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## Predisease: When Does it Make Sense?

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Screening often leads to finding conditions that are not at the stage or level that would classify them as disease but, at the same time, are not at a stage or level at which people can be declared entirely disease free. These “in-between” states have sometimes been designated as “predisease.” Examples include precancerous lesions, increased intraocular pressure (“preglaucoma”), prediabetes, and prehypertension. When the goal of preventing adverse health outcomes is kept in mind, this review poses the idea that “predisease” as a category on which to act makes sense only if the following 3 conditions are met. First, the people designated as having predisease must be far more likely to develop disease than those not so designated. Second, there must be a feasible intervention that, when targeted to people with predisease, effectively reduces the likelihood of developing disease. Third, the benefits of intervening on predisease must outweigh the harms in the population. A systematic review of screening guidelines (published in 2003–2010) for 4 sample conditions (cervical cancer, glaucoma, diabetes, and hypertension) is included to assess whether they address these issues, followed by a discussion of the framework questions as they pertain to each condition.

early detection of cancer; mass screening; secondary prevention

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Abbreviations: JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; POAG, primary open-angle glaucoma.

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### INTRODUCTION

Screening is the systematic use of a test for a health problem or risk factor when no recognized signs or symptoms would indicate the presence of that problem or risk factor. Importantly, the goal of screening is not merely to find problems but to identify asymptomatic persons for whom an intervention will help reduce progression of early disease to advanced disease or prevent an adverse health event. A critically important point is that screening helps a person only when the offered intervention is more effective (e.g., in reducing morbidity or mortality) if given during the asymptomatic stage than if delayed until the symptomatic stage.

If disease is thought of as a condition when it manifests as something that perceivably disturbs or disrupts health, then in one sense all screening is screening for “predisease.” However, there is no generally accepted or standard definition for “predisease.” This paper explores the origins of predisease, presents questions that might help judge when explicitly designating a predisease category is worthwhile, incorporates a systematic review to assess whether such questions are generally considered, and concludes with an

assessment of the answers to these questions using several prediseases as examples.

### ORIGINS OF PREDISEASE

The concept of predisease likely has its origins in cancer biology. The term “precancerous” appeared in the medical literature over a century ago, when it was recognized that no sharp line demarcated the histology between benign and malignant tissues (1–3). There were borderline cases that some pathologists would call cancer and some would not. This recognition advanced the idea that cancer was an evolutionary process—a progression from normal, healthy tissues to benign abnormalities to advanced malignancy. In 1914, Dr. William Rodman expressed the idea that lives could be saved “by operating in the precancerous stage” (4, p. 63). Even at that time, however, 2 important points were already acknowledged. Rodman wrote, “I am well aware that the term ‘precancerous’ will be objected to for at least two reasons: first, that there is not always a precancerous stage; second, that when it does exist it does not necessarily mean that cancer must eventuate” (4, p.63). Over the ensuing 4 decades,

precancerous lesions in nearly every region of the body where cancer occurs were described, including the uterus, colon, prostate, and breast (5–17).

Recognizing the potential of prevention, screening programs for several cancers soon developed (18–20). The Papanicolaou smear was introduced in 1928, and even early screening programs demonstrated the potential of preventing cancer of the cervix by intervening in precancerous states (6). It has been known since the 1950s that the majority of cancers of the colon arise from adenomatous polyps, and even at that time sigmoidoscopy with removal of polyps was advocated as a method for prevention of colon cancer (7). Today, screening for cervical cancer and screening for colorectal cancer both have grade A recommendations from the U.S. Preventive Services Task Force (21, 22).

### PREDISEASE IN NONCANCEROUS CONDITIONS

Perhaps the earliest example of predisease among conditions other than cancer is latent tuberculosis infection. In the early 1900s, tuberculin was being investigated for its potential diagnostic value (23). Three to 4 decades later, the refined product known as purified protein derivative was being used to identify people with latent infection based on the skin's hypersensitivity reaction to purified protein derivative (23). Screening for tuberculosis is still performed with this type of skin testing. Those who test positive are offered medication to reduce the likelihood of developing active tuberculosis.

Today, there are predisease states for many of the common chronic diseases (Table 1). Prediabetes and prehypertension are obvious examples, but “conditions” such as mild cognitive impairment, mild depression, borderline glaucoma, and osteopenia could all be considered “in-between” states. Even asymptomatic human immunodeficiency virus infection could be considered a predisease. Most predisease is found as a consequence of screening.

### SCREENING AS A PREVENTIVE STRATEGY

In his classic paper, “Sick Individuals and Sick Populations,” Geoffrey Rose discussed 2 broad strategies for preven-

tion: the population strategy and the “high-risk” strategy (24). These strategies emerge from considering that the factors that render an individual person to have (or be susceptible to) a condition are not necessarily the same as the factors that contribute to the incidence of the condition in a population. Causes of incidence act on the population as a whole, and the population strategy of prevention seeks to identify and mitigate such causes. There exists a “prevention paradox” however, in that a prevention strategy that brings much benefit to a population offers little benefit on an individual level. Said another way, in a population strategy of prevention, everyone “participates,” but few actually benefit. A law mandating wearing of an automobile safety belt is a useful example. On any particular day for any individual, the likelihood that wearing the safety belt will yield a benefit (i.e., prevent injury or death from an automobile crash) is extremely low. However, on a population level, everyone (or almost everyone) wearing a safety belt translates into many lives saved in automobile crashes per year.

In truth, most people will never actually benefit from wearing a safety belt. If wearing a safety belt had a significant downside (e.g., inconvenient, expensive, risk of harm), then this population strategy for preventing serious injury or death from automobile crashes might not be reasonable. One could alternatively propose a strategy of advising only those at increased risk to wear a safety belt. However, this strategy presupposes that there is a reliable method to identify individuals at increased risk of being involved in an automotive crash. This latter strategy is what Rose termed the “high-risk” strategy. Were it possible to reliably identify people and designate them “precrash,” then advice to wear the safety belt could be targeted.

In the high-risk strategy, the goal is to identify people at increased risk of developing an adverse health outcome and offer some intervention to try to reduce that risk. Some advantages of such a strategy are that it (ideally) is motivating to the person giving the advice or intervention (usually a clinician) as well as to the individual (who in most cases then becomes a patient if not one already) because the intervention is deemed appropriate to that individual. In other words, the person offered the intervention is led to understand his or her “need” for it. Additionally, any risks from the intervention are (or should be) outweighed by the potential benefits.

**Table 1.** Examples of Conditions and Their “Predisease” States

Condition	“Predisease”	Typical Screening Test Option(s)
Acquired immunodeficiency syndrome	HIV infection	Rapid HIV antibody testing or enzyme immunoassay followed by Western blot
Cervical cancer	Cervical intraepithelial neoplasia	Cytology (Papanicolaou test)
Colon cancer	Adenomatous polyp	Fecal occult blood test, endoscopy
Dementia	Mild cognitive impairment	Mini-Mental State Examination
Diabetes	Prediabetes	Fasting serum glucose or 2-hour glucose tolerance test
Hypertension	Prehypertension	Office blood pressure measurement
Hypo- or hyperthyroidism	Subclinical thyroid dysfunction	Thyroid-stimulating hormone
Osteoporosis	Osteopenia	Bone density scan
Primary open-angle glaucoma	Increased intraocular pressure	Tonometry
Tuberculosis	Latent tuberculosis infection	Tuberculin skin test

Abbreviation: HIV, human immunodeficiency virus.

The high-risk strategy obviously requires some way to identify those individuals at high risk. Thus, this strategy in most instances relies on screening. The goal of screening is to find people at sufficiently increased risk of an adverse health outcome for whom an intervention (e.g., special advice, a medication, a procedure) sufficiently reduces the likelihood of that adverse health outcome.

With this strategy, there exists a critically important question: how do we define “high-risk”? The implication is that there are 2 categories: “high risk” and “not high risk.” This kind of dichotomous thinking is analogous to the clinical act of making a diagnosis; the person is either given the diagnosis or is not. Clinicians operationalize their work in this way for a very logical reason. They need to make a decision about whether or not to intervene. For few conditions for which we screen, however, is there actually an unambiguous “lesion” that allows a clear-cut diagnosis (25).

### FALSE DICHOTOMY OF DISEASES AND RISK FACTORS

Disease is not dichotomous but rather reflects a progressive process and a wide spectrum of severity. In some instances, screening finds advanced disease; in others, it finds mild disease. For example, a screening colonoscopy could lead to finding late-stage colon cancer or a small adenomatous polyp. Some screening is performed not to find disease per se but to find risk factors for disease. Cardiovascular disease risk factors are the classic examples. In fact, the term “risk factor” was coined by the Framingham Study investigators (26). Most risk factors, however, are also not dichotomous. Rather, there is a continuous and graded relation between risk factor levels (e.g., blood pressure level, cholesterol level) and future disease events. Diagnoses such as hypertension and hypercholesterolemia are simply ways to organize people into 2 categories: those who merit some intervention and those who do not. Predisease could be thought of as simply adding a third category.

### WHEN DOES PREDISEASE MAKE SENSE?

As part of a screening strategy designed to reduce the burden of suffering from a health problem in a population, it may be useful to know when the explicit recognition of a predisease state or stage would be helpful. Three questions can serve as a guide (Table 2). First, what is the discriminating ability of the predisease category? In other words, how much more likely to develop disease are people designated as having predisease than those not so designated? The answer to this question provides some indication of the discriminating ability the predisease recognition confers. Second, is there a feasible intervention that, when targeted to people with predisease, effectively reduces the likelihood of developing disease? Just as there is no reason to screen if there is no effective intervention to offer, there is also no reason to label people with predisease if there is no effective intervention to offer. Third, do the benefits of intervening in the predisease stage outweigh the harms? It must be remembered that with screening, a sizable portion of the population may be identified as having predisease. If the magnitude of the benefit from the intervention in reducing an adverse health outcome is small for this group of people, the potential for harm needs to be exceedingly small.

**Table 2.** Basic Framework for Thinking About Predisease

Discriminating ability
How much more likely to develop disease are people designated as having predisease than those not so designated?
Effective intervention
Is there a feasible intervention that, when targeted to people with predisease, effectively reduces the likelihood of developing disease?
Benefits exceed harms
Do the benefits of intervening in the predisease stage outweigh the harms in the population?

#### Discriminating ability

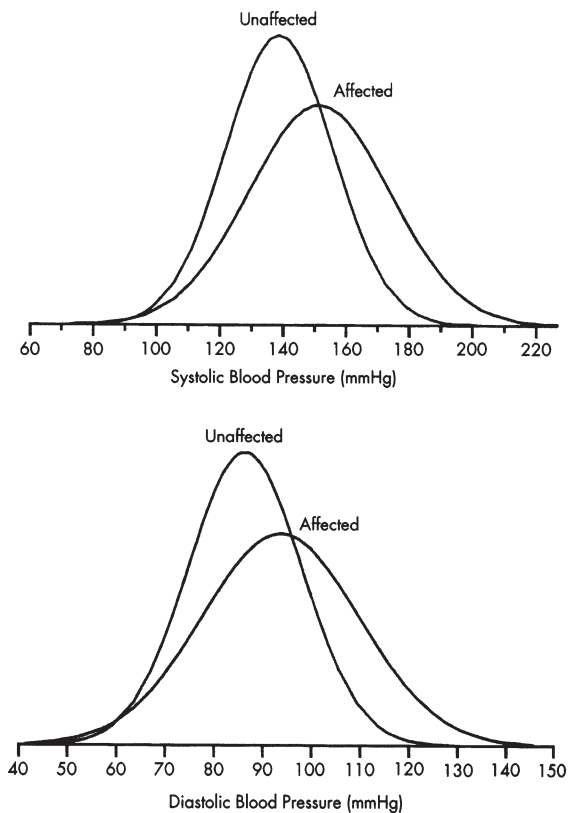
The word “predisease” implies that disease will develop if nothing is done. While disease does not necessarily need to develop in all people designated as having predisease (if nothing is done) for predisease to be a meaningful category, the distributions of the health outcome between people designated as having predisease and those not designated as such should have minimal overlap. In other words, the risk of developing the disease should be substantially greater for those with predisease. This risk also should be much greater than the risk conferred by a risk factor. One reason screening for risk factors for adverse health outcomes turns out not to discriminate well between people who eventually do and do not develop the adverse health outcome is that the risk factors have nowhere near the magnitude of association that would be necessary (27, 28). For example, hypertension is an important modifiable risk factor for stroke (29). However, hypertension would not be appropriately thought of as “prestroke” because most people with hypertension actually do not develop a stroke. Further, the distributions of people with hypertension who develop a stroke and people without hypertension who develop a stroke have a large amount of overlap (Figure 1) (30).

#### Effective intervention

There must be an effective intervention that can be offered to people with predisease that reduces the risk of the adverse health outcome occurring. This is analogous to the fact that screening is beneficial only when earlier treatment is more effective in reducing the adverse health outcome than treatment when symptoms appear. If the intervention involves lifestyle modifications, it is important to know whether the predisease label meaningfully increases adoption of the lifestyle modifications. If the intervention is medication, it is important to know whether the medication reduces the rate of progression of the disease or risk factor level or whether it merely represents earlier treatment of the disease or risk factor, and, if the latter, whether earlier treatment reduces the risk of adverse health outcomes.

#### Benefits exceed harms

As implied by the fact that there must be an effective intervention, an issue with predisease is that it is usually treated. This treatment must do more good than harm. In some people, predisease may in fact never become disease



**Figure 1.** Blood pressure as a “screening test” for stroke. Distributions of systolic (top panel) and diastolic (bottom panel) blood pressures in men who died of stroke and men who did not (age-adjusted data from the British United Provident Association cohort study). Note that, although elevated blood pressure is a risk factor for stroke, it does not discriminate well between those who will and will not suffer from a stroke. (Reprinted with permission from the Royal Society of Medicine Press Ltd: Law MR, Wald NJ, Morris JK. The performance of blood pressure and other cardiovascular risk factors as screening tests for ischaemic heart disease and stroke. *Journal of Medical Screening* 2004;11(1):3–7.)

and never cause any untoward health effects. This lack of progression could be because the predisease would have never progressed (or progressed only slowly), in which case the predisease category did not discriminate very well. In such instances, the treatment was not needed. This kind of “needless” diagnosis is what has been termed “overdiagnosis” (31). Any harms from the evaluation (e.g., invasive tests, biopsies) or the treatment itself (e.g., complications, side effects) would in effect be caused by assigning the predisease state to the person. Additionally, there is the potential psychological harm of the predisease label. Finally, there are the financial costs to the patient and the health care system that did not need to be incurred.

## SYSTEMATIC REVIEW

### Methods

I chose 4 conditions—cervical cancer, primary open-angle glaucoma (POAG), diabetes, and hypertension—to serve as

examples of how to use the questions proposed in this paper as a framework for thinking about predisease in the context of screening. For each of these conditions, I searched Medline for systematic reviews and published guidelines on screening for these conditions from 2003 (the year that “prehypertension” was introduced) to October 2010. The search strategies are shown in the Appendix. Articles were retrieved if they were 1) systematic reviews of screening or 2) guidelines containing screening recommendations for adults. Systematic reviews of cost-effectiveness (by itself), short summaries of larger publications, narrative reviews of screening, and guidelines pertaining to pregnancy were excluded. Duplicate publications were retrieved from only one source; if a group issued more than one guideline during the time frame, only the most recent publication was included. Included articles from these searches were reviewed to determine whether 1) they explicitly mentioned a predisease stage and, if so, 2) they incorporated some consideration of the answers to the basic framework questions shown in Table 2.

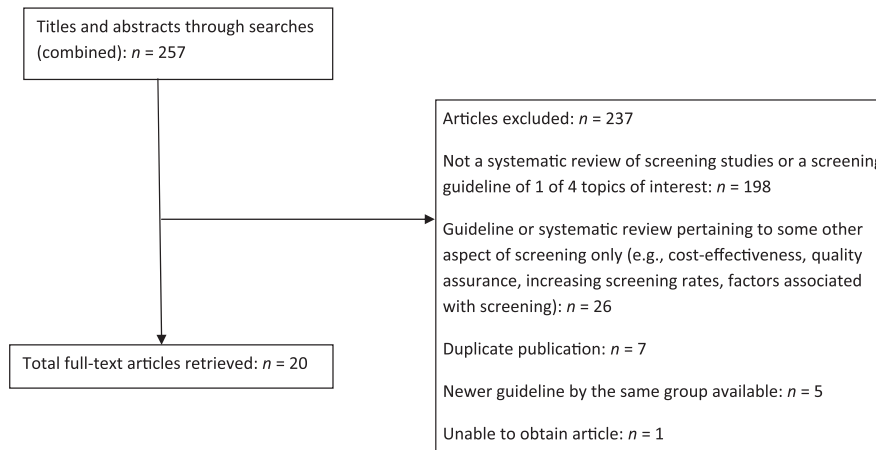
### Results of review

The Medline searches yielded 257 titles, 20 of which were included (4 cervical cancer, 4 glaucoma, 6 diabetes, and 6 hypertension) (29, 32–50) (Figure 2). These articles are summarized in Table 3. Two of the 4 cervical cancer screening guidelines (32, 33) mentioned cervical lesions that were precursors to cervical cancer, and a third focused on human papilloma virus infection as a necessary factor for development of cervical cancer (34). The guidelines included a variable amount of evidence or discussion relevant to the other framework questions. All 4 glaucoma screening articles mentioned increased intraocular pressure as a risk factor for glaucoma (36–39). Except for 1 article focused on accuracy of screening tests (39), they all had at least some information on discriminating ability, effectiveness of the intervention, and consideration of potential harms. Four of the 6 diabetes screening articles mentioned prediabetes (40, 41, 43, 45), but they varied in their discussion of issues relevant to the framework questions. Lastly, of 6 hypertension (or related cardiovascular) screening guidelines, only 1 included clinical recommendations to detect and address prehypertension (29). However, no substantive discussion of the issues relevant to the framework questions was included. In the next section, I offer some discussion relevant to each framework question for each of these sample conditions, summarized in Table 4.

## FRAMEWORK APPLIED TO EXAMPLES

### Cervical intraepithelial neoplasia

Screening as a strategy to prevent cervical cancer has been remarkably successful (51). In the United States since 1975, the age-adjusted annual incidence of invasive cervical cancer has declined from 15 per 100,000 females to approximately 6 per 100,000 females (52). Dramatic and consistent reductions in cervical cancer morbidity and mortality (60%–90%) are evident within a few years in every population that introduces a Papanicolaou test screening program (51). The



**Figure 2.** Articles selected from a systematic review of Medline.

Papanicolaou test enables detection of cytologic cervical abnormalities that are premalignant.

**Discriminating ability.** For the most part, cervical cancer progresses very slowly from early cellular changes to severe dysplasia to carcinoma in situ and on to invasive cancer. The Papanicolaou test reveals whether the cervix exhibits cellular changes that warrant further testing. Colposcopic examination with targeted biopsies then reveals whether histologic findings of cervical intraepithelial neoplasia exist. Cervical intraepithelial neoplasia is subdivided into grades 1, 2, and 3 corresponding to mild, moderate, and severe dysplasia. While some women who exhibit mild dysplasia will “clear” it without treatment, higher grade dysplasia, left untreated, progresses to cervical cancer (51).

**Effective intervention.** Screening for cervical cancer is effective not simply because the cancer develops slowly and its premalignant stages are readily detectable but because premalignant lesions (cervical intraepithelial neoplasia grade 2 or higher) can be definitively treated. Women who exhibit low-grade dysplasia receive close surveillance.

**Benefits exceed harms.** With a cervical cancer screening program, the strategy would be to screen all sexually active women who have a cervix until they reach older age. The discomfort of the screening test aside, there are the potential psychological harms (and associated health care system costs) of labeling many young women with a “precancerous lesion.” Unfortunately, little is known about these potential effects. The benefits of labeling women with a precancerous lesion, however, are what drive the effectiveness of cervical cancer screening programs. Women are aptly placed into a risk category that warrants intervention, and the intervention prevents death from invasive cervical cancer.

### Increased intraocular pressure

Glaucoma refers to a group of eye diseases characterized by optic nerve damage that can lead to visual field loss and

irreversible blindness. The most common type of adult glaucoma is POAG (53). The diagnosis is made by visualizing the characteristic pattern of optic nerve damage on fundus examination or noting the characteristic deficit on visual field testing (in the absence of other causes). Because POAG is asymptomatic, prevention of its consequences has relied on screening. The main screening test for POAG is measurement of intraocular pressure. People with elevated intraocular pressure (also termed “ocular hypertension”) are offered treatment to reduce it. Patients with increased intraocular pressure might be labeled as having “borderline glaucoma” or being “glaucoma suspects.”

**Discriminating ability.** The upper limit of “normal” intraocular pressure is considered 21 mm Hg. Based on sensitivity and specificity data, this cutoff yields a positive likelihood ratio of about 6 and a negative likelihood ratio of 0.6 for the diagnosis of POAG (54). As many as half of the people with POAG have intraocular pressure below the normal level, and most people with increased intraocular pressure never develop glaucoma (55). In a study published in 1977, 75 patients with intraocular pressure above 21 mm Hg were followed for over 9 years without treatment (56). Only 7 developed POAG as manifest by visual field loss. Thus, although increased intraocular pressure is considered a risk factor for POAG, it is not a necessary part of the pathway.

**Effective intervention.** A randomized trial has demonstrated that topical medication to reduce elevated intraocular pressure reduces the progression to POAG from 9.5% to 4.4% over 5 years (57). Topical agents are generally considered easy to use, but it is interesting to note the high rates of nonadherence (up to 60% over 1 year) and non-persistence (up to 95% at 1 year) (58). Other interventions that can be offered to people with increased intraocular pressure include laser therapy and surgery (53).

**Benefits exceed harms.** While treatment of screen-identified increased intraocular pressure can decrease the number of adults who develop small visual field deficits, there

is no clear evidence that this treatment leads to a reduction in vision-related function or quality of life (53). The harms of treatment include local eye irritation and increased cataract formation (which itself can lead to visual impairment) (53). In the general adult population, in which the prevalence of POAG is quite small, of every 12 people labeled as having increased intraocular pressure, 11 will receive unnecessary evaluation and possibly treatment. It is this uncertainty around the magnitude of benefit of early treatment, coupled with the certainty that treatment will cause some harms, that led the U.S. Preventive Services Task Force to give an I recommendation (insufficient evidence) to screen adults for glaucoma (36).

### Prediabetes and prehypertension

The term “prediabetes” has actually appeared in the medical literature since the 1940s, although at that time it was used to refer to what has become known as gestational diabetes (59). The most current guideline from the American Diabetes Association defines asymptomatic type 2 diabetes by either a fasting plasma glucose of  $\geq 126$  mg/dL (7.0 mmol/L), a 2-hour plasma glucose of  $\geq 200$  mg/dL (11.1 mmol/L) during an oral glucose tolerance test, or an A1C (glycated hemoglobin) of  $\geq 6.5\%$  (60). Individuals with a fasting plasma glucose of 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L), a 2-hour oral glucose tolerance test plasma glucose of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L), or an A1C of 5.7%–6.4% are classified as having prediabetes (60). Prediabetes can be subdivided into impaired fasting glucose or impaired glucose tolerance, depending on which test is used.

“Prehypertension” is a much newer term, introduced in 2003 by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (29). According to JNC 7, adults (not receiving blood-pressure-lowering treatment) with a systolic blood pressure of 120–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg (on 2 occasions), with neither in the hypertensive range ( $\geq 140/90$  mm Hg), are said to have prehypertension (29). Of note, the JNC 7 report included the statement that “[p]rehypertension is not a disease category. Rather, it is a designation chosen to identify individuals at high risk of developing hypertension, so that both patients and clinicians are alerted to this risk and encouraged to intervene and prevent or delay the disease from developing” (29, p. 1211).

*Discriminating ability.* For conditions such as diabetes and hypertension, when diagnosis is based on reaching a threshold level, there exists the very intuitive notion that one must pass through the lower levels before reaching the “diagnostic” threshold level. People with prediabetes progress to diabetes at a rate of about 5%–10% per year (61). Prehypertension progresses to hypertension at a rate of 19% over 4 years (62). Definitions of such diseases (or risk factors) based on a threshold level are quite arbitrary. Indeed, the thresholds—and hence the definitions—of both diabetes and hypertension have changed over time. Many people categorized as having diabetes or hypertension today would have been categorized as the prediabetics and prehypertensives of yesteryear, if those categories existed. It should come as no surprise that people with higher levels of glycemia or blood pressure within the

prediabetes and prehypertension ranges are more likely to develop diabetes and hypertension. As is so often the case, the best predictor of future moderate or severe disease is the presence of existing mild disease.

To bolster the case for prediabetes, the guidelines remind us that as levels of plasma glucose increase, the risk of retinopathy and cardiovascular events increases (60). A recent systematic review estimated the relative risk of cardiovascular disease to be approximately 1.1–1.2 among people with prediabetes compared with those without prediabetes (63). Similarly, JNC 7 points out that starting at 115/75 mm Hg, with each blood pressure increment of 20/10 mm Hg, the risk of a cardiovascular event doubles (29). While these reasons are used as part of the rationale for designating the prediabetes and prehypertension categories, they are not truly informing us of anything new. These associations simply reflect the graded, continuous associations of the risk factor level with increasing likelihood of an adverse health outcome.

*Effective intervention.* Since diabetes and hypertension are conditions (risk factors) based on a cutoff of a continuous measure, the question is whether a feasible intervention exists that reduces progression from the “predisease” level to the “disease” level. Current guidelines recommend that people with prediabetes be informed of their increased risk of diabetes and cardiovascular disease and be counseled about lifestyle modifications (weight loss and exercise) to reduce their risk (64). Similarly, in an effort to prevent or delay hypertension, JNC 7 recommends that people with prehypertension be counseled to adopt lifestyle modifications to lower their blood pressure (29).

Evidence exists that aggressive lifestyle modifications can prevent diabetes. In the Diabetes Prevention Program, more than 3,200 obese adults with prediabetes were randomized to a regimen of intensive lifestyle modifications, metformin, or placebo (65). At an average follow-up of 3 years, 14% of those in the intensive lifestyle modifications group developed diabetes compared with 29% in the placebo group. Of note, the lifestyle group lost an average of 15 pounds (6.8 kg) through diet and exercise. The program, designed to achieve a 7% weight loss, consisted of a 16-lesson curriculum taught one-on-one by case managers and followed by individualized reinforcement sessions. Of course, such programs are not routinely available, and the generalizability to people not volunteering for a trial is questionable. It is uncertain whether coupling the prediabetes label with a message to lose weight is any more effective than general advice to do so.

While there is also evidence that lifestyle modifications can lower blood pressure in people with hypertension, there is no evidence that a counseling message targeted to people with prehypertension reduces progression to hypertension. One study examined whether an antihypertensive medication given to people with upper-range prehypertension could prevent or delay the onset of hypertension (66). Investigators randomized approximately 800 prehypertensive adults to 2 years of candesartan or placebo, followed by 2 more years of placebo for all. Not surprisingly, blood pressure was lower in the first 2 years among those allocated to candesartan. Within 9 months of stopping active therapy, blood pressure was similar in both groups. In cases such as this, the medication is not truly

**Table 3.** Summary of Articles From the Systematic Review

Article, Year (Reference No.)	Publication Type	Predisease Stage Mentioned	Discriminating Ability Addressed	Effectiveness of Intervention in Predisease Stage Addressed	Discussion of Benefits vs. Harms
<i>Cervical Cancer</i>					
Screening for cervical cancer: recommendations and rationale, 2003 (32)	Guideline (based on systematic review) issued by USPSTF	Cervical intraepithelial neoplasia as "precursor"	Somewhat	Somewhat	Yes
Ontario cervical cancer screening practice guidelines, 2007 (33)	Guideline (with systematic review) issued by the Ontario [Canada] Cervical Cancer Screening Program	Cervical "precursor lesions"	No	No	No
ACOG Practice Bulletin no. 109: Cervical cytology screening, 2009 (34)	Guideline issued by the American College of Obstetricians and Gynecologists	Not explicitly, but discusses human papilloma virus infection as a necessary factor	Somewhat	Not explicitly	Not explicitly
The Japanese guideline for cervical cancer screening, 2010 (35)	Guideline (with systematic review) issued by the National Cancer Center, Tokyo, Japan	Not explicitly	Somewhat	Yes	Yes
<i>Glaucoma</i>					
Screening for primary open-angle glaucoma in the primary care setting: an update for the US Preventive Services Task Force, 2005 (36)	Guideline (based on systematic review) issued by USPSTF	Discusses increased intraocular pressure as a "risk factor for glaucoma"	Yes	Yes	Yes
Screening for glaucoma in Canada: a systematic review of the literature, 2006 (37)	Guideline (based on systematic review) issued by the Canadian Task Force on Periodic Health Examination	Discusses increased intraocular pressure as a risk factor for glaucoma	Somewhat	Yes	Somewhat
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation, 2007 (38)	Systematic review by the Health Technology Assessment Programme of the United Kingdom	Discusses increased intraocular pressure as a risk factor for glaucoma	Yes	Yes	Yes
Screening tests for detecting open-angle glaucoma: systematic review and meta-analysis, 2008 (39)	Systematic review	Discusses increased intraocular pressure as a risk factor for glaucoma	Yes	No (by design, was focused on comparing accuracy of screening tests)	No (by design, was focused on comparing accuracy of screening tests)
<i>Diabetes</i>					
The prevention or delay of type 2 diabetes, 2003 (40)	Position statement issued by the American Diabetes Association	Prediabetes	Somewhat	Yes	Somewhat
Screening for type 2 diabetes, 2004 (41)	Position statement issued by the American Diabetes Association	Prediabetes	No	Somewhat	No
Screening for type 2 diabetes mellitus to prevent vascular complications: updated recommendations from the Canadian Task Force on Preventive Health Care, 2005 (42)	Guideline (based on systematic review) issued by the Canadian Task Force on Preventive Health Care	No	N/A	N/A	N/A
Prediabetes: a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association, 2007 (43)	Position statement from the Australian Diabetes Society and Australian Diabetes Educators Association	Prediabetes	Yes	Yes	No

HbA(1c) as a screening tool for detection of type 2 diabetes: a systematic review, 2007 (44)	Systematic review	No	N/A	N/A	N/A
Screening for type 2 diabetes mellitus in adults: a review of the evidence for the U.S. Preventive Services Task Force, 2008 (45)	Systematic review on which guidelines of USPSTF were based	Prediabetes	Somewhat	Yes	Yes
<i>Hypertension</i>					
Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 2003 (29)	Guideline issued by the National High Blood Pressure Education Program	Prehypertension	No	No	No
2007 ESH-ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), 2007 (46)	Guideline issued by ESH and ESC	Explicitly decided not to use the term "prehypertension"	N/A	N/A	N/A
European guidelines on cardiovascular disease prevention in clinical practice, 2007 (47)	Guideline issued by ESC	No	N/A	N/A	N/A
Screening for high blood pressure: U.S. Preventive Services Task Force reaffirmation recommendation statement, 2007 (48)	Guideline (based on systematic review) issued by USPSTF	No	N/A	N/A	N/A
The 2009 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 1—blood pressure measurement, diagnosis and assessment of risk, 2009 (49)	Guideline issued by the Canadian Hypertension Education Program	No	N/A	N/A	N/A
The Japanese Society of Hypertension Guidelines for the Management of Hypertension, 2009 (50)	Guideline issued by the Japanese Society of Hypertension	No	N/A	N/A	N/A

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ESC, European Society of Cardiology; ESH, European Society of Hypertension; N/A, not applicable; USPSTF, U.S. Preventive Services Task Force.



**Table 4.** Application of Basic Framework to Selected “Prediseases”

	Discriminating Ability	Effective Intervention	Benefits to Harms
CIN	CIN, particularly moderate to severe, progresses over time to cervical cancer.	Removal or destruction of CIN is highly effective in preventing invasive cervical cancer.	Harms from labeling are unknown, but benefits outweigh harms.
IOP	Increased IOP discriminates poorly between those who develop POAG and those who do not.	Interventions (topical agents, laser or surgery) can reduce IOP and prevent progression to POAG and development of small visual field deficits.	Harms include false positives, local eye irritation, and cataract formation. It is unclear whether the small benefit (unproven to improve vision-related function) exceeds these harms.
Prediabetes	Progresses to diabetes at rate of 5%–10% per year.	Intensive lifestyle modifications or metformin reduces rate of development of diabetes. However, an intensive lifestyle modification program is not generally available.	Unlikely to be harm from lifestyle interventions. Effects of labeling are unknown. Prevention of diabetes is an intermediate outcome.
Prehypertension	Progresses to hypertension at a rate of 19% over 4 years.	No evidence that the coupling of the prehypertension label to a counseling message to adopt lifestyle modifications is more effective than a general message.	Harms seem unlikely unless medication is the intervention for people not otherwise at increased risk (e.g., because of diabetes or chronic kidney disease). Prevention of hypertension is an intermediate outcome.

Abbreviations: CIN, cervical intraepithelial neoplasia; IOP, increased intraocular pressure; POAG, primary open-angle glaucoma.

preventing the disease (hypertension) at all but merely represents earlier treatment of the risk factor (elevated blood pressure). One letter writer summed up the concern as follows: “The TROPHY (Trial for Preventing Hypertension) study drew the absurd conclusion that we could prevent hypertension (a condition effectively defined as eligibility for drug treatment) by starting drug treatment” (67, p. 145).

For some patients with prediabetes, drug treatment with metformin is advocated for prevention of diabetes (64). In the Diabetes Prevention Program, the 3-year incidence of diabetes among those randomized to twice-daily metformin was 7% less than the incidence among those randomized to placebo (22% vs. 29%) (65). This absolute reduction was less than that achieved with the intensive lifestyle intervention. A meta-analysis of randomized trials of metformin for prevention of diabetes demonstrated a relative odds reduction of 40% (68). Whether “preventive” treatment with metformin truly prevents diabetes or just represents earlier treatment of elevated blood glucose is less clear than in the situation with blood-pressure-lowering drug treatment of prehypertension to “prevent” hypertension (69).

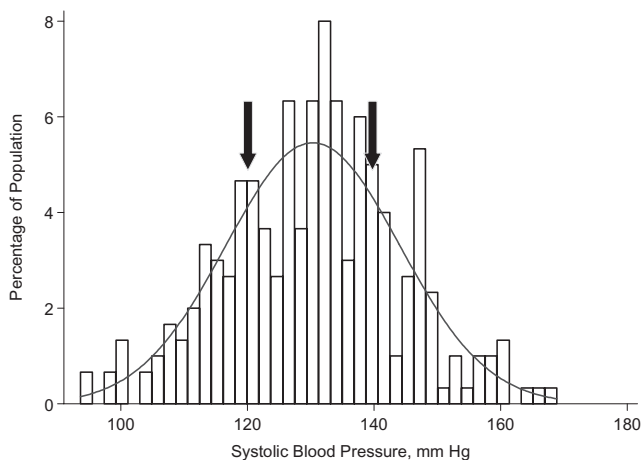
*Benefits exceed harms.* Telling people to adopt healthier lifestyles probably poses little to no harm. Ideally, the label of prediabetes or prehypertension would motivate people to adopt the lifestyle modifications but, as noted above, probably does not do so to any substantial degree. One then needs to consider whether the label itself could cause harm. For example, multiple studies have demonstrated that the label of hypertension causes psychological stress and adoption of the “sick role” (70–78). Only one study has attempted to examine the potential harms associated with labeling patients as prehypertensive (79). In that small study, the label did not appear to increase reports of worse health. Still, there could be harms that are transient or difficult to measure. Treatment of prediabetes or prehypertension with medication raises other concerns, however, with the potential for harms being more

considerable, especially when treating people who are at low risk of an adverse health outcome.

## RISK PREDICTION AS AN ALTERNATIVE

With any preventive strategy, it should be remembered that the goal is to prevent adverse health outcomes. As alluded to earlier, many common “diseases” are not defined by a sharp line separating disease from nondisease but rather by some threshold along a continuous spectrum. For many of these kinds of conditions, an alternative to diagnosis is risk prediction, or giving a person his or her estimated probability of an adverse health event (25). Thus, while not part of the 3-question framework, another question is whether the predisease category offers any advantage over risk prediction.

For many modern diseases, risk prediction can be of much greater value than diagnostic categories when it comes to shared decision making with patients (25). As an example, risk prediction is the basis for the global risk (e.g., Framingham calculation) approach to cardiovascular disease prevention (80). Such an approach facilitates a prevention strategy that keeps the goal on preventing the adverse health outcome (e.g., heart attack) using thresholds at which action is warranted based on the balance of benefits and harms (81). A man 60 years of age with a blood pressure of 138/80 mm Hg could be told he has prehypertension and “counseled” to adopt a low-sodium Dietary Approaches to Stop Hypertension (DASH) diet and to exercise more (and this counseling probably will not be effective). Alternatively, he could be informed that his risk of having a heart attack is about 13% over the next 10 years. He could be informed of the absolute benefit achievable by taking a blood-pressure-lowering medicine (and an aspirin) and, based on such discussion, could be offered blood-pressure-lowering medication (and aspirin) to reduce his risk (82). Of course, he could still be counseled to diet and exercise.

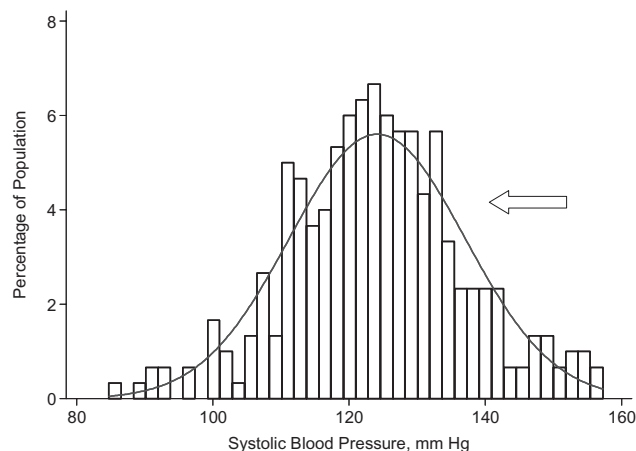


**Figure 3.** Graph of systolic blood pressure in a sample population. With the “high-risk” strategy, the goal would be to truncate the tail of the distribution of systolic blood pressure above 140 mm Hg (beyond the second black arrow). The addition of “prehypertension” (the segment of distribution between the arrows) could be thought of as a strategy that attempts to shift more people into the “high-risk” category.

### POPULATION STRATEGY REVISITED

For the most part, the “high-risk” strategy (which relies on screening) focuses on and tries to truncate the risk distribution. This truncation focuses on one tail of the distribution. The screening, diagnosis, and treatment of hypertension would ideally eliminate the tail of the distribution above a systolic blood pressure of 140 mm Hg, for example (Figure 3). For this group, the potential reduction in cardiovascular disease risk from identification and treatment of hypertension outweighs the downsides (from labeling and drug treatment). A high-risk strategy such as this unfortunately offers little potential for the population. For most “risk factor” conditions, many more adverse health events occur among people who have “average” risk factor levels because there are far more people in the middle of the distribution.

Rather than try to truncate the tail of a risk factor distribution, a population strategy of prevention would aim to shift the entire curve in the favorable direction. One effect that might be seen with a predisease category is that it shifts more people into the high-risk category (Figure 3). In the hypertension example, the prehypertension category can be viewed as an attempt to place more people in the high-risk category. However, if the motivational advantage of the high-risk strategy is lost, it will not work. In countries such as the United States, where the lifetime prevalence of hypertension is 90%, virtually everyone has “prehypertension” (83). The “cases” of hypertension do not come from just a high-risk group; they come from all groups. Since the intervention is healthy lifestyle, everyone could theoretically benefit from it. Neither patients nor clinicians seem particularly motivated by “prehypertension” (79, 84). This notion that the “cases” cannot be reliably predicted to come from a high-risk group also greatly limits the potential of screening and ought to make one final question come to mind: Would a population strategy make more sense?



**Figure 4.** Shift in the distribution of blood pressure in the population. In a population strategy of hypertension control, the goal would be to shift the entire blood pressure curve to the left (arrow). This figure shows that the mean systolic blood pressure has “shifted” to 124 mm Hg.

As mentioned earlier, in a population strategy, the goal is to eliminate (or at least mitigate) causes of incidence. Rather than just truncate the tail of the blood pressure distribution, a population strategy would shift the entire blood pressure distribution curve to the left (Figure 4). The effort to reduce sodium consumption is a good example of a population strategy (85–88). The blood pressure of the population would fall only a few mm Hg, but the reduction in cardiovascular disease events would be substantial. For many prevention efforts, some combination of high-risk and population strategies are used, but a population strategy almost always offers the most potential for prevention. In one sense, a population strategy simply views everyone as having “predisease.”

### CONCLUSIONS

This paper has sought to stimulate thinking about “predisease” (which is almost always tied to screening) and when the explicit designation of a predisease category makes sense. On one hand, for screening to be effective, there actually does need to be some type of “predisease,” at least in the sense that it represents the detectable, asymptomatic stage of disease. The detectable predisease must also progress slowly enough to allow detection by screening. If it progresses too rapidly, screening will not catch it in time for an intervention to be of benefit. Of course, diseases that have no discernible predisease phase are not going to be prevented by screening. On the other hand, predisease as an explicit category does not always make sense as part of a preventive strategy. If predisease does not discriminate well, if the offered intervention is not effective, or if the harms exceed the benefits, the use of “predisease” ought to be rethought. There are many examples of predisease (largely found by screening) that constitute overdiagnosis. In such cases, we have little to no evidence that finding these “conditions” leads to better health outcomes.

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## APPENDIX

### Article Search Strategies for Systematic Review Portion

#### *Cervical Cancer*

(“uterine cervical neoplasms”[MeSH Terms] OR (“uterine”[All Fields] AND “cervical”[All Fields] AND “neoplasms”[All Fields]) OR “uterine cervical neoplasms”[All Fields] OR (“cervical”[All Fields] AND “cancer”[All Fields]) OR “cervical cancer”[All Fields]) AND (“screening”[All Fields] OR “mass screening”[MeSH Terms] OR (“mass”[All Fields] AND “screening”[All Fields]) OR “mass screening”[All Fields] OR “screening”[All Fields] OR “early detection of cancer”[MeSH Terms] OR (“early”[All Fields] AND “detection”[All Fields] AND “cancer”[All Fields]) OR “early detection of cancer”[All Fields]) AND (“guideline”[Publication Type] OR “systematic review”[All Fields] AND (English[lang] AND (“2003”[PDAT] : “2010”[PDAT]))

#### *Glaucoma*

(“glaucoma”[MeSH Terms] OR “glaucoma”[All Fields]) AND (“screening”[All Fields] OR “mass screening”[MeSH Terms] OR (“mass”[All Fields] AND “screening”[All Fields]) OR “mass screening”[All Fields] OR “screening”[All Fields]) AND (“guideline”[Publication Type] OR “systematic review”[All Fields]) AND (English[lang] AND (“2003”[PDAT] : “2010”[PDAT]))

#### *Diabetes*

(“diabetes mellitus”[MeSH Terms]) AND (“screening”[All Fields] OR “mass screening”[MeSH Terms] OR (“mass”[All Fields] AND “screening”[All Fields]) OR “mass screening”[All Fields] OR “screening”[All Fields]) AND (“guideline”[Publication Type] OR “systematic review”[All Fields]) AND (English[lang] AND (“2003”[PDAT] : “2010”[PDAT]))

#### *Hypertension*

(“hypertension”[MeSH Terms]) AND (“screening”[All Fields] OR “diagnosis”[Subheading] OR “mass screening”[MeSH Terms] OR (“mass”[All Fields] AND “screening”[All Fields]) OR “mass screening”[All Fields] OR “screening”[All Fields]) AND (“guideline”[Publication Type] OR “systematic review”[All Fields]) AND (English[lang] AND (“2003”[PDAT] : “2010”[PDAT]))