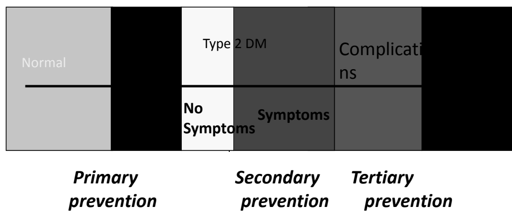
Screening for Undiagnosed Type 2 diabetes and Prediabetes

Background

- Identifying persons with undiagnosed dysglycemia may appear straightforward.
- There is an established literature on screening as well as technical reviews of screening tests for dysglycemia.
- Questions about the value of early identification of dysglycemia continue to be investigated, but there is evidence that it may reduce health care costs.
- Regardless, identification of dysglycemia remains a common activity.
- However, clinical and public health practitioners are sometimes unclear about:
  - the process of identification,
  - the distinct roles of screening versus diagnosis,
  - the implications of their decisions.

Application of Screening for Diabetes



Primary prevention *Secondary prevention* *Tertiary prevention*

1. Allocating <u>scarce resources</u> for dysglycemia <u>intervention</u> requires identification of persons who will benefit.

- **A basic ethical principle is that intervention resources should be focused on those most likely to benefit:**
  - *because health resources are limited and have alternative uses.*
- **If resources are spent on persons who will <u>not</u> benefit then:**
  - these resources are forgone because:
    - cannot now be spent on those who would benefit, or
    - cannot now be spent on interventions for other conditions.
  - This occurs when identification results in falsely characterizing some normoglycemic persons as dysglycemic.
- **Conversely, when identification falsely characterizes some dysglycemic persons as normoglycemic:**
  - these persons are effectively denied interventions that could improve their health.
- **An additional principal is to "do no harm" because some persons:**
  - may be psychologically impacted
  - may be misclassified and receive more invasive and time consuming tests
  - may be misclassified and receive interventions which have side effects

2. Identification has <u>two steps</u>: screening followed by diagnosis.

SCREENING

In terms of practical significance, and in order to avoid confusion with diagnostic testing, we define **SCREENING** simply as:

The use of <u>any criteria</u> to decide who should receive a diagnostic test.

The **GOAL OF SCREENING** is to <u>accurately distinguish</u> between:

- people with a low probability ("screen-negatives"), and
- people with a high probability ("screen-positives")

of being **DIAGNOSED** with dysglycemia.

After screening a bunch of people, what have you learned?

	"TRUTH"		
Result of Screening Test	Has Dysglycemia	Does Not Have Dysglycemia	
Screen (+)	**?**	**?**	**Total Screen-Positives**
Screen (-)	**?**	**?**	**Total Screen-Negatives**
	?	**?**	**N**

Types of Screening Tests:

"Risk Factor Tests"

(aka – "Paper-and-Pencil tests")

- **These tests often use self-reported information:**
  - age, ethnicity, sex, body weight, family Hx of DM, personal Hx of GDM, etc.
- **Often administered as questionnaires in non-clinical settings:**
  - health fairs, worksite, internet (ADA Risk Calculator)

Table 1 – FINDRISK risk factor scoring (from Ref. [20]; Table 1 p. 726).

	Score
Age (years)	
45–54	2
55–64	3
BMI (kg/m^2)	
≥25–30	1
≥30	3
Waist circumference (cm)	
Men, 94 to ≤102; women, 80 to ≤88	3
Men, >102; women, >88	4
Use of blood pressure medication[a]	2
History of high blood glucose[b]	5
Physical activity 4 h/week[c]	2
Daily consumption of vegetables, fruits, or berries	1

Risk factor screening is often implicit especially in the clinical setting

For example, the ADA recommends that candidates for the fasting or 2-h blood tests (FPG, OGTT) be chosen based on assessment of risk factors:

". . .screening should be considered by health care providers at 3-year intervals beginning at age 45, particularly in those with BMI≥25 kg/m^2"

(ADA, Screening for type 2 diabetes, Diab. Care 27 (Suppl. 1) (2004) p. S12).

Here the clinician is actually screening patients based on age and BMI in order to decide who should receive a second screening blood test [25].

Types of Screening Tests:

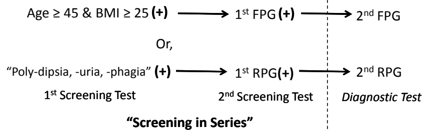
"Blood Tests"

ADA, **Screening** for type 2 diabetes, Diab. Care 27(Suppl. 1) (2004).

"The FPG is the recommended screening test… The FPG is preferred for screenings because it is faster and easier to perform, more convenient, acceptable to patients, and less expensive. "(p. S13)

"… a diagnosis of diabetes must be confirmed, on a subsequent day, by measurement of, FPG,2-h PG, or random plasma glucose (if symptoms are present). The FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost. "(p. S12)

Therefore,



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2. Identification has two steps: screening followed by diagnosis.

DIAGNOSIS

In terms of practical significance, and in order to avoid confusion with with screening, we define **DIAGNOSIS** simply as:

The use of any criteria to decide who should receive intervention for dysglycemia.

Evaluating Performance of a Screening Test by Comparing it with "Truth"*

	Result of Diagnostic Test*		
Result of Screening Test	**Has Dysglycemia**	**Does Not Have Dysglycemia**	**Predicted Totals**
Screen (+)	True Positive (TP)	**False Positive (FP)**	Positives (TP+FP)
Screen (-)	**False Negative (FN)**	True Negative (TN)	Negatives (FN+TN)
True Totals	Prevalent cases	Normals	N

Artithmetic and Definitions		
Sensitivity = (True positive rate)	TP / (TP + FN)	The probability that a person with dysglycemia will have a positive screening test.
Specificity = (True negative rate)	TN / (TN + FP)	The probability that a person without dysglycemia will have a negative screening test.
Pos. Pred. Value = (Yield)	TP / (TP + FP)	The probability that a person with a positive screening test will have dysglycemia.

3. Lowering a screening test's cut-off score identifies more persons with dysglycemia, but *causes more normoglycemic persons to receive diagnostic testing*.

Example 1: Screening test with "low cutoff": very sensitive but not specific

(prevalence of dysglycemia = 10%)

	Result of Diagnostic Test		
Result of Screening Test	**Has Dysglycemia**	**Does Not Have Dysglycemia**	**Predicted Totals**
Screen (+)	9 (TP)	**50 (FP)**	**59**
Screen (-)	**1 (FN)**	40 (TN)	**41**
True Totals	**10**	**90**	**100**

Arithmetic		
Sensitivity = (True positive rate)	TP / (TP + FN)	9/10 = **90%**
Specificity = (True negative rate)	TN / (TN + FP)	40/90 = **44%**
Pos. Pred. Value = (Yield)	TP / (TP + FP)	9/59 = **15%**

4. Raising a screening test's cut-off score reduces needless diagnostic testing, but *increases the number with dysglycemia who are never diagnosed.*

Example 2: Screening test with "high cutoff": very specific but insensitive
(prevalence of dysglycemia = 10%)

	Result of Diagnostic Test		
Result of Screening Test	**Has Dysglycemia**	**Does Not Have Dysglycemia**	**Predicted Totals**
Screen (+)	1 (TP)	2 (FP)	3
Screen (-)	9 (FN)	88 (TN)	97
True Totals	10	90	100

Arithmetic		
Sensitivity = (True positive rate)	TP / (TP + FN)	1/10 = **10%**
Specificity = (True negative rate)	TN / (TN + FP)	88/90 = **98%**
Pos. Pred. Value = (Yield)	TP / (TP + FP)	1/3 = **33%**

5. With limited budgets for intervention, raising a screening test's cut-off score may be appropriate. With ample budgets, lowering the test's cut-off score may be appropriate.

6. Screening tests are most efficient in populations with high prevalence of dysglycemia.

Example 1-A: Same as Example 1; very sensitive but not specific

However, now the prevalence of dysglycemia = 30%

	Result of Diagnostic Test		
Result of Screening Test	**Has Dysglycemia**	**Does Not Have Dysglycemia**	**Predicted Totals**
Screen (+)	27 (TP)	39 (FP)	66
Screen (-)	3 (FN)	31 (TN)	34
True Totals	30	70	100

Arithmetic		
Sensitivity = (True positive rate)	TP / (TP + FN)	27/30 = **90%**
Specificity = (True negative rate)	TN / (TN + FP)	31/70 = **44%**
Pos. Pred. Value = (Yield)	TP / (TP + FP)	27/66 = **41%** (vs. **15%** @ 10% prevalence)

Remember Example 1

	Diagnostic Test		
Screening Test	**Has Dysglycemia**	**Does Not Have Dysglycemia**	**Predicted Totals**
Screen (+)	9 (TP)	50 (FP)	59
Screen (-)	1 (FN)	40 (TN)	41
True Totals	10	90	100

9/59 = 15%

Example 2-A: Screening test with "high cutoff": very specific but insensitive

However, now the prevalence of dysglycemia = 30%

	Result of Diagnostic Test		
Result of Screening Test	**Has Dysglycemia**	**Does Not Have Dysglycemia**	**Predicted Totals**
Screen (+)	3 (TP)	2 (FP)	5
Screen (-)	27 (FN)	68 (TN)	95
True Totals	30	70	100

Arithmetic		
Sensitivity = (True positive rate)	TP / (TP + FN)	3/30 = **10%**
Specificity = (True negative rate)	TN / (TN + FP)	68/70 = **97%**
Pos. Pred. Value = (Yield)	TP / (TP + FP)	3/5 = **60%** (vs. **33%** @ 10% prevalence)

Remember Example 2

	Diagnostic Test		
Screening Test	**Has Dysglycemia**	**Does Not Have Dysglycemia**	**Predicted Totals**
Screen (+)	1 (TP)	2 (FP)	3
Screen (-)	9 (FN)	88 (TN)	97
True Totals	10	90	100

1/3 = 33%

Broadening definition of dysglycemia improves the yield of the screening test: A real-world example

Table 3 – Performance of the FINDRISC screening test compared to the oral glucose tolerance diagnostic test in 1617 women[a].

FINDRISC cut-off for diabetes	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Undiagnosed diabetes (prevalence = 6%)			
11	70	61	11
15	38	85	16
FINDRISC cut-off for dysglycemia	**Sensitivity (%)**	**Specificity (%)**	**Positive predictive value (%)**
Dysglycemia (diabetes + pre-diabetes) (prevalence = 27%)			
11	53	66	55
15	27	88	57

What is the "Area Under the Curve"?

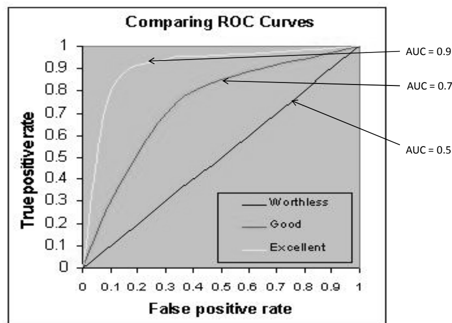
• It is common for evaluations of screening tests that have continuous scores (such as blood glucose values or risk factor scores) to report the area under the curve" (AUC). (aka: C-statistic)

• The AUC is the area under the Receiver Operating Characteristic (ROC) curve.

•It is calculated across the entire range of a screening test's scores because for each score there is a mathematical relationship between the sensitivity (true positive rate) and 1-specificity (false positive rate).

• The AUC represents the probability that, when we select at random one person with diabetes and one person without diabetes, the screening test will assign a higher score to the person with diabetes than to the person without diabetes.

What is the AUC?



Weighing the Benefits and Risks

- Reasons to Screen:
  - Effective early treatment for diabetes.
  - Effective preventive intervention.
  - Good cost-effectiveness ratios for screening and preventive interventions.
- Reasons not to Screen:
  - No direct (i.e., experimental) evidence shows that earlier detection leads to better outcomes.
  - Adverse psychological and social ramifications; labeling.
  - Unintended consequences of medical care and may violate the public health principal of "do no harm".
  - Poor health system capacity.

Summary of Current Screening Recommendations

- USPSTF: Don't screen asymptomatic people unless they have hypertension.
- World Health Organization:
  - Countries should develop context-specific policies.
  - Testing in health care systems may be justified with appropriate health system capacity and follow-up.
  - Haphazard screening not justified.
- CDC/ADA Technical Report:
  - Opportunistic screening in health care settings recommended for people with risk factors.

Recent Findings from Simulations of Pre-Diabetes Screening Programs

- Screening and intervention for pre-diabetes among overweight or obese adults age 45-74 is highly cost-effective (~$8000/QALY) (Hoerger et al., 2007).
- CE ratios best for group intervention, middle age, screening every 3 yr, and for lifestyle (Hoerger et al., 2007).
- Screening + intervention for pre-diabetes and diabetes in combination is highly cost-effective and more so than screening for DM or pre-DM alone (Gillies et al., 2007).

Recommendation #1: Actively screen for diabetes *and* pre-diabetes in adults in health care settings and in *established clinical/community partnerships*.

- Risk factor-based risk scores most appropriate first stage screening tools.
- More efficient in settings where the prior probability of diabetes is high (e.g., high risk counties, minority communities, Medicare).
- More efficient in "integrated" manner, connected to lipid, blood pressure.
- Use A1c or FPG to confirm diagnoses and refer.

Application of Risk Scores to Public Health Intervention

TYPE 2 DIABETES RISK ASSESSMENT FORM

Diabetes incidence, %

Men Women

Risk Score

Risk Reduction with Lifestyle:

FINDRISC Score	Reduction
<10	0
10-14	16%
15-19	66%
>19	78%

The Canadian Diabetes Risk Assessment Questionnaire

CANRISK

FIGURE 1 The Cambridge Diabetes Risk

Screening for Type 2 Diabetes

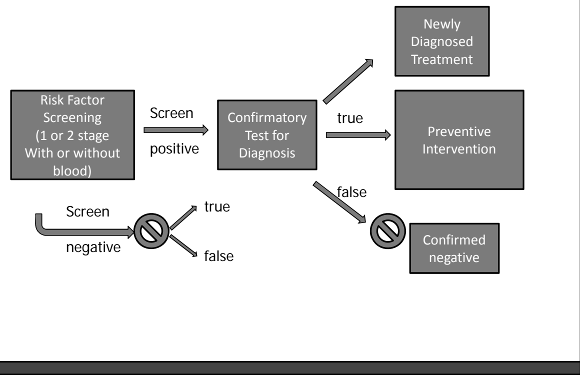
© World Health Organization 2003

Figure 2 – considerations relevant to the development of a screening policy

To Screen	Not to screen
Clear evidence that screening is beneficial	Clear evidence that screening is harmful
High prevalence of undiagnosed type 2 diabetes	Low prevalence of undiagnosed type 2 diabetes
High prevalence of cardiovascular disease (CVD) risk and other complications amongst people with type 2 diabetes	Low prevalence amongst people with type 2 diabetes
High capacity of health care system for screening	Low capacity of health care system for screening
High capacity of the health care system for effective clinical management of those who screen positive	Low capacity of the health care system for effective clinical management of those who screen positive
High capacity of the health care system for supporting the psycho-social effects of screening	Low capacity of the health care system for supporting the psycho-social effects of screening
High capacity of the health care system to implement prevention strategies in individuals at high risk of the future development of diabetes even those who screen negative on that occasion	Low capacity of the health care system to implement these prevention strategies
Low cost of early detection	High cost of early detection
Low cost of clinical management	High cost of clinical management

Epidemiological considerations | Considerations of health system capacity | Economic considerations

Key Steps in a Screening Program



Recommendation #2: <u>Discourage</u> diabetes screening under the following conditions:

- Population-wide blood screening in the absence of risk factor assessment or in settings dominated by low-risk persons.
- Community settings (health fairs, malls, retail stores, etc.) that lack a direct relationship with a health care provider.
- Youth and adolescents
  - (Instead, the focus should be on access and quality care for diabetes and on obesity prevention).

Practicum / Activity

Conditions Necessary for Screening Asymptomatic Populations:

1. Significant health burden
2. "Preclinical" detectable phase exists
3. Good screening tests exist
   1. Safe
   2. Accurate (sensitivity, specificity, PPV)
   3. Practical and cost-effective
4. Early treatment is beneficial
5. Health care system can handle case finding as well implementation of interventions.

*Engelgau et al Diabetes Care 2000

Example #1: In a community of 1000 people a screening program was conducted. Following complete follow-up to determine case status, the following results were observed:

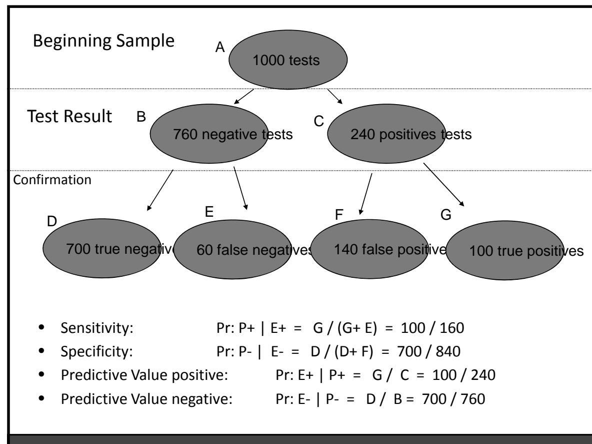
- 100 diabetes cases were correctly identified.
- 60 diabetes cases were missed
- 700 healthy individuals were *correctly* determined to *not have* diabetes
- 140 healthy individuals were *incorrectly* determined to have diabetes

	Disease Status		
Results of screen test	Positive	Negative	Total
Positive	100	140	240
Negative	60	700	760
Total	160	840	1000

Example #1: Sensitivity, specificity, and PV+ of capillary testing in the general population.

	Disease Status		
Results of screen test	Positive	Negative	Total
Positive	100	140	240
Negative	60	700	760
Total	160	840	1000

Sensitivity = 100/160 = 63% (A/ (A+C))
Specificity = 700/840= 83% (D/ (B+D))
PV + = 100 /240 = 42%
Prevalence = 160/1000= 16%
Accuracy = 800/1000= 80%



Example #2: A follow-up screening program conducted among a community thought to have many *high risk adolescents* yielded the following:

- 10 diabetes cases were correctly identified.
- 6 diabetes cases were missed
- 820 healthy individuals were *correctly* determined to *not have* diabetes
- 164 healthy individuals were *incorrectly* determined to have diabetes

What is the:

- Sensitivity ?
- Specificity ?
- Predictive Value Positive ?
- Prevalence ?

Example #2: Sensitivity, specificity, and PV+ of capillary testing among adolescents

Results of screen test	Disease Status: Positive	Negative	Total
Positive	10	164	174
Negative	6	820	826
Total	16	984	1000

Sensitivity = 10/16 = 63% (A/ (A+C))
Specificity = 820/984= 83% (D/ (B+D))
Accuracy = (10 +820) / 1000 = 83%
PV + = 10/174 = 6%
Prevalence = 16/1000= 1.6%