proportion of subjects tested who have positive screening results: An increase of 1 percent in the prevalence of elevated serum TSH levels (from 6 percent to 7 percent) would raise the base cost estimate for hypothyroidism by $16.5 million per million subjects screened. An increase in the prevalence of low serum TSH levels from 1 percent to 2 percent would increase the base cost estimate for hyperthyroidism by $11.1 million.

Combining our estimates of the number of beneficiaries screened with the estimates of costs per million beneficiaries screened, we can estimate the annual cost to the Medicare program. These results are given in Tables 5-7A through 5-7C. Our base estimates of 250,000 beneficiaries screened would cost Medicare $5.9 million for the screening tests, $11.6 million for follow-up and treatment of suspected hypothyroidism and $2.1 million for follow-up and treatment for suspected hyperthyroidism.

CONCLUSIONS

Estimates of the costs of screening require an estimate of the number of subjects who will be screened and the net costs incurred (or saved) as a result of screening.

Historically, the use of preventive services by Medicare beneficiaries has been considerably less than universal among those covered for the service; important factors have limited demand or created other barriers to use. In the case of serum TSH testing, more than 90 percent of Medicare beneficiaries have indications for testing that are already covered by the Medicare program. Aside from beneficiaries with known thyroid disease, fewer than 25 percent of beneficiaries with these indications are tested annually. On this basis, the Committee estimates that a relatively small number of Medicare beneficiaries would take advantage of a serum TSH screening benefit; our best estimate is 250,000 annually.

The Committee found a widespread lack of information necessary to make a meaningful assessment of the true economic costs of screening. It could not estimate costs avoided or other possible benefits resulting from screening or whether any costs incurred would be postponed rather than avoided if screening were not done. The Committee was able to estimate the health care resources likely to be expended as a consequence of screening. Our best estimate for 250,000 beneficiaries screened was $33.3 million annually. The Medicare program would pay $19.6 million of this total; supplementary insurance or the beneficiaries themselves would pay the remainder.

TABLE 5-7A Cost Estimates Based on Size of Screening Population: Initial Screening Tests – Cost to Medicare

Number Screened	Base	Lowest	Highest
250,000	$5,867,500	$5,867,500	$5,867,500
40,000	$938,800	$938,800	$938,800
2,500,000	$58,675,000	$58,675,000	$58,675,000

NOTE: No payment by other sources

TABLE 5-7B Cost Estimates Based on Size of Screening Population: Follow-up and Treatment for Suspected Hypothyroidism

Number Screened	Base	Lowest	Highest
Medicare			
250,000	$11,641,790	$5,946,519	$23,498,751
40,000	$1,862,686	$951,443	$3,759,800
2,500,000	$116,417,903	$59,465,190	$234,987,512
Other Payers			
250,000	$13,049,893	$5,850,835	$28,096,621
40,000	$2,087,983	$936,134	$4,495,459
2,500,000	$130,498,928	$58,508,353	$280,966,211
Total Cost			
250,000	$24,691,683	$11,797,354	$51,595,372
40,000	$3,950,669	$1,887,577	$8,255,260
2,500,000	$246,916,831	$117,973,543	$515,953,722

TABLE 5-7C Cost Estimates Based on Size of Screening Population: Follow-up and Treatment for Suspected Hyperthyroidism

Number Screened	Base	Lowest	Highest
Medicare			
250,000	$2,132,865	$958,602	$5,224,210
40,000	$341,258	$153,376	$835,874
2,500,000	$21,328,646	$9,586,019	$52,242,102
Other Payers			
250,000	$638,067	$269,582	$1,592,459
40,000	$102,091	$43,133	$254,793
2,500,000	$6,380,671	$2,695,818	$15,924,593
Total Cost			
250,000	$2,770,932	$1,228,184	$6,816,670
40,000	$443,349	$196,509	$1,090,667
2,500,000	$27,709,316	$12,281,837	$68,166,696

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6

Conclusions and Recommendations

The issue of screening for thyroid dysfunction has been a difficult and contentious one for several years and, as discussed in previous sections, has been debated in the literature and among those groups who promulgate clinical guidelines. Much of the debate continues, as described in the preceding chapters, because of the absence of critical evidence on (1) the definition and physiological concomitants of early thyroid dysfunction; (2) the effects of early dysfunction on target tissues and organs; (3) the presence or absence of clinical manifestations in these early stages; (4) the natural history of early dysfunction; and (5) the net personal and population benefits and harms of long-term treatment. However, it should be pointed out that the absence of evidence does not mean that important benefits do not exist.

Based on existing data and analyses of Medicare data performed under contract, the Committee first turned to the question about whether there were obvious deficits in access to thyroid function tests and thyroid care in the absence of a policy allowing periodic screening. Based on this evidence, the Committee concludes that current Medicare coverage of thyroid function testing does not impede the timely diagnosis of thyroid disease. At least 90 percent of all Medicare beneficiaries are currently eligible for thyroid stimulating hormone (TSH) testing under current coverage due to the high prevalence of a wide range of symptoms and conditions that are compatible with common manifestations of thyroid dysfunction but are not specific for such dysfunction.

As noted previously, even when excluding the substantial number of Medicare beneficiaries who carry a diagnosis of thyroid disease or are receiving thyroid hormone therapy, there is a nearly universal prevalence of conditions or symp-

toms associated with thyroid disease. These include diabetes, hypertension, elevated serum cholesterol or general systemic symptoms such as fatigue, skin problems, undetected cardiac arrhythmias, weight gain or loss, altered bowel habits, and a host of other clinical complaints common in the population, and particularly among persons aged 65 and older. This high prevalence allows TSH testing as a part of nearly all comprehensive clinical assessments under current Medicare coverage policy. Medicare considers TSH testing under these circumstances to be a standard part of clinical evaluations of symptoms and conditions rather than the screening of individuals who are asymptomatic or who have unrecognized clinical symptoms or other abnormalities.

To address the specific question as to whether routine TSH testing is beneficial in persons 65 years and older who have no recognized clinical symptoms or abnormalities related to thyroid dysfunction, the Committee adopted a process for reviewing the evidence similar to the methodology of the United States Preventive Services Task Force, an evidence-based approach that places a premium on published, peer-reviewed, and systematically scrutinized scientific information. In fact, the review materials being prepared for the Task Force were available to the Committee and formed part of the decision-making process. Based on this method for examining the available evidence, the Committee concluded:

> *Conclusion #1: There is insufficient evidence to recommend periodic, routine screening for thyroid dysfunction among asymptomatic persons using serum TSH levels.*

While the evidence is considered in detail in previous chapters, the basic reasons for this conclusion stemmed from several general considerations:

1. It is uncertain whether asymptomatic persons with abnormal TSH levels but normal thyroid hormone levels actually have some degree of physiologically meaningful abnormalities that would benefit from early treatment in the absence of clinical manifestations. While a few general, small studies suggest that some "asymptomatic" persons with altered TSH levels have detectable physiological or anatomic abnormalities, questions concerning the factors selecting these individuals for study, how these persons relate to defined populations, and whether these intermediate outcomes presage worse overall morbidity and mortality rates compared to appropriate contrast groups leave doubt as to the significance of these findings.

2. Some of the potentially important consequences of clinical, if not subclinical, thyroid disease, such as altered blood cholesterol and lipid levels and bone density levels, are themselves the subject of recommended, routine clinical screening procedures, and these should be performed as part of a general program of preventive care regardless of a potential relation to possible thyroid dys-

function. Conversely, if these abnormalities are discovered as part of this program, then Medicare will cover the thyroid function evaluation.

3. While some individuals with unrecognized clinical or physiological abnormalities associated with thyroid dysfunction do progress to overt thyroid disease over several years, the rates, timing, and risk factors for this progression are only partly understood. Furthermore, the Committee could find no evidence that would inform the decision about how often to screen for abnormal TSH levels to optimally detect those who might be progressing to overt disease. Undetected progression of subclinical thyroid dysfunction to overt, life-threatening thyroid disease is rare.

4. Routine TSH screening of asymptomatic persons over 65 years of age may lead to large numbers of persons receiving thyroid hormone therapy, but no randomized clinical trials have been performed that assess the long-term benefits or adverse effects of early treatment of subclinical thyroid dysfunction. Thus, it is difficult to evaluate the net outcomes of long-term hormonal interventions. Population-based samples of patients receiving thyroid hormone therapy consistently show important proportions of these patients to be either undertreated (elevated levels of TSH) or overtreated, in the range of iatrogenic subclinical hyperthyroidism.

Screening with modern, "third-generation" serum TSH assays will detect thyroid dysfunction among older persons with unrecognized symptoms and clinical abnormalities with reasonable efficiency. However, in the absence of evidence on the occurrence of benefits and harms and the incumbent medical care costs during long-term treatment of these patients, it is not possible to determine the long-term costs and the cost/benefit ratio of such a screening program. In Chapter 5, the cost elements for such an initial screening activity and diagnostic evaluation were estimated, as well as subsequent yearly management. Even using these figures, the cost of adding serum TSH screening as a benefit clearly could be substantial. Predicting subsequent costs for a screening benefit would be hampered further by the unpredictability of whether and to what degree clinicians would adopt the screening activities or how rapidly such adoption would take place. Thus, the Committee concluded

> *Conclusion #2: Given insufficient evidence about the health benefits of a serum TSH screening program, the cost implications for the Medicare program are uncertain.*

Because evidence is lacking on the likely health benefits of screening, there is no reasonable basis for estimating whether a screening program would detect thyroid dysfunction more effectively than usual care and, hence, how the costs of treating thyroid dysfunction under the alternative strategies would compare. We do not have an adequate basis for estimating whether there would be any net savings in the costs of treating future consequences of thyroid dysfunction.

Based on these conclusions, the Committee makes the following recommendation:

> **The Medicare program at this time should not cover screening for thyroid dysfunction as a preventive services benefit. This recommendation is based on the lack of sufficient evidence of either net benefit or harm. Additional evidence is required for a definitive conclusion.**

The clinical practice of medicine suffers from the lack of a stronger evidence base. Most decisions made by medical practitioners do not lead to results that clearly and promptly demonstrate the wisdom of those decisions. In the case of screening for thyroid dysfunction, if their actions are repeated millions of times, the cumulative costs can become enormous while the net health effects remain unknown. Because of the large number of older persons who possess biochemical thyroid abnormalities, screening and treating for these abnormalities could generate substantial benefit or harm at considerable financial cost. Randomized, controlled trials of TSH screening, pragmatic in approach, could assess the effectiveness of screening and treatment obtained under usual community conditions and consider both health and economic outcomes.

APPENDIX A

Workshop on Screening for Thyroid Dysfunction

OCTOBER 31, 2002, IRVINE, CALIFORNIA

8:00 a.m. - Screening for Thyroid Disease - Systematic Evidence Review
Mark Helfand, M.D., M.P.H.
Oregon Health and Science University

8:40 a.m. - Thyroid Disease, Osteoporosis and Lipids in the Elderly
Douglas C. Bauer, M.D.
University of California - San Francisco

9:20 a.m. - Subclinical Thyroid Disease in a Screening Population
E. Chester Ridgway, M.D.
University of Colorado Health Sciences Center

10:00 a.m. - Break

10:30 a.m. - Thyroid Disease in the New Mexico Elder Health Survey
Robert D. Lindeman, M.D.
University of New Mexico Health Sciences Center

11:10 a.m. – Studies of Lipids and Thyroid Dysfunction
Marc Stone, M.D.
The Institute of Medicine

11:50 a.m. - Medicare Experience with Screening and Preventive Services Benefits
A. Marshall McBean, M.Sc., M.D.
University of Minnesota School of Public Health

12:30 p.m. - Lunch

1:30 p.m. - TSH Screening for Medicare - Results from a Cost-Effectiveness Model
Neil Powe, M.D., M.P.H., M.B.A.
Johns Hopkins School of Public Health
Mark Danese, Ph.D.
Amgen, Inc.

2:10 p.m. - Roundtable Discussion

3:00 p.m. - Break

3:20 p.m. - Roundtable Discussion (Continued)

4:30 p.m. - Adjournment

APPENDIX B

Screening for Thyroid Disease: Systematic Evidence Review

*Mark Helfand, M.D., M.P.H.**

INTRODUCTION

Burden of Illness

Hyperthyroidism and hypothyroidism are common conditions that have lifelong effects on health. About 5 percent of U.S. adults report having thyroid disease or taking thyroid medication.[1, 2] In a cross-sectional study of 2,799 well-functioning adults ages 70 to 79, 9.7 percent of black women, 6 percent of white women, 3.2 percent of black men, and 2.2 percent of white men reported a history of hyperthyroidism.[3] In the same study, 6.2 percent of black women, 16.5 percent of white women, 1.7 percent of black men, and 5.6 percent of white men reported a history of hypothyroidism.

Hyperthyroidism has several causes. Graves' disease, the most common intrinsic cause, is an autoimmune disorder associated with the development of long-acting thyroid stimulating antibodies (LATS). Single or multiple thyroid nodules that produce thyroid hormones can also cause hyperthyroidism. The use of excessive doses of the thyroid hormone supplement levothyroxine is also a common cause.

*This evidence review was developed by the Evidence-based Practice Center, Oregon Health & Science University, for the Institute of Medicine and the U.S. Preventive Services Task Force and was reviewed and approved by both groups. This paper may differ slightly from the version that will be released by the Task Force.

The most common cause of hypothyroidism is thyroiditis due to antithyroid antibodies, a condition called "Hashimoto's thyroiditis." Another common cause of hypothyroidism is prior treatment for Graves' disease with surgery or radioiodine.

Consequences of untreated hyperthyroidism include atrial fibrillation, congestive heart failure, osteoporosis, and neuropsychiatric disorders. Both hyperthyroidism and hypothyroidism cause symptoms that reduce functional status and quality of life.

Subclinical thyroid dysfunction, which can be diagnosed by thyroid function tests before symptoms and complications occur, is viewed as a risk factor for developing these complications. The goal of screening is to identify and treat patients with subclinical thyroid dysfunction before they develop the complications of hyperthyroidism and hypothyroidism.

This appendix focuses on whether it is useful to order a thyroid function test in patients who have no history of thyroid disease when they are seen by a primary care clinician for other reasons. The review is intended for use by two expert panels: the United States Preventive Services Task Force, which will make recommendations regarding screening in the general adult population, and the Institute of Medicine, which will focus on the Medicare population.

Definition of Screening and Casefinding

Screening can be defined as "the application of a test to detect a potential disease or condition in a person who has no known signs or symptoms of that condition at the time the test is done."[4] By this definition, screening with thyroid function tests may identify asymptomatic individuals as well as patients who have mild, nonspecific symptoms such as cold intolerance or feeling "a little tired."

The symptoms associated with thyroid dysfunction are shown in Table B-1.[5, 6] When many of these symptoms and signs occur together, the clinician may have a strong suspicion that the patient has thyroid disease. However, patients who complain of one or two of the symptoms in Table B-1 may be no more likely to have abnormal thyroid function tests than those who have no complaints. In older patients[7] and in pregnant women, such symptoms are so common that it becomes meaningless to try to distinguish between "asymptomatic" patients and those who have symptoms that may or may not be related to thyroid status.

Studies of screening can be classified according to the setting in which the decision to screen takes place. In *casefinding,* testing for thyroid dysfunction is performed among patients who come to their physicians for unrelated reasons. When the screening test is abnormal, the patient is called back for a detailed thyroid-directed history. Studies of casefinding programs provide the most realistic estimates of the effects and costs of screening in clinic or office practice. *Population-based studies* of screening use special methods to recruit, contact, and follow patients in the context of an epidemiologic research effort. Such

TABLE B-1 Symptoms and Signs of Thyroid Dysfunction

	Hypothyroidism	Hyperthyroidism
Symptoms	Coarse, dry skin and hair	Nervousness and irritability
	Cold intolerance	Heat intolerance
	Constipation	Increased frequency of stools
	Deafness	Muscle weakness
	Diminished sweating	Increased sweating
	Physical tiredness	Fatigue
	Hoarseness	Blurred or double vision
	Paraesthesias	Erratic behavior
	Periorbital puffiness	Restlessness
		Heart palpitations
		Restless sleep
		Decrease in menstrual cycle
		Increased appetite
Signs	Slow cerebration	Distracted attention span
	Slow movement	Tremors
	Slowing of ankle jerk	Tachycardia
	Weight gain	Weight loss
	Goiter	Goiter

studies show the extent of unsuspected thyroid disease in a population sample of a particular geographic area but do not reflect the yield or costs of screening in office-based practice. Population-based studies of screening serve as a benchmark against which the yield and benefits of more practical clinic-based screening programs can be measured.

Classification of Thyroid Dysfunction

Thyroid dysfunction is a graded phenomenon and progresses from early to more advanced forms. As better biochemical tests have come into use, classification of the grades of thyroid dysfunction has changed dramatically. Historically, clinical, biochemical, and immunologic criteria have been used to classify patients with milder degrees of thyroid dysfunction.[8, 9] Today, the most common approach is to classify patients primarily according to the results of thyroid function tests (Table B-2). In this classification, "overt hypothyroidism" refers to patients who have an elevated thyroid stimulating hormone (thyrotropin or TSH) and a low thyroxine (T_4) level. "Overt hyperthyroidism" refers to patients who have a low TSH and an elevated T_4 or triiodothyronine (T_3).

The primary rationale for screening is to diagnose and treat subclinical thyroid dysfunction.[10-12] This rationale views subclinical thyroid dysfunction as a

TABLE B-2 Classification of Thyroid Dysfunction

	TSH	Thyroid Hormones
Overt hyperthyroidism	Low or undetectable	Elevated T_4 or T_3
Subclinical hyperthyroidism	Low or undetectable	Normal T_4 and T_3
Overt hypothyroidism	>5 mU/L*	Low T_4
Subclinical hypothyroidism	>5 mU/L*	Normal T_4

*Some use higher or lower values

risk factor for the later development of complications and as a condition that may have symptoms that respond to treatment. Controversy centers on whether early treatment or close follow-up is warranted in apparently healthy persons in whom the only indication of a thyroid disorder is an abnormal TSH result.

The terms "subclinical hypothyroidism" and "mild thyroid failure" refer to patients who have an elevated TSH and a normal thyroxine level (Table B-2).[12] In some classification schemes, patients who have an elevated TSH and a normal thyroxine level are subclassified according to the degree of TSH elevation and the presence of symptoms, signs, and antithyroid antibodies.[13]

In the literature, the term "subclinical hypothyroidism" has been used to describe several conditions:

1. Patients who have subclinical hypothyroidism as a result of surgery or radioiodine treatment for Graves' disease.
2. Patients who take inadequate doses of levothyroxine therapy for known thyroid disease.
3. Patients who have mildly elevated TSH levels and normal T_4 levels and nonspecific symptoms that could be due to hypothyroidism.
4. Asymptomatic patients who are found by screening to have elevated TSH and normal T_4.

The term "subclinical hyperthyroidism" is used to describe conditions characterized by a low TSH and normal levels of circulating thyroid hormones (thyroxine and triiodothyronine). Subclinical hyperthyroidism has the same causes as overt hyperthyroidism. These include excessive doses of levothyroxine, Graves' disease, multinodular goiter, and solitary thyroid nodule. Most studies of the course of subclinical hyperthyroidism concern patients whose history, physical examination, ultrasound, or thyroid scan suggests one of these causes. There are relatively few studies of patients found by screening to have a low TSH, normal T_4 and T_3 levels, and a negative thyroid evaluation, the largest group identified in a screening program.

Accuracy of Screening Tests

Screening for thyroid dysfunction can be done using a history and physical examination, antithyroid antibodies, or thyroid function tests, including various assays for TSH and T_4. Today the TSH test is usually proposed as the initial test in screening because of its ability to detect abnormalities before serum thyroxine and triiodothyronine levels are abnormal. When used to confirm suspected thyroid disease in patients referred to an endocrine specialty clinic, the sensitive TSH has a sensitivity above 98 percent and a specificity greater than 92 percent for the clinical and functional diagnosis.[14]

The accuracy of a TSH when used to screen primary care patients has been difficult to evaluate. The greatest difficulty is in classifying a patient who has an abnormal TSH, normal T_4 and T_3 levels, and no evidence supporting thyroid disease on physical examination. Those who consider the TSH to be the "gold standard" determination of disease would define such a patient as a "true positive." Others argue that patients who have an abnormal TSH but who never develop complications and never progress should be considered "false positives." They argue that these patients happen to have TSH levels outside the 95-percent reference limits for the general population but never truly had a thyroid disorder.[13]

In screening programs and in the primary care clinic, many patients found to have an abnormal TSH revert to normal over time. In one randomized trial, for example, mildly elevated TSH level reverted to normal in 8 of 19 patients given placebo.[15] In older subjects, only 59 percent (range 14 percent to 87 percent) of patients with an undetectable TSH on initial screening had an undetectable TSH level when the TSH was repeated.[16, 17] In the Framingham cohort, screening identified 41 people with an undetectable serum TSH ($\leq$ 0.1 mU/L) and a normal serum T4 level (<129 nmol/L).[18] After 4 years of follow-up, when 33 of these people were retested, 29 had higher serum TSH levels (>0.1 mU/L).

Nonthyroidal illness is an important cause of false-positive TSH test results. In a recent systematic review of screening patients admitted to acute care and geriatric hospitals, the positive predictive value of a low serum TSH (<0.1 mU/L) was 0.24, meaning that approximately one in four patients proved to have hyperthyroidism.[19] For hypothyroidism, the predictive value of a serum TSH between 6.7 and 20 mU/L was 0.06.

The predictive value of a low TSH may also be low in frail or very elderly subjects.[20-22] One retrospective study reviewed the course of 40 female nursing home residents who had a low TSH and initially normal T_4.[21] In 10 subjects (3 with low T_3 levels and 7 who died), nonthyroidal illnesses probably caused the low TSH. In 18 other women, the TSH subsequently normalized but the reason for the initially low TSH was not apparent. Only three subjects were later diagnosed to have thyroid disease as the cause of the low TSH (positive predictive value 0.075).

Prevalence

In a population that has not been screened previously, the prevalence of the disease, along with the sensitivity of the screening test and follow-up tests, determine the potential yield of screening. These factors, along with the proportion of subjects who have a screening test and comply with follow-up testing if indicated, determine the actual yield of a screening program.

More than 40 studies reported the prevalence of thyroid dysfunction in defined geographic areas, in health systems, in primary care clinics, and at health fairs.[1, 2, 23-33]

In cross-sectional, population-based studies, a serum TSH ≥ 4 mU/L in conjunction with a normal thyroxine level (subclinical hypothyroidism) is found in about 5 percent of women and in up to 3 percent of men. In an analysis of the third National Health and Nutrition Examination Survey (NHANES-III), a population-based survey of 17,353 people aged ≥ 12 or more years representing the U.S. population, subclinical hypothyroidism was defined as a serum TSH level above 4.5 mU/L and a serum T_4 ≥57.9 nmol/L.[1] Among those who did not have a history of thyroid disease, the prevalence was 5.8 percent among white, non-Hispanic females; 1.2 percent among black, non-Hispanic females; and 5.3 percent among Mexican Americans. For men, the prevalence was 3.4 percent among whites, 1.8 percent among blacks, and 2.4 percent among Mexican Americans. Older age and female sex are well-documented risk factors for subclinical hypothyroidism. In the NHANES-III survey, the overall prevalence of a serum TSH≥ 4.5 mU/L was about 2 percent at ages 30 to 49, 6 percent at ages 50 to 59, 8 percent at ages 60 to 69, and 12 percent at ages 70 to 79. In a population-based study in Whickham, England, the prevalence (serum TSH ≥ 6 mU/L and normal T_4) was 4 percent to 5 percent in women ages 18 to 44, 8 percent to 10 percent in women ages 45 to 74, and 17.4 percent in women over age 75.[34] The prevalence was 1 percent to 3 percent in men ages 18 to 65 and 6.2 percent in men over age 65.

Population factors, such as iodine intake and ethnicity, affect the prevalence of subclinical hypothyroidism, but differences among studies are also due to differences in the definition of an abnormal TSH level and ascertainment of a history of thyroid disease or levothyroxine use.

The prevalence of subclinical hyperthyroidism (a low TSH in conjunction with normal T_4 and T_3 levels) depends on how a low TSH is defined. A meta-analysis found that, when defined as an undetectable TSH level in a person with a normal free thyroxine level, the prevalence of subclinical hyperthyroidism was about 1 percent (CI, 0.4 percent to 1.7 percent) in men older than 60 years of age and 1.5 percent (CI, 0.8 percent to 2.5 percent) in women older than 60 years of age.[25] Other studies defined subclinical hyperthyroidism as a TSH below the lower limit of the normal range (about 0.4 mU/L) in a person with a normal T_4

level. When defined in this way, the prevalence of subclinical hyperthyroidism in men and women 60 years and older is as high as 12 percent.[35]

Incidence

In a population that has been screened previously, the incidence of new cases of thyroid dysfunction is the most important factor in determining the yield of a second round of screening. In a 20-year follow-up of the Whickham population, the annual incidence of overt thyroid dysfunction was 4.9 per 1,000 in women (4.1 hypothyroid and 0.8 hyperthyroid) and 0.6 per 1,000 in men (all hypothyroid).[36] In most other studies, the incidence of hyperthyroidism is lower in women (0.3 to 0.4 per 1,000) and slightly higher in men (0.01 to 0.1 per 1,000).[23]

Within a given geographic region, older age, an elevated TSH level, antithyroid antibodies, and female sex are the strongest risk factors for developing overt hypothyroidism. In the Whickham survey, for a 50-year-old woman who has a serum TSH level of 6 mU/L and positive antithyroid antibodies, the risk of developing overt hypothyroidism over 20 years was 57 percent; for a serum TSH of 9 mU/L, the risk was 71 percent.[36] A 50-year-old woman who had a normal TSH and negative antibody test had a risk of only 4 percent over 20 years. The risk of progression was not evenly distributed throughout the follow-up period. Nearly all women who developed hypothyroidism within 5 years had an initial serum TSH greater than 10 mU/L.

Exposure to ionizing radiation has also received attention as a potential risk factor for thyroid dysfunction. In general, studies of populations exposed to radioactive fallout have focused primarily on screening for thyroid cancer. A large cohort study of populations exposed to radiation from the Hanford nuclear facility provides the best quality evidence about the risk of thyroid dysfunction. The study proved definitively that exposure to radioactive fallout from Hanford conferred no additional risk of hyperthyroidism or hypothyroidism compared to unexposed populations.[37] Specifically, the study found that there was no dose-response relationship between exposure to radioactive fallout and the incidence of thyroid disease. It also found that the rate of thyroid dysfunction in the Hanford region was no higher than that reported in areas that had not been exposed.

Evidence Regarding the Complications of Subclinical Hyperthyroidism

Advocates of screening for subclinical hyperthyroidism argue that early treatment might prevent the later development of atrial fibrillation, osteoporotic fractures, and complicated overt hyperthyroidism. Other potential benefits are earlier treatment of neuropsychiatric symptoms and prevention of the long-term consequences of exposure of the heart muscle due to excessive stimulation from thyroid hormones.

Atrial Fibrillation

A good-quality cohort study in the Framingham population found that, in subjects over age 60 who did not take levothyroxine and had a low TSH, the risk of atrial fibrillation was 32 percent (CI, 14 percent to 71 percent) over 10 years.[35] The risk for subjects who had a normal TSH level was 8 percent. The patients with low serum TSH values were stratified into two groups, those with serum TSH values ≤ 0.1 mU/L and those with values of >0.1 to 0.4 mU/L; only in the former group was the risk of atrial fibrillation increased. A more recent cross-sectional study of atrial fibrillation in overt and subclinical hyperthyroidism had serious flaws and was rated as being of poor quality.[38]

The clinical consequences of atrial fibrillation in patients who have a low TSH have not been studied. In general, chronic atrial fibrillation is associated with stroke and other complications and with a higher risk of death.[39]

Mortality

A population-based, 10-year cohort study of 1,191 people age 60 or over found a higher mortality rate among patients who had a low TSH initially.[40] The excess mortality was due primarily to higher mortality from cardiovascular diseases. In this study, the recruitment strategy and the statistical adjustment for potential confounders were inadequate; patients who had a low TSH may have had a higher prevalence of other illnesses, but adjustment was done only for age and sex and not for co-morbidity. Such adjustment would be critical because acutely ill and chronically ill elderly patients have more falsely low TSH levels than relatively healthy elderly patients, presumably as a result of their illness.[19] Thus, although it is possible that patients who had a low initial TSH had higher mortality because of their thyroid disease, it is also possible that patients who were ill to begin had a low TSH as a result of their illness.

Osteoporosis and Fracture

A good-quality study from the Study of Osteoporotic Fractures (SOF) cohort found similar bone loss among women with undetectable, low, and normal TSH levels.[41] Two meta-analyses of older studies[42, 43] suggest that women who have a low TSH because they take thyroid hormones are at higher risk of developing osteoporosis. Other studies of the risk of osteoporosis concern small numbers of subjects with nodular thyroid disease or Graves' disease[44-47] rather than patients who have no obvious clinical signs of thyroid disease.

Among women in the SOF population, a history of treated hyperthyroidism is associated with an increased risk of having a hip fracture later in life.[48] A more recent nested sample of cases and controls from SOF examined the relationship between fractures and a low TSH in a broader group of women who had been

followed for 6 years.[49] The sample consisted of 148 women with hip fractures, 149 with vertebral fractures, and 304 women without fracture who were selected as controls. The subjects were classified according to their initial TSH level. Among the 148 women with hip fractures, 22 had an undetectable serum TSH (<0.1 mU/L); approximately 19 of these took thyroid hormones when their initial TSH measurement was made. At baseline, the cases were significantly older, weighed less, and were less likely to be healthy by self-report than controls. They were also twice as likely to have a history of hyperthyroidism and had lower bone density at baseline. After adjustment for all of these confounding factors, the risk of hip fracture among women who had an undetectable TSH was elevated, but the value was of borderline statistical significance (adjusted relative hazard ratio 3.6; CI, 1.0-12.9). Similarly, after adjustment for confounders, the risk of vertebral fracture among women who had an undetectable TSH was significantly elevated when compared with 235 controls (odds ratio 4.5; CI, 1.3-15.6). Among women who had a borderline low serum TSH (0.1 to 0.5 mU/L), the risk for vertebral fracture (odds ratio 2.8; CI, 1.0-8.5), but not hip fracture, was elevated.

The main weakness of this study is that the number of women with an undetectable TSH (14 with hip fracture and 14 with vertebral fracture versus 8 controls) was small relative to the number of confounders included in the analyses (6 to 7). Interactions could be important in this analysis because the relationship between the number of risk factors and the incidence of fracture is not linear. The number of important baseline differences between cases and controls raises the possibility that some of the women with low TSH levels had multiple factors and that other factors concomitant with age or socioeconomic status could also have been confounders. The study's relevance to screening is limited because 86 percent of the women who had undetectable TSH levels were taking thyroid hormones. The authors state that "thyroid hormone use was not associated with increased risk for . . . fracture," but there were not enough women with undetectable TSH levels not taking thyroid hormone to make a valid comparison.

Complicated Thyrotoxicosis and Progression to Overt Hyperthyroidism

Thyrotoxicosis can be complicated by severe cardiovascular or neuropsychiatric manifestations requiring hospitalization and urgent treatment. There are no data linking subclinical hyperthyroidism to the later development of complicated thyrotoxicosis. Such a link is unlikely to be made because (1) complicated thyrotoxicosis is rare, (2) one half of cases occur in patients with known hyperthyroidism, and (3) complications are associated with social factors, including insurance status, that may also affect access to screening and follow-up services.[50]

Progression from subclinical hyperthyroidism is well documented in patients with known thyroid disease (goiter or nodule) but not in patients found by screening to have a low TSH and no thyroid signs. Based on the sparse data from screening studies, each year 1.5 percent of women and 0 percent of men who

have a low TSH and normal T_4 and T_3 levels develop an elevated T_4 or T_3.[16, 25, 51] In one population-based study (n=2,575), 33 of 41 patients who had an initially low TSH had a serum TSH higher than 0.1 mU/L on repeat testing 4 years later.[18] Two patients developed overt hyperthyroidism during the follow-up period. In another population-based study, screening in 886 85-year-olds found 6 women and 2 men who had an undetectable TSH and were not already taking levothyroxine.[51] After 3 years of follow-up, two women were diagnosed to have hyperthyroidism: One was apparently healthy initially, while the other had atrial fibrillation on the initial examination.

Dementia

In the Rotterdam study, a population-based, longitudinal study with 2-year follow-up (to be discussed in detail), persons with reduced TSH levels at baseline had more than a threefold increase in the incidence of dementia (RR = 3.5; 95 percent CI, 1.2-10.0) and Alzheimer's disease (RR = 3.5; 95 percent CI, 1.1-11.5), after adjustment for age and sex.[52] With respect to this result, the authors stated that the results were similar "when controlling for the effects of atrial fibrillation or excluding subjects taking beta-blockers." These results are not reported; it is unclear whether they were statistically significant. Later, after presenting several other results, they state that "adjustments for education, symptoms of depression, cigarette smoking, or apolipoprotein E4 did not alter any of these findings," but it is not clear whether this statement pertains to the main result.

Symptoms and Cardiac Effects

Untreated or inadequately treated hyperthyroid patients may present with neuropsychiatric symptoms or congestive heart failure that may be responsive to treatment. In the setting of nodular thyroid disease, Graves' disease, or long-term use of suppressive doses of levothyroxine, subclinical hyperthyroidism also has been associated with cognitive abnormalities, abnormalities in cardiac contractility, and exercise intolerance.[53-58] However, the frequency of symptoms or myocardial contractility abnormalities in patients who have subclinical hyperthyroidism found by screening is not well studied, and no study has linked abnormalities in cardiac contractility or output to the development of clinically important heart failure.

Evidence Regarding Complications of Subclinical Hypothyroidism

The best studied potential complications of hypothyroidism are hyperlipidemia, atherosclerosis, symptoms, and (for subclinical disease) progression to overt hypothyroidism. In pregnancy, subclinical hypothyroidism confers additional risks to both mother and infant.

Hyperlipidemia

Overt hypothyroidism has long been known to be associated with elevated levels of cholesterol,[59] but patients in the earliest studies had very severe hypothyroidism. In more recent studies, there is a clinically important increase in total cholesterol and LDL cholesterol among men[60] and women[61, 62] with overt hypothyroidism, usually with serum TSH levels higher than 20 mU/L.

In women with milder forms of hypothyroidism, the relation between TSH and total cholesterol or LDL cholesterol is inconsistent. About one in four patients with subclinical hypothyroidism has a total cholesterol concentration higher than 6.2 mmol/L. The Whickham survey found no relationship between subclinical hypothyroidism and hyperlipidemia. Recent cross-sectional, population-based studies of the relation between TSH and lipid levels in women have had mixed results. In the Rotterdam study[33] (discussed in detail below), lipid levels were significantly *lower* among women with subclinical hypothyroidism than among euthyroid women. A fair-quality study of randomly selected Medicare recipients found no differences in total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides between subjects who had a serum TSH <4.6 (n=684) and those who had a serum TSH between 4.7 and 10 (n=105). There were nonsignificant increases in LDL cholesterol and HDL cholesterol among women who had a serum TSH >10 (LDL cholesterol 143 versus 128 in euthyroid women, p=0.08; HDL cholesterol 41.6 versus 47.5, p=0.053).[31]

Conversely, a cross-sectional, population-based study from the Netherlands found that the prevalence of subclinical hypothyroidism was correlated with lipid levels; the prevalence was 4 percent among women with a total cholesterol level < 5 mmol/l; 8.5 percent when total cholesterol was 5 to 8 mmol/l; and 10.3 percent when total cholesterol was >8 mmol/L.[63] Another recent cross-sectional study of 279 women over age 65 found a strong relationship between hyperlipidemia and serum TSH levels.[64] Of the 279 women, 19 (6.8 percent) had a serum TSH >5.5 mU/L. After adjustment for age, weight, and estrogen use, women who had a serum TSH >5.5 mU/L had 13 percent higher LDL cholesterol (95 percent CI, 1 percent to 25 percent) and 13 percent lower HDL cholesterol (CI, -25 percent to 0 percent) than women with a normal serum TSH (0.1 to 5.5 mU/L). However, 2 of the 19 women who had an elevated TSH used thyroxine, suggesting they had inadequately treated overt hypothyroidism. Because T_4 and T_3 levels were not measured, it is possible that others in this group had overt hypothyroidism as well. Moreover, only 1 of the 19 women (6 percent) took estrogen replacement therapy, whereas 32 of 250 women in the euthyroid group used estrogen. The analysis adjusted for estrogen use but not for other factors, such as socioeconomic status, that are associated with lipid levels and are also known to be associated with estrogen use.

Men with a mildly elevated TSH generally do not have an increased risk of hyperlipidemia, but data on men are sparse. Hypercholesterolemic men do not

have a higher prevalence of subclinical hypothyroidism than men with low lipid levels.[63]

Another cross-sectional study of 2,799 adults ages 70 to 79 illustrates some of the difficulties in determining whether subclinical hypothyroidism is associated with hypercholesterolemia, especially in men.[3] For the entire group, a serum TSH >5.5 mU/L was associated with a 9 mg/dL (0.23 mmol/L) higher total cholesterol after adjustment for age, sex, race, body mass index, current smoking, alcohol use, estrogen use, and diabetes. Among men, the association was statistically significant for a cutoff serum TSH ≥ 7.0 mU/L but not for a serum TSH ≥ 5.5 mU/L. About 23 percent of white subjects and 14 percent of black subjects took lipid-lowering medication and a substantial proportion took thyroid hormones (e.g., 18 percent of white women, 6.1 percent of white men). Among subjects taking thyroid hormones but not lipid-lowering medication, a serum TSH ≥5.5 mU/L was associated with a 15 mg/dL higher total cholesterol. However, the results for subjects not taking either medication were not reported.

Atherosclerosis

The relationship of subclinical hypothyroidism to the later development of atherosclerosis is unclear.[31, 33, 65] The Whickham survey found no relationship between initial TSH levels and the subsequent development of ischemic heart disease over 20 years of follow-up.[65]

A widely publicized population-based study of 1,149 women age 55 or older from Rotterdam came to a different conclusion.[33] The main analysis in the paper was cross-sectional. In that analysis, after adjustment for age, body mass index, cholesterol level, blood pressure, and smoking status, a serum TSH >4.0 mU/L was associated with a history of myocardial infarction (odds ratio 2.3; CI, 1.3 to 4.2) and with atherosclerosis of the abdominal aorta, diagnosed by blinded review of a lateral radiograph of the lumbar spine (odds ratio 1.9; CI, 1.2 to 3.1). An analysis of incident myocardial infarction over 3 to 6 years of follow-up found a statistically nonsignificant increased risk in women with a serum TSH >4.0 mU/L (adjusted relative risk 2.5; CI, 0.7 to 9.1).

The strengths of the Rotterdam study are the relatively large sample size, adjustment for some potential confounders, and validated, blinded assessment of outcomes. Because the study was primarily cross-sectional, however, the findings do not prove that an elevated TSH precedes the development of atherosclerosis. The prospective part of the study adds little because, at baseline, the women who had an elevated TSH had a higher prevalence of atherosclerotic disease; they would be expected to have a higher incidence of myocardial infarction over 3 to 6 years in any case. The prospective analysis would have been more consequential if subjects who had atherosclerosis at baseline were excluded. In contrast, the long follow-up period in the Whickham study reduces the chance that baseline differences in the prevalence of coronary disease affected the results. None of the

cross-sectional studies adequately adjusted for several factors that may influence rates of cardiovascular disease, such as socioeconomic status, diet, diabetes, estrogen use, and other health practices. The relation of these factors to the development of subclinical hypothyroidism has not been well studied, so it is possible one or more of them are confounders.

In the Rotterdam study, women with subclinical hypothyroidism had lower lipid levels than euthyroid women; this might be an artifact of higher use of diet or other lipid-lowering therapy in women with known cardiovascular risk factors, but it also might suggest that atherosclerosis developed by another mechanism. One hypothesis is that elevations in both homocysteine and cholesterol may contribute to the elevated risk of atherosclerosis in overt hypothyroidism. In cross-sectional studies, including an analysis of the second National Health and Nutrition Examination Survey (NHANES-II) sample, patients who had overt hypothyroidism had higher homocysteine levels than euthyroid subjects.[66, 67] Although no single study has adjusted statistically for all potential confounders, the association of elevated homocysteine and hypothyroidism appears to persist after controlling for serum folate levels, which are decreased in hypothyroidism.[66-70] In overtly hypothyroid patients, homocysteine levels decreased after treatment with levothyroxine in small, observational studies.[69-73] The association of homocysteine levels with *subclinical* hypothyroidism has not yet been established.

Symptoms, Mood, and Quality of Life

In its 1998 review and guideline, the American College of Physicians concluded that, in the general population, it was not clear that the prevalence and severity of symptoms and the quality of life differs for individuals who have mildly elevated TSH levels.[7, 74] Since then, two cross-sectional studies in volunteers have addressed this question, with mixed results. A cross-sectional interview survey of 825 Medicare enrollees in New Mexico found no differences in the age-adjusted frequency of self-reported symptoms between participants with serum TSH elevations from 4.7 to 10 mU/L and those with normal TSH concentrations.[31] A larger survey from Colorado (n=25,862) is less pertinent because it included subjects who took levothyroxine in the analysis of symptoms. It also found no difference between euthyroid subjects and those with subclinical hypothyroidism in current symptoms but found a higher percentage of "changed symptoms" in the subclinical hypothyroid group (13.4 percent versus 15.4 percent).[2]

Patients who have subclinical hypothyroidism and a history of antithyroid treatment for Graves' disease or nodular thyroid disease have a higher prevalence of symptoms than healthy controls.[75, 76] This observation is likely to be valid, but an important limitation of the evidence should be noted: The appropriate comparison group is not healthy volunteers but patients who have a normal TSH and a history of antithyroid treatment. The reason is that euthyroid patients who have

a history of treatment for hyperthyroidism also have a higher prevalence of anxiety, depression, and psychosocial dysfunction than healthy controls.[77]

Prior Recommendations

In 1996 the United States Preventive Services Task Force recommended against routine screening for thyroid disease in asymptomatic adults (D recommendation).[81] They found insufficient evidence to recommend for or against routine screening with thyroid function tests in the elderly but recommended screening based on the higher prevalence of disease and the increased likelihood that symptoms of thyroid disease will be overlooked (C recommendation). At that time, two randomized trials of treatment for subclinical hypothyroidism had been done. The Task Force found that one of them[75] was not relevant to screening because the subjects had a known history of thyroid disease. They found the other trial to be methodologically flawed.[74] There were no trials of treatment for subclinical hyperthyroidism.

Analytic Framework and Key Questions

In this appendix we address whether the primary care physician should screen for thyroid function in patients seen in general medical practice who have no specific indication for thyroid testing and who come to the physician for other reasons. We focus on whether screening should be aimed at detection of subclinical thyroid dysfunction and whether individuals who have mildly abnormal TSH values can benefit.

We used the analytic framework shown in Figure B-1 to guide the literature review. The population of interest was adults who are seeing a primary care clinician, have no history of thyroid disease, and have no or few signs or symptoms of thyroid dysfunction.

Arrows 2 and 3 represent the ability of screening to detect unsuspected thyroid dysfunction, the false-positive rate of the screening tests, and the symptom status of the patients diagnosed by screening. These issues, summarized above, were reviewed in detail elsewhere.[14, 25] In this appendix, we address key questions related to Arrows 4 and 5, focusing primarily on evidence about the benefits and harms of treating early thyroid dysfunction. Specifically, we addressed

Arrow 4. What are the benefits of earlier treatment of subclinical hyperthyroidism and hypothyroidism?

Arrow 5. What are the adverse effects of treatment?

A thorough review of the adverse effects of antithyroid drugs, radioiodine therapy, thyroid surgery, and thyroid replacement therapy was beyond the scope of this review. Instead, we emphasize the frequency of adverse effects in trials of levothyroxine therapy for subclinical hypothyroidism and the potential adverse effects of long-term treatment with levothyroxine.

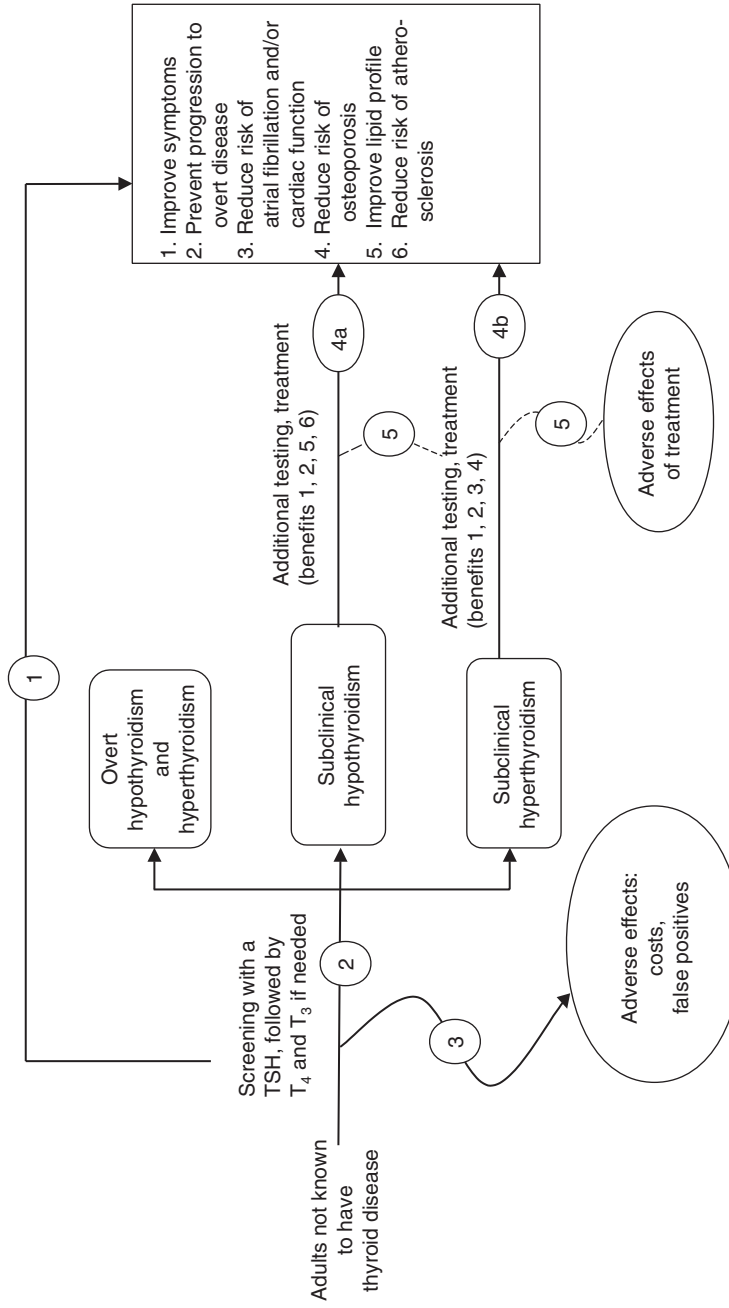

FIGURE B-1 Screening with thyroid function tests analytic framework

METHODS

Search Strategy

We identified articles published before 1998 from the reference lists of previous reviews[9, 12, 13, 23, 24, 76, 82-87] and by searching our own files of more than 1,600 full-text articles from the period 1910 to 1998. We then searched MEDLINE and EMBASE from 1996 to February 2002, PREMEDLINE for March 2002, and the Cochrane Library (2002, Issue 2) to identify additional articles. In a MEDLINE search, the medical subject headings (MeSH) *thyroid function tests* and *thyroid diseases* were combined with the term *mass screening* and the text words *screening* or *casefinding*. We conducted a separate search for controlled studies of the effect of thyroid-directed treatments on potential complications of subclinical thyroid disease, using the word *levothyroxine* in title, abstract, or keywords combined with terms for clinical trials. We also searched MEDLINE from 1966 to May 2002 for articles about the adverse effects of thyroid hormone replacement. Periodic hand searching of endocrinologic and major medical journals, review of the reference lists of retrieved articles, and suggestions from peer reviewers of earlier versions of this appendix supplemented the electronic searches.

Inclusion Criteria

We selected controlled trials of treatment of thyroid dysfunction that reported at least one health outcome (symptoms, cognitive function, or quality of life) or lipid levels. Broad inclusion criteria were used to get a picture of the benefits and adverse effects of treatment on patients with different degrees of thyroid dysfunction. Specifically, we included any trial that used TSH levels as a criterion for entry, in any population, including patients with known thyroid disease. We also identified observational studies of treatment for subclinical thyroid dysfunction; we included recent ones that had not been included in previous meta-analyses.[13, 24, 25, 88]

To assess the prevalence of thyroid disease and the causal relationships between thyroid dysfunction and potential complications, we used the following sources:

- Previous meta-analyses and systematic reviews.
- More recent cross-sectional, cohort, and case control studies of the prevalence of overt or subclinical thyroid dysfunction.
- Cross-sectional and longitudinal studies of the relationship between an elevated or low TSH to potential complications of subclinical hypothyroidism or subclinical hyperthyroidism.

For these categories of studies, we included studies in the general adult population, in a demographic segment of the adult population, or among patients seen in the general clinic setting. We excluded studies of screening for congenital or familial thyroid disorders and studies of screening in inpatients, institutionalized patients, and series of patients seen in specialized referral clinics for depression or obesity.

Finally, we identified observational studies of the long-term adverse effects of levothyroxine therapy. We excluded studies of suppressive doses of thyroxine; to be included, the study had to include at least some patients taking replacement doses of thyroxine.

Data Extraction

We used predefined criteria from the Task Force to assess the internal validity of trials, which we rated as "good," "fair," or "poor." We also rated the applicability of each study to screening. The rating system is described in detail elsewhere.[89] (The criteria are listed as column headings in Table B-3.) We also abstracted information about its setting, patients, interventions, and outcomes. When possible we recorded the difference between the probability of a response in the treatment and control groups for each complication studied.

RESULTS

Efficacy of Treatment for Subclinical Hyperthyroidism

No controlled trials of treatment for subclinical hyperthyroidism have been done. Small observational studies of patients with nodular thyroid disease not detected by screening have shown improvements in bone metabolism and hemodynamic measures after treatment.[53, 90-92]

Efficacy of Treatment for Subclinical Hypothyroidism

We identified 14 randomized trials of levothyroxine therapy. We excluded two trials that compared levothyroxine to levothyroxine plus triiodothyronine in patients with overt hypothyroidism,[93, 94] one trial of different levothyroxine preparations,[95] and one of levothyroxine suppressive therapy for solitary nodules.[96] Two trials of levothyroxine treatment in patients with subclinical hypothyroidism reported no clinical outcomes or lipid results; one of these concerned bone density[97] and the other, cardiac function parameters from Doppler echocardiography and videodensitometric analysis.[98] These trials are not included in evidence tables but are discussed briefly.

Of the eight included trials,[15, 74, 75, 99-103] six concerned patients with elevated TSH levels. One concerned hyperlipidemic patients with high-normal TSH levels,[99]

TABLE B-3 Quality of Randomized Trials of Thyroxine Replacement Therapy

Study and Year	Random Assignment?	Allocation Concealed?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Blinded?	Care Provider Blinded?
Cooper, 1984	Yes, by individual	Not stated	LT_4 subjects were older (58.2 vs.50.2) and had fewer symptoms (2.1 vs. 2.4), but otherwise similar	Yes	Probably; one investigator was not blinded; article states "patients were questioned in a blinded manner by one of the investigators," but doesn't say which investigator.	
Meier, 2001	Sequential assignment using a predefined list; randomized by matched pairs	No	LT_4 subjects had higher TSH (14.4±1.7 vs. 11.3±1.0) and LDLc (4.1 vs. 3.7), but groups were otherwise similar for the whole groups (n=66); comparisons were not presented for the analyzed group (n=63).	Yes	Not stated	Yes
Caraccio, 2002	Yes, by individual	Not stated	Generally yes, but mean TSH (6 vs. 4.9) and LDLc (3.6 vs. 3.3) were higher in LT_4 group.	Yes	No	No

Patient Unaware of Treatment?	Intention-to-Treat Analysis?	Maintenance of Comparable Groups?	Reporting of Attrition, Crossovers, Adherence, and Contamination?	Differential Loss to Follow-up or Overall High Loss to Follow-up?	Statistical Analysis Appropriate?	Score (Good/ Fair/ Poor)
Yes-not verified	No	The number of patients randomized appears to be 41; 33 patients were analyzed; it is not clear to which group the other 8 belonged.	Partially	Unclear, probably not	Yes, except it did not address dropouts.	Good
Yes—not verified	No	Yes	No	No	No—analyzed as RCT, but reported primarily as a before/after study	Poor
Probably were aware because dosing and length of follow-up differed; not clear whether patients were informed of their lipid levels	Yes, assuming that completion of study was not a criterion for inclusion		No	No	Yes (when analyzed as an RCT)	Poor

continued

TABLE B-3 Continued

Study and Year	Random Assignment?	Allocation Concealed?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Blinded?	Care Provider Blinded?
Jaeschke, 1996	Yes, by individual	Not stated	LT_4 subjects had higher TSH (12.1 vs. 9.4) and slightly more symptoms (14 vs. 13), but similar in age.	Yes	Yes; one investigator was not blinded but was not involved in assessment or care.	
Kong, 2002	Yes, in blocks of 6	Yes	LT_4 subjects were older (53 vs. 45 years), had lower FT_4 (.9 vs. 1), and higher TSH (8 vs. 7.3).	Yes	Yes; one investigator was not blinded, but was not involved in assessment or care.	
Nystrom, 1988	Not stated	Not stated	No baseline data were given for the groups initially assigned LT_4 and placebo.	Yes	Yes	Yes
Michal - opoulou, 1998	Yes, method not stated	Not stated	Inadequately described; LDL was higher in 50 mg group (6.8 vs. 6.2).	Yes	Not stated	Not stated
Pollack, 2001	Yes, by coin toss in blocks of 4	No	No baseline data were given for the groups initially assigned LT_4 and placebo.	Yes	Not stated	Yes

Patient Unaware of Treatment?	Intention-to-Treat Analysis?	Maintenance of Comparable Groups?	Reporting of Attrition, Crossovers, Adherence, and Contamination?	Differential Loss to Follow-up or Overall High Loss to Follow-up?	Statistical Analysis Appropriate?	Score (Good/ Fair/ Poor)
Yes—not verified	No	Probably, 3 dropouts in each group	Partially	Overall 6 out of 40 dropped out	Yes, except it did not address dropouts.	Fair
Yes—not verified	No	Unknown	Yes	Yes, especially for lipid comparison	Yes, except it did not address dropouts.	Poor
Probably aware—verified	No	Yes	No	No	No—no baseline comparisons or results provided about the first assignment	Poor
Not stated	Probably yes	Yes	No	No	No—analyzed as before/after	Poor
Yes—verified	No	Probably, but all 3 dropouts were from the LT_4 group	No	No	Yes	Fair

and the last trial concerned patients with a normal TSH who had symptoms of hypothyroidism.[101]

Randomized trials of levothyroxine treatment in subclinical hypothyroidism and in symptomatic patients who have a normal TSH are described in Table B-3 (quality ratings) and in Tables B-4A through B-4C (description and results). The first two trials listed in the tables concerned patients followed in thyroid specialty clinics. In both trials subjects had a mean serum TSH above 10 mU/L. The first trial (Cooper) concerned patients who had been treated for Graves' disease in whom TSH was rising relatively quickly.[75] Symptoms were rated on the "Cooper Questionnaire," a 24-point scale that records how six symptoms of hypothyroidism change over time. After 1 year, patients taking levothyroxine improved by 2.1 points, while patients taking placebo deteriorated by 1.2 points (p=0.037). The difference (3.3 points) is roughly equivalent to complete relief of one symptom and partial relief of a second symptom per patient. Eight (47 percent) of 17 treated patients reported reduced or milder symptoms; 4 felt worse; and 5 reported no change in symptoms. In the placebo group, 3 (19 percent) of 16 patients felt better, 6 felt worse, and 7 reported no change. The difference between the proportion of patients who felt better in each group was 0.28 (CI, -0.09 to 0.65), indicating that the Number Needed to Treat to benefit one patient is 3.5.[75] Treatment had no effect on lipid levels. The internal validity of this trial was rated "good quality"; it was the highest quality trial of the group.

The second trial (Meier) concerned patients with thyroiditis or a history of Graves' disease.[100] In this trial, treatment with levothyroxine had no effect on symptoms. In reporting results, the authors emphasized that there was a significant reduction in LDL cholesterol in the levothyroxine-treated group, from 4.0 to 3.7 mmol/L (p=0.004), and no significant reduction in the placebo group. The difference appears to be related to an imbalance in the groups at baseline: pretreatment LDL cholesterol was 4.0 mmol/L in the treatment group versus 3.7 mmol/L in the placebo group. In fact, posttreatment LDL cholesterol was the same in both groups (3.7±0.2, p=0.11). When analyzed as a randomized trial, the difference between the treatment and control groups in lipid levels was not significant. The discrepancy suggests that randomization may have been flawed.

We rated the relevance of these two studies to screening to be "low." The Cooper study supports treatment in patients with a history of treated Graves' disease, especially if the serum TSH is above 10 mU/L, but it has little relevance to screening because the natural history of treated Graves' disease differs from the natural history of spontaneous hypothyroidism in the general population.

The third trial, in patients known to have Hashimoto's thyroiditis and positive antithyroid antibodies who had mildly elevated TSH levels, had a similar flaw.[102] When analyzed as a randomized trial, there were no significant differences between levothyroxine-treated and placebo groups in any lipid parameter. When analyzed as a pre-/post-treatment study, there was a statistically significant reduction in LDL cholesterol levels (3.6 to 3.1 mmol/L) in the levothyroxine-

treated group but not in the control group. The study appeared to be unblinded; this could be a major flaw because differential attention to lipid levels in the treatment and control groups could lead to different behavioral approaches to reducing lipid levels. If the results are valid, they would be fairly relevant to screening; the mean TSH was only slightly elevated, and patients who have antithyroid antibodies and a modestly elevated TSH are found commonly in screening programs.

The next three studies may have had more relevance to screening or primary care. They generally concerned patients, mostly women, with subclinical hypothyroidism who were not previously treated for Graves' disease or nodular thyroid disease. However, two of the three studies had poor internal validity. In the fair-quality trial by Jaeschke and colleagues, 37 patients with subclinical hypothyroidism were recruited from the outpatient clinics of a community hospital and randomized to levothyroxine treatment or placebo.[15] Patients given placebo did as well as or better than those given levothyroxine. After 6 months, in the levothyroxine group, eight patients improved, three were worse, and five were the same according to the "Cooper Questionnaire." In the placebo group, 11 patients improved, 1 was worse, and 4 were the same. After 11 months, patients treated with levothyroxine had a small but statistically significant improvement in short-term memory, but treatment did not improve general health status as measured by a standardized questionnaire, the Sickness Impact Profile (SIP). In that study, the mean SIP score in patients with subclinical hypothyroidism recruited from a general medical clinic was initially 3.1 out of 100. On this scale, a score of 3.0 is usually interpreted as the border between no disability and mild disability. A random sample of healthy older adults had a similar mean SIP of 3.4.

The other negative trial was too small to achieve balance in the compared groups and had high loss to follow-up.[103]

A small crossover trial[74] concerned women identified by screening in the general population. The 20 subjects were women over age 50 who had an initial serum TSH between 4 and 15 mU/L. After 6 months of treatment, the mean symptom score improved by 1.81 units, equivalent to complete relief of one symptom per patient. As judged by subjective improvement and cognitive measures, 4 (24 percent) of the 19 patients who received levothyroxine improved, while 2 (12 percent) felt worse with treatment.

The last two studies listed in Table B-4 concern patients who have TSH levels in the normal range. In one of these, 50 micrograms of levothyroxine therapy reduced LDL cholesterol levels from 6.8 to 5.9 mmol/L in patients with elevated total cholesterol levels (>7.5 mmol/L) and normal TSH levels.[99] In the other trial, levothyroxine was ineffective in patients who had symptoms of hypothyroidism but normal TSH and T_4 levels.[101] The latter trial, designed as a crossover study, found that levothyroxine significantly reduced SF-36 vitality score compared to placebo, whereas placebo improved SF-36 general health and physical well-being scores significantly.

TABLE B-4A Description and Results of Randomized Trials of Thyroxine Replacement Therapy

Study and Year	Study Design	Patients	Setting
Known history of thyroid disease			
Cooper, 1984	Randomized, double-blind, placebo-controlled trial	Previously treated Graves' disease, stage c subclinical hypothyroidism	Thyroid specialty clinic, Boston
Meier, 2001	Double-blind, placebo-controlled trial	Autoimmune thyroiditis (n=33), previously treated Graves' disease (n=22), previously treated goiter (7)	Thyroid specialty clinic, Switzerland
Caraccio, 2002	Unblinded, placebo-controlled, randomized trial	Hashimoto's thyroiditis (48) or Graves' disease (1)	Medical school internal medicine clinic, Italy
No known history or not stated			
Jaeschke, 1996	Randomized, double-blind, placebo-controlled trial	Diagnosis of subclinical hypothyroidism	Unclear setting, Ontario
Kong 2002	Randomized, double-blind placebo-controlled trial	Women with a diagnosis of subclinical hypothyroidism	Referrals from GPs for thyroid function tests, London
Nystrom 1988	Randomized, double-blind placebo controlled crossover trial	Women identified by screening	Population-based screening study, Gothenburg
Biochemically euthyroid patients			
Michalopoulou, 1998	Randomized trial with active control group	Patients referred for lipid assessment	Preventive medicine (lipid) hospital-based clinic, Greece
Pollack, 2001	Double-blind, placebo-controlled, randomized crossover trial	Symptomatic patients with normal TSH and T_4	Referrals from GPs, hospital clinic, and response to newspaper ad, Glasgow

Age and Gender	Eligibility Criteria	Other Population Characteristics
32 women and 1 man, mean age 55 years	TSH >3.5 mU/L on 2 occasions	History of Graves' disease
63 women, mean age 58.5±1.3 years	Women 18-75 years; TSH >6.0 mU/L on 2 occasions; exaggerated TSH response to TRH; good general health	History of autoimmune thyroiditis (n=33), Graves' disease (n=22), goiter (n=7); only 4 had idiopathic subclinical hypothyroidism.
42 premenopausal women, 7 men	TSH >3.6 mU/L for >6 months, + atP and anti-Tg, good general health	SCH patients had higher TC, LDL, and ApoB levels than healthy controls.
28 women and 9 men over age 55, mean age 68 years	TSH >6 mU/L on 2 occasions	
45 women, mean age ~49 years	Women over 18 years; 5<TSH<10 mU/L	Most patients were referred because of symptoms.
20 women, aged 51-73	Women over 18 years; 4<TSH<15 mU/L, exaggerated TSH response to TRH	Symptoms did not differ between subjects and healthy controls.
Not stated	TC >7.5 mmol/L and TSH 0.4-4.0 mU/L	
25 symptomatic and 19 asymptomatic subjects, sex and age not given	a) at least 3 symptoms of hypothyroidism (tiredness, lethargy, weight gain, or 3 others) or (b) no symptoms	Symptomatic subjects weighed more and had worse memory and psychological function than healthy controls.

TABLE B-4B Description and Results of Randomized Trials of Thyroxine Replacement Therapy

Study and Year	Exclusion Criteria	Funding Sources and Role of Funder	Interventions (Dose, Duration)
Known history of thyroid disease			
Cooper, 1984	None stated	U.S. PHS (Armour supplied LT_4)	LT_4 50 micrograms then titrated up
Meier, 2001	Coronary heart disease, lipid-lowering drugs, history of poor compliance (estrogen therapy allowed)	Swiss Research Foundation, Henning Berlin, Sandoz, Roche	LT_4 titrated over 6 months (mean final dose 85.5 ±4.3), with similar visits and changes in control group. Total follow-up 50 weeks
Caraccio 2002	Diabetes, renal or liver disease, TC>7.8 mmol/L	Grant from university	LT_4 25 then titrated up
No known history or not stated			
Jaeschke, 1996	Medications that interfere with TFTs; serious medical conditions	Ontario Ministry of Health, Boots Pharmaceuticals	LT_4 25 then titrated up (mean final dose 68±21)
Kong, 2002	History of thyroid disease, psychiatric disorder, anticipated pregnancy	Medical Research Council	LT_4 50 then titrated up to 100 if TSH >6 mU/L
Nystrom, 1988	History or signs of thyroid disease, history of cardiovascular disease	Nonindustry grants (Nyegaard supplied LT_4)	LT_4 50 for 2 weeks, then 100 mg for 2 wks, then 150 daily
Biochemically euthyroid patients			
Michalopoulou, 1998	Conditions and medications that affect lipid profiles		LT_4 50
Pollack, 2001	Current medical disorders	Association of Clinical Biochemists	LT_4 100

Control	Baseline TSH	Number Screened/ Eligible/Enrolled	Number Withdrawn/Analyzed
Placebo	11 (mean); 3.6-55 (range); mean TSH in control group increased to ~15 by the end of the study	656/91/41	8/33
Placebo	12.8 (mean); 5-50 (range)	NR/NR/66	3/63
Placebo	5.43 (mean) 3.65-15 (range)	NR/NR/49	0/49
Placebo	9.4 (mean); 6-32 (range)	NR/NR/37	6/31
Placebo	~7.7 (mean)	NR/52/45	10/34 (for quality of life); 18/27 for lipids
Placebo	~7.7 (mean); 2.9-16.3 (range)	1,192/22/20	3/17
LT_4 25 mg	stratified 1.0 (mean) or ~2.6 (mean)	NR/NR/110	0/110
Placebo	1.9 (mean)	NR/NR/25*	3/22

TABLE B-4C Description and Results of Randomized Trials of Thyroxine Replacement Therapy

Study and Year	Outcomes Assessed/When Assessed	How Outcomes Assessed (e.g., Scales Used)
Known history of thyroid disease		
Cooper, 1984	Symptoms, lipid profile at 1 year	Symptom change scores ("Cooper questionnaire")
Meier, 2001	Symptoms, lipid profile at 1 year	Thyroid symptom questionnaire
Caraccio, 2002	Lipid profile at 6 months for placebo group vs. about 11 months for LT_4 group	Biochemical tests
No known history or not stated		
Jaeschke, 1996	Quality of life, symptoms, lipid profile at 6 months	Chronic Thyroid Questionnaire, Cooper questionnaire, SIP, cognitive tests
Kong, 2002	Quality of life, symptoms, lipid profile at 6 months	Thyroid symptom questionnaire, GHQ-30, HADS
Nystrom, 1988	Quality of life, symptoms, psychometric tests, vital signs, ECG, lipid profile at 6 months	Thyroid symptom questionnaire, reaction time, Bingley's memory test
Biochemically euthyroid patients		
Michalopoulou, 1998	Lipid profile	
Pollack, 2001	Symptoms, vital signs, biochemical tests after 14 weeks	SF-36 plus validated cognitive/ memory testing

Many observational studies have examined the effects of treatment in patients with subclinical hypothyroidism. One meta-analysis of these observational studies found that treatment reduced LDL cholesterol levels by 0.4 mmol/L and a more recent meta-analysis of both observational and randomized studies found that, in previously untreated patients, total cholesterol was reduced by 0.14 mmol/L (-5.6 mg/dL).[104] Another review concluded that levothyroxine treatment might

LT_4 vs. Placebo Group Results	Before/After Results
Improved symptoms (-1.2 vs. +2.1) in LT_4 group. 47% improved in LT_4 group vs. 19% in placebo group (NNT=3.6); No difference in lipid profiles	Placebo group's TSH and symptoms rose during the year, suggesting the patients had rapidly advancing subclinical hypothyroidism
Post-treatment LDLc was the same in both groups (3.7±0.2, p=0.11), and symptoms scores were not significantly different (p=.53)	LDLc reduced from 4.0 to 3.7 in the LT_4 group (p=0.004) and there were borderline improvements in symptom scores (p=0.02); Placebo group TSH was stable
There were no significant differences between LT_4 and placebo groups in any lipid parameter	LT_4 group: TC reduced from 5.5 to 5.0; LDLc from 3.6 to 3.1
No improvement in symptoms or lipids; improved memory in LT_4 group (mean difference of .58 on z score scale, described as "small and of questionable clinical importance")	Placebo group's TSH rose from 9.42 to 10.32 over 6 months
No improvement in symptoms or lipids	Placebo group's TSH dropped from 7.3 to 5.6 over 6 months
No difference in lipids; in before/after comparisons, symptom scores improved by the equivalent of 1 symptom per subject (p<0.001), and 4 patients felt better with LT_4 than with placebo	
LDL reduced from 6.2 to 6.1 in 25 mg group and from 6.8 to 5.9 in 50 mg group	LDLc reduction was significant in 50 mg group
Among symptomatic patients (n=22), there were no important differences between LT_4 and placebo groups in any SF-36, memory, or cognitive measures	Placebo significantly improved SF-36 general health and physical health scores

reduce serum cholesterol by 8 percent in selected patients who have both a serum TSH >10 mU/L and an elevated total cholesterol (>6.2 mmol/L). About 7 percent of individuals with subclinical hypothyroidism meet these criteria.

Most of the studies on which these analyses are based have important limitations.[13, 25, 104] Many of these studies were before/after studies in which reductions in serum lipids could have been due to regression toward the mean. In most,

samples were small, selection of patients was poorly described, clinicians and patients were aware of the treatment and of the need to lower lipid levels, and outcome assessment may have been biased. That is, the problem is not that these studies are observational but that many of them are poor-quality observational studies.

The hazards of relying on observational studies of the effect of drug therapy is illustrated by a large (n=139) open study of levothyroxine to treat symptoms of hypothyroidism in patients who had normal thyroid function tests. This study found that the mean number of signs and symptoms of hypothyroidism decreased from 13 to 3 following 6 months or more of treatment; 76 percent of patients had improvement or disappearance of more than 12 findings.[105] Whether or not these effects are real,* they illustrate that only well-controlled trials can determine the effects of thyroxine therapy in patients with subclinical hypothyroidism.

In summary, treatment of subclinical hypothyroidism appears to reduce symptoms in the subset of patients who have a history of Graves' disease and a serum TSH >10 mU/L. In other subgroups of patients with subclinical hypothyroidism, there is insufficient evidence to determine whether or not treatment is effective in reducing symptoms. Most trials found tno effect on lipid levels but, because of the number of subjects and the limited quality of the trials, the evidence from randomized trials is insufficient to determine whether treatment has a clinically important effect. No trials of treatment for subclinical hypothyroidism in pregnant patients were identified.

Other Benefits

One randomized trial of levothyroxine versus placebo used Doppler echocardiography and videodensitometric analysis to assess myocardial structure and parameters of myocardial contractility in 20 patients followed for 1 year.[98] We excluded this trial because it did not report any clinical outcome measures.

Another benefit of treating subclinical hypothyroidism is to prevent the spontaneous development of overt hypothyroidism, diagnosed when a patient with subclinical hypothyroidism develops a low free thyroxine (FT_4) level (see Table B-2). This potential benefit has not been studied in randomized trials, so it is necessary to estimate it based on data from observational studies. Based on data from the Whickham study, a previous analysis estimated that if 1,000 women age 35 and over are screened, 80 will be diagnosed to have subclinical hypothyroidism; 43 of these will have a mildly elevated TSH and positive antithyroid antibodies. If these 43 individuals were treated with levothyroxine, by 5 years overt hypothyroidism would be prevented in 3 women (NNT=14.3), while 40

*A subsequent randomized trial was negative (see Table B-3), but it was too small to exclude a clinically significant effect.

will have taken medication for 5 years without a clear benefit. By 20 years, overt hypothyroidism would be prevented in 29 (67 percent) of the 43 women, but 14 otherwise healthy women will have taken medication for 20 years.

In assessing the balance of benefits and harms, the key uncertainties are the following questions: (1) Without screening or prophylaxis, how long would overt hypothyroidism be undetected? (2) How much morbidity would undiagnosed overt hypothyroidism cause while undetected? (3) What are the harms of treatment in those who do not progress? No studies have measured the severity of symptoms or degree of disability in newly hypothyroid patients or the length of time spent in that state. There are no published data on the effect of careful follow-up on health outcomes in patients with subclinical hypothyroidism. The case for treatment to prevent progression of subclinical hypothyroidism would be greatly strengthened by data showing that this progression is associated with significant burden of illness that could be prevented by earlier treatment.

Adverse Effects of Levothyroxine

Adverse effects of replacement doses of levothyroxine include nervousness, palpitations, atrial fibrillation, and exacerbation of angina pectoris. Adverse effects were not assessed carefully in the randomized trials listed in Table B-4A, although some studies reported them incidentally. In one of the trials, 2 of 20 (10 percent) patients taking levothyroxine quit the protocol because of nervousness and a sense of palpitations.[74] In another, 2 of the 18 (11 percent) patients assigned to levothyroxine withdrew because of complications: one because of an increase in angina, and one because of new-onset atrial fibrillation.[15] In a third, anxiety scores were higher in the levothyroxine group.[103]

A systematic review of observational studies published from 1966 to 1997 found that replacement doses of levothyroxine have not been associated with osteoporosis or with any other serious long-term adverse effects.[106] A short-term randomized trial of levothyroxine for subclinical hypothyroidism confirms this view.[97] By contrast, thyroid hormone to suppress TSH because of thyroid cancer, goiters, or nodules contributed to osteoporosis in postmenopausal women.[106]

Overtreatment with levothyroxine, indicated by an undetectable TSH, is another potential risk. About one-fourth of patients receiving levothyroxine for primary hypothyroidism are maintained unintentionally on doses sufficient to cause the TSH to be below normal.[2, 35] Data from the Framingham cohort suggest that one excess case of atrial fibrillation might occur for every 114 patients treated with doses of levothyroxine sufficient to suppress the TSH.[35] As mentioned above, two meta-analyses of older studies and a recent nested case control study from SOF suggest that, in patients taking levothyroxine, a low TSH is associated with an increased risk of osteoporosis[42, 43] and of osteoporotic fractures.[49] Another potential risk of overtreatment is left ventricular hypertrophy

and abnormalities of cardiac output,[54, 58] but there is insufficient evidence for these effects in patients inadvertently overtreated for hypothyroidism.

SUMMARY

The results of this review are summarized in Table B-5. The ability of screening programs to detect subclinical thyroid dysfunction has been demonstrated in

TABLE B-5 Summary of Findings of Systematic Review

Arrow in Figure 1	Question	Level and Type of Evidence	Overall Evidence for the Link
1	Is there direct evidence from controlled studies linking screening to improved health outcomes?	None	N/A
2	What is the yield of screening with a TSH test?	II-2. Well-designed cohort studies	Good
3	What are the adverse effects of screening (false positives)?	II-2. Well-designed cohort studies (for frequency of false-positive results)	Poor for consequences of false-positive screening test results
4a	Is treatment effective for subclinical hypothyroidism found by screening?	Small, poor-to-fair-quality trials, most of limited relevance to screening, and 1 good-quality trial in a population not relevant to screening	Poor
4b	Is treatment effective for subclinical hyperthyroidism found by screening?	None	Poor
5	What are the adverse effects of treatment?	II-3. Cross-sectional studies (for osteoporosis and overtreatment). For short-term complications and long-term cardiac effects, there are only incidental findings from randomized trials.	Good (for osteoporosis and overtreatment) Poor (for other complications)

good-quality cohort studies, and some of the complications of subclinical thyroid dysfunction are well documented. The main gap in the evidence is the lack of convincing data from controlled trials that early treatment improves outcomes for patients with subclinical hypothyroidism and subclinical hyperthyroidism detected by screening.

Findings

No controlled studies link screening directly to health outcomes.

Screening detects symptomatic, overt thyroid dysfunction in 4-8 per 1,000 adult women, up to 14 per 1,000 elderly women, and 0-4 per 1,000 adult men. It also detects unsuspected subclinical hyperthyroidism in 5 to 20 per 10,000 adults. Subclinical hypothyroidism is found in 5% of women and 3% of men; the yield varies with age and is highest in elderly women.

Some consider positive TSH test results in patients who never develop complications to be "false positives." A false-positive TSH test result can be harmful if it leads to anxiety or labeling or if it leads to a treatment that has adverse effects.

The efficacy of treatment for reducing lipids or improving symptoms is inconsistent. A good-quality trial found treatment improved symptoms and had no effect on lipid levels in patients with a history of treatment for Graves' disease. In an overview of observational studies, thyroxine reduced total cholesterol by 0.14 mmol/L (5.6 mg/dL) in previously untreated patients, but the quality of the observational studies was generally poor.

Subclinical hyperthyroidism is a risk factor for developing atrial fibrillation, but no studies have been done to determine whether screening and early treatment are effective in reducing the risk.

Replacement doses of levothyroxine have not been shown to have any serious long-term adverse effects. Cross-sectional studies consistently find no adverse effect of replacement doses on bone mineralization. Overtreatment with levothyroxine is present in about one-fourth of patients, but the duration and long-term consequences of inadvertent overtreatment have not been established. Evidence regarding the incidence of serious short-term complications of levothyroxine therapy (atrial fibrillation, angina, myocardial infarction) is poor.

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APPENDIX C

Diagnoses Currently Covered by Medicare for Serum TSH Testing

ICD-9-CM Code	Persistent (P), Thyroid (T), or Short-term (S)?	Diagnosis
017.50–017.56	T	Tuberculosis of the thyroid gland
183	P	Malignant neoplasm of ovary
193	T	Malignant neoplasm of thyroid gland
194.8	P	Malignant neoplasm of other endocrine glands and related structures, other
198.89	P	Secondary malignant neoplasm of the thyroid
220	S	Benign neoplasm of ovary
226	T	Benign neoplasm of thyroid gland
227.3	P	Benign neoplasm of pituitary gland and craniopharyngeal duct
234.8	P	Carcinoma in situ of other and unspecified sites
237.4	P	Neoplasm of uncertain behavior of other and unspecified endocrine glands
239.7	T	Neoplasm of unspecified nature, thyroid gland
240.0–240.9	T	Goiter specified and unspecified
241.0–241.9	T	Nontoxic nodular goiter
242.00–242.91	T	Thyrotoxicosis with or without goiter
243	T	Congenital hypothyroidism
244.0–244.9	T	Acquired hypothyroidism
245.0–245.9	T	Thyroiditis
246.0–246.9	T	Other disorders of thyroid
250.00–250.93	P	Diabetes mellitus
252.1	P	Hypoparathyroidism

ICD-9-CM Code	Persistent (P), Thyroid (T), or Short-term (S)?	Diagnosis
253.1	P	Other and unspecified anterior pituitary hyper function
253.2	P	Panhypopituitarism
253.3–253.4	P	Pituitary dwarfism
253.4	P	Other anterior pituitary disorders
253.7	P	Iatrogenic pituitary disorders
255.2	P	Adrenogenital disorders
255.4	P	Corticoadrenal insufficiency
256.3	P	Ovarian failure
257.2	P	Testicular hypofunction
258.0–258.9	P	Polyglandular dysfunction
262	S	Malnutrition, severe
263.0–263.9	S	Malnutrition, other and unspecified
266	S	Ariboflavinosis
272	P	Pure hypercholesterolemia
272.2	P	Mixed hyperlipidemia
272.4	P	Other and unspecified hyperlipidemia
275.40–275.49	S	Calcium disorders
276	S	Hyposmolality and/or hypernatremia
276.1	S	Hyposmolality and/or hyponatremia
278.3	S	Hypercarotinemia
279.4	P	Autoimmune disorder, not classified elsewhere
281	P	Pernicious anemia
281.9	S	Unspecified deficiency anemia
283	S	Autoimmune hemolytic anemia
285.9	S	Anemia, unspecified
290	P	Senile dementia, uncomplicated
290.10–290.13	P	Presenile dementia
290.20–290.21	P	Senile dementia with delusional or depressive features
290.3	P	Senile dementia with delirium
293.0–293.1	S	Delirium
293.81–293.89	S	Transient organic mental disorders
294.8	S	Other specified organic brain syndromes
296.00–296.99	P	Affective psychoses
297	S	Paranoid state, simple
297.1	S	Paranoia
297.9	S	Unspecified paranoid state
298.3	S	Acute paranoid reaction
300.00–300.09	S	Anxiety states
307.9	S	Agitation—other and unspecified special symptoms or syndromes, not elsewhere classified
310.1	P	Organic personality syndrome
311	S	Depressive disorder, not elsewhere classified
331.0–331.2	P	Alzheimer's, Pick's disease, Senile degeneration of brain

ICD-9-CM Code	Persistent (P), Thyroid (T), or Short-term (S)?	Diagnosis
333.1	P	Essential and other specified forms of tremor
333.99	P	Other extrapyramidal diseases and abnormal movement disorders
354	S	Carpal tunnel syndrome
356.9	S	Idiopathic peripheral neuropathy, unspecified polyneuropathy
358.1	S	Myasthenic syndromes in diseases classified elsewhere
359.5	S	Myopathy in endocrine diseases classified elsewhere
359.9	S	Myopathy, unspecified
368.2	S	Diplopia
372.71	S	Conjunctival hyperemia
372.73	S	Conjunctival edema
374.41	S	Lid retraction or lag
374.82	S	Eyelid edema
376.21	T	Thyrotoxic exophthalmos
376.22	P	Exophthalmic ophthalmoplegia
376.30–376.31	P	Exophthalmic conditions, unspecified and constant
376.33–376.34	S	Orbital edema or congestion, intermittent exophthalmos
378.50–378.55	P	Paralytic strabismus
401.0–401.9	P	Essential hypertension
403.00–403.91	P	Hypertensive renal disease
404.00–404.93	P	Hypertensive heart and renal disease
423.9	S	Unspecified disease of pericardium
425.7	S	Nutritional and metabolic cardiomyopathy
427	S	Paroxysmal supraventricular tachycardia
427.2	S	Paroxysmal tachycardia, unspecified
427.31	S	Atrial fibrillation
427.89	S	Other specified cardiac dysrhythmia
427.9	S	Cardiac dysrhythmia, unspecified
428	P	Congestive heart failure
428.1	P	Left heart failure
429.3	P	Cardiomegaly
511.9	S	Unspecified pleural effusion
518.81	S	Acute respiratory failure
529.8	S	Other specified conditions of the tongue
560.1	S	Paralytic ileus
564	S	Constipation
564.7	P	Megacolon, other than Hirschsprung's
568.82	P	Peritoneal effusion (chronic)
625.3	S	Dysmenorrhea
626.0–626.2	S	Disorders of menstruation
626.4	S	Irregular menstrual cycle

ICD-9-CM Code	Persistent (P), Thyroid (T), or Short-term (S)?	Diagnosis
648.10–648.14	S	Other current conditions in the mother, classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium, thyroid dysfunction
676.20–676.24	S	Engorgement of breast associated with childbirth and disorders of lactation
698.9	S	Unspecified pruritic disorder
701.1	S	Keratoderma, acquired (dry skin)
703.8	S	Other specified diseases of nail (brittle nails)
704.00–704.09	S	Alopecia
709.01	P	Vitiligo
710.0–710.9	P	Diffuse disease of connective tissue
728.2	S	Muscle wasting
728.9	S	Unspecified disorder of muscle, ligament, and fascia
729.1	S	Myalgia and myositis, unspecified
729.82	S	Musculoskeletal cramp
730.30–730.39	S	Periostitis without osteomyelitis
733.09	S	Osteoporosis, drug induced
750.15	P	Macroglossia, congenital
759.2	S	Anomaly of other endocrine glands
780.01	S	Coma
780.02	S	Transient alteration of awareness
780.09	S	Alteration of consciousness, other
780.50–780.52	S	Insomnia
780.6	S	Fever
780.71–780.79	S	Malaise and fatigue
780.8	S	Hyperhidrosis
780.9	S	Other general symptoms (hyperthermia)
781	S	Abnormal involuntary movements
781.3	S	Lack of coordination, ataxia
782	S	Disturbance of skin sensation
782.3	S	Localized edema
782.8	S	Changes in skin texture
782.9	S	Other symptoms involving skin and integumentary tissues
783.1	S	Abnormal weight gain
783.2	S	Abnormal loss of weight
783.6	S	Polyphagia
784.1	S	Throat pain
784.49	S	Voice disturbance
784.5	S	Other speech disturbance
785	S	Tachycardia, unspecified
785.1	S	Palpitations
785.9	S	Other symptoms involving cardiovascular system
786.09	S	Other symptoms involving respiratory system

ICD-9-CM Code	Persistent (P), Thyroid (T), or Short-term (S)?	Diagnosis
786.1	S	Stridor
787.2	S	Dysphagia
787.91–787.99	S	Other symptoms involving digestive system
789.5	S	Ascites
793.9	S	Nonspecific abnormal findings on radiological and other examination, other (neck)
794.5	T	Thyroid, abnormal scan or uptake
796.1	S	Other nonspecific abnormal findings, abnormal reflex
799.2	S	Nervousness
990	S	Effects of radiation, unspecified
V10.87	T	Personal history of malignant neoplasm of the thyroid
V10.88	P	Personal history of malignant neoplasm of other endocrine gland
V12.2	P	Personal history of endocrine, metabolic, and immunity disorders
V58.69	P	Long-term (current) use of other medications
V67.0-V67.9	S	Follow-up examination

APPENDIX D

Committee Biographies

ROBERT B. WALLACE, M.D. (*Chair*) is the Irene Ensminger Stecher Professor of Epidemiology and Internal Medicine at the University of Iowa College of Medicine. Dr. Wallace is Co-Director of the University of Iowa Center on Aging and is the former head of the Department of Preventive Medicine and Environmental Health. He is Editor of the *Maxcy-Rosenau-Last Public Health and Preventive Medicine* textbook and Co-Editor of *The Epidemiologic Study of the Elderly*. Dr. Wallace is the current chair of the IOM Board on Health Promotion and Disease Prevention and has served on numerous IOM Committees.

GAY J. CANARIS, M.D., M.S.P.H., is Assistant Professor of Medicine in the Department of Internal Medicine at the University of Nebraska Medical Center, College of Medicine. Dr. Canaris has worked on clinical studies to develop prediction rules for hypothyroidism and influenza infection. She has published studies on predictors of hypothyroidism as well as the Colorado Thyroid Disease Prevalence Study.

INDER J. CHOPRA, M.D., is Professor of Medicine at the University of California at Los Angeles Center for Health Services. Dr. Chopra is widely recognized for his contributions in both clinical and basic science investigation in the field of thyroid research. He is one of the few clinical investigators who have developed and characterized the metabolism of thyroid hormones, disease effects, and therapeutic implications. He has also had a major role in development of thyroid hormone immunoassay methods**.**

LAURENCE MAURICE DEMERS, Ph.D., is Distinguished Professor of Pathology and Medicine at the Pennsylvania State University College of Medicine and Associate Director of the Section of Clinical Pathology and Director of Clinical Chemistry and the Automated Testing Laboratory at the Penn State University, M.S. Hershey Medical Center. Dr. Demers is past-president of the American Association for Clinical Chemistry and has served as both Secretary and President of the National Academy of Clinical Biochemistry. He was co-editor for the NACB-sponsored thyroid testing clinical guidelines document first published in 1997 and revised in 2002.

NEIL R. POWE, M.D., M.P.H., M.B.A., is Professor of Medicine in the Department of Medicine at the Johns Hopkins University School of Medicine and Director of the Welch Center for Prevention, Epidemiology and Clinical Research. He also is Professor of Epidemiology and Health Policy and Management at the Johns Hopkins University Bloomberg School of Public Health, where he directs the Clinical Epidemiology Program and the Johns Hopkins Evidence-Based Practice Center. In additional to his general expertise in clinical medicine, epidemiology, prevention, and health services research; he is an author of decision and cost-effectiveness analyses on screening practices including thyroid screening.

JANE E. SISK, Ph.D., is an Economist and Professor in the Department of Health Policy and Co-Director of the Center on Evidence-Based Medicine and Aging at the Mount Sinai School of Medicine. Her current research is focused on the implementation of evidence-based guidelines; evaluation of Medicaid managed care, and cost-effectiveness of health care interventions, including pneumococcal vaccination for elderly people.

ROBERT D. UTIGER, M.D., is Clinical Professor of Medicine and at the Harvard University School of Medicine, Editor-in-Chief of *Clinical Thyroidology,* former Deputy Editor of the *New England Journal of Medicine,* and Co-Editor of *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text.*

STEPHEN D. WALTER, Ph.D., is Professor of Clinical Epidemiology and Biostatistics at the Faculty of Health Sciences of McMaster University. Dr. Walter has published over 200 refereed journal articles and book chapters on epidemiology and biostatistical methods. Particular interests include disease screening and diagnosis; risk assessment; environmental health; and analysis of spatial and temporal data patterns. He is a former Editor of the *American Journal of Epidemiology* and is currently Section Editor for Clinical Epidemiology in the *Wiley Encyclopedia of Biostatistics*

STEVEN H. WOOLF, M.D., M.P.H., is Professor of Family Practice and Preventive and Community Medicine at Virginia Commonwealth University and is

Director of Research for the Department of Family Practice. Dr. Woolf is interested in the methods used in evidence-based medicine, including the critical appraisal of evidence, systematic reviews, and the development of evidence-based clinical practice guidelines. He has helped develop advanced methods for reviewing evidence of the effectiveness of clinical preventive services, focusing on health services research and evidence-based medicine. He is a member of the U.S. Preventive Services Task Force and has served on numerous IOM Committees.