

Methods: Mind the Gap  
Webinar Series

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# The Importance of Epidemiology in Screening and Diagnosis of Diabetes



Presented by:

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# The Importance of Epidemiology in Screening and Diagnosis of Diabetes

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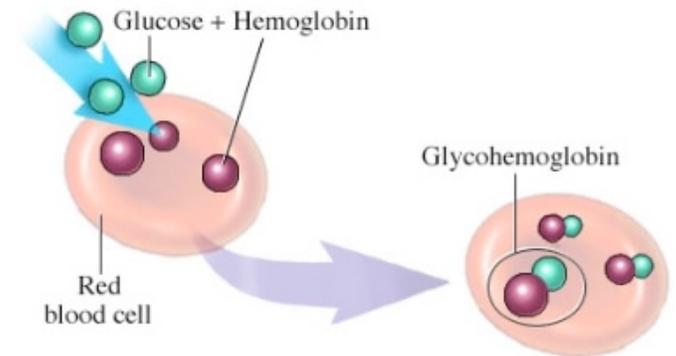
# Measures of glycemia

- Fasting glucose
- Post-prandial (2-hour) glucose (OGTT)
- Glycated hemoglobin (hemoglobin A1c or HbA1c)



# Glycated hemoglobin (HbA1c)

- Glucose binds to hemoglobin in red blood cells (RBCs), forming “glycated hemoglobin”
- Related to average lifespan of RBCs, the HbA1c value provides a measure of the average glucose level or “glycemic control”
- %HbA1c is reliable measure of glucose exposure in past 2-3 months
- “Normal” (non-diabetic) level <6.5%



# Tests of Glycemia

Tests of Glycemia	Characterization of Glycemia	Intra-assay CV	Within-person CV <sup>1</sup>	Factors Affecting Absolute Values
<b>Glucose</b> (modified hexokinase method)	<ul style="list-style-type: none"> <li>• Acute (immediate)</li> </ul>	<3%	<b>5.7%</b>	<ul style="list-style-type: none"> <li>• Subject preparation, i.e. fasting status</li> <li>• Illness</li> <li>• Stress, including recent activity levels</li> </ul>
<b>2-hour Glucose</b> (modified hexokinase method)	<ul style="list-style-type: none"> <li>• Post-prandial (response to glucose challenge)</li> </ul>	<3%	<b>16.6%</b>	<ul style="list-style-type: none"> <li>• Subject preparation and burden, fasting and testing period</li> <li>• Illness</li> <li>• Stress, including recent activity levels</li> </ul>
<b>Hemoglobin A1c</b> (Primus or HPLC)	<ul style="list-style-type: none"> <li>• 2-3 month endogenous glucose exposure</li> </ul>	<2%	<b>3.6%</b>	<ul style="list-style-type: none"> <li>• Alterations in red cell turnover (e.g., hemolysis, anemia)</li> <li>• Dialysis / renal failure</li> <li>• Hemoglobinopathies</li> <li>• Large doses of vitamin C, aspirin</li> </ul>

<sup>1</sup>Selvin et al, 2007 Arch Int Med



# What is a diagnostic test?

- A test that classifies *individuals with signs and symptoms* as having the disease or not.
- Requires high probability that the diagnostic test is correct.
- Diagnosis involves *individual classification*, NOT statistical distinction of *group averages*.



# Goals of diagnosis

- In patients in whom the diagnostic test is applied, the goals are to:
  - Improve overall health outcomes
  - Reduce suffering
- On balance, do more **good** than **harm**.

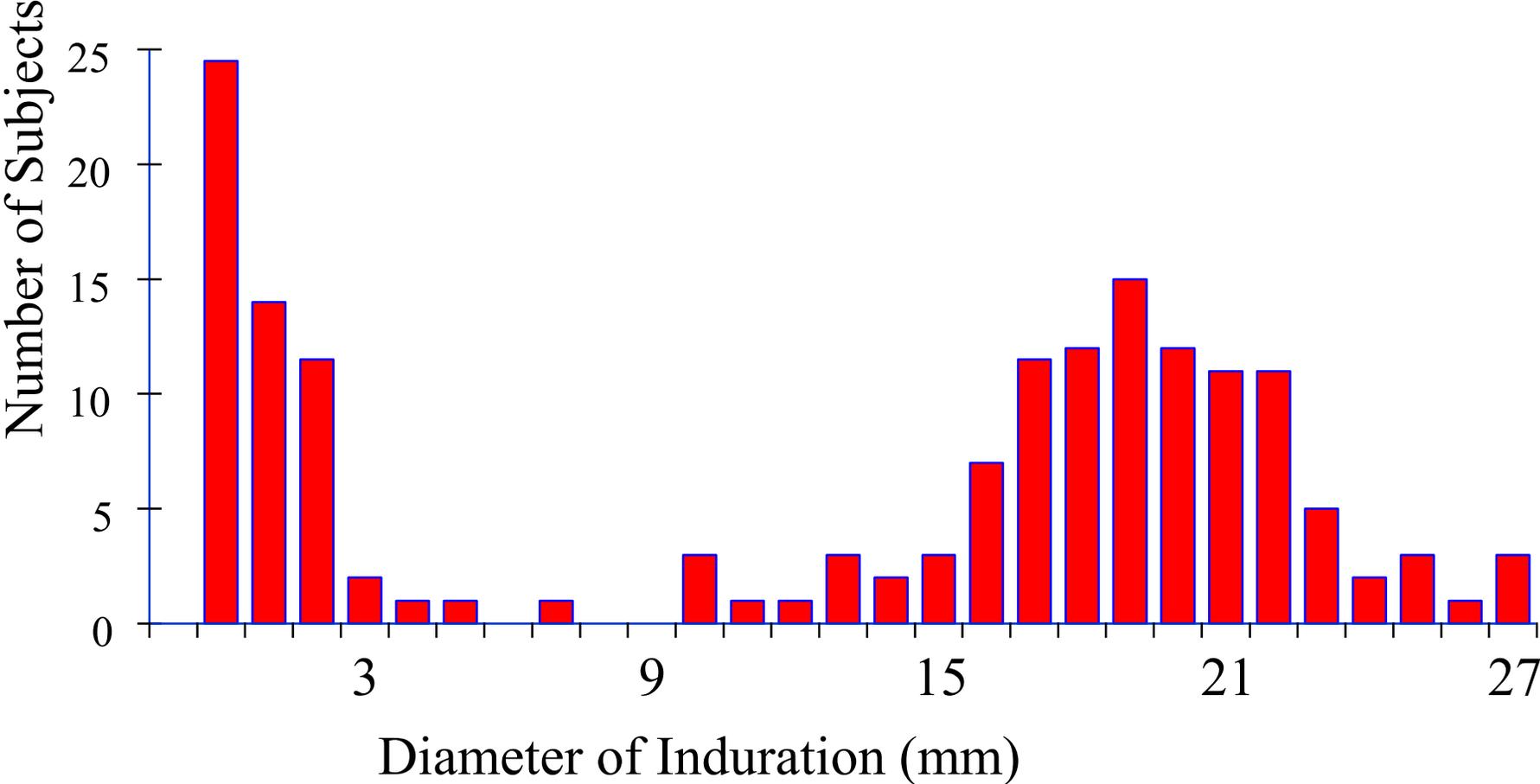


# What is a screening test?

- A test that classifies *apparently healthy individuals* (e.g., asymptomatic) as likely to have the disease (or not).



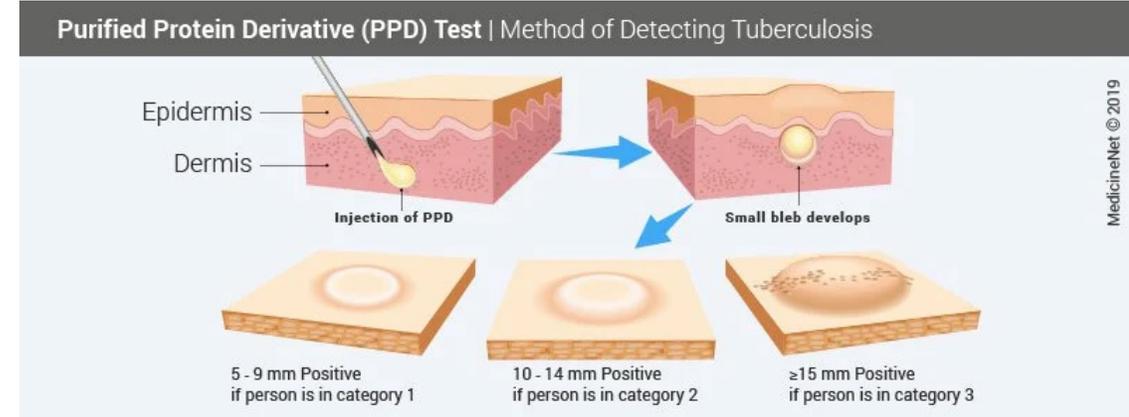
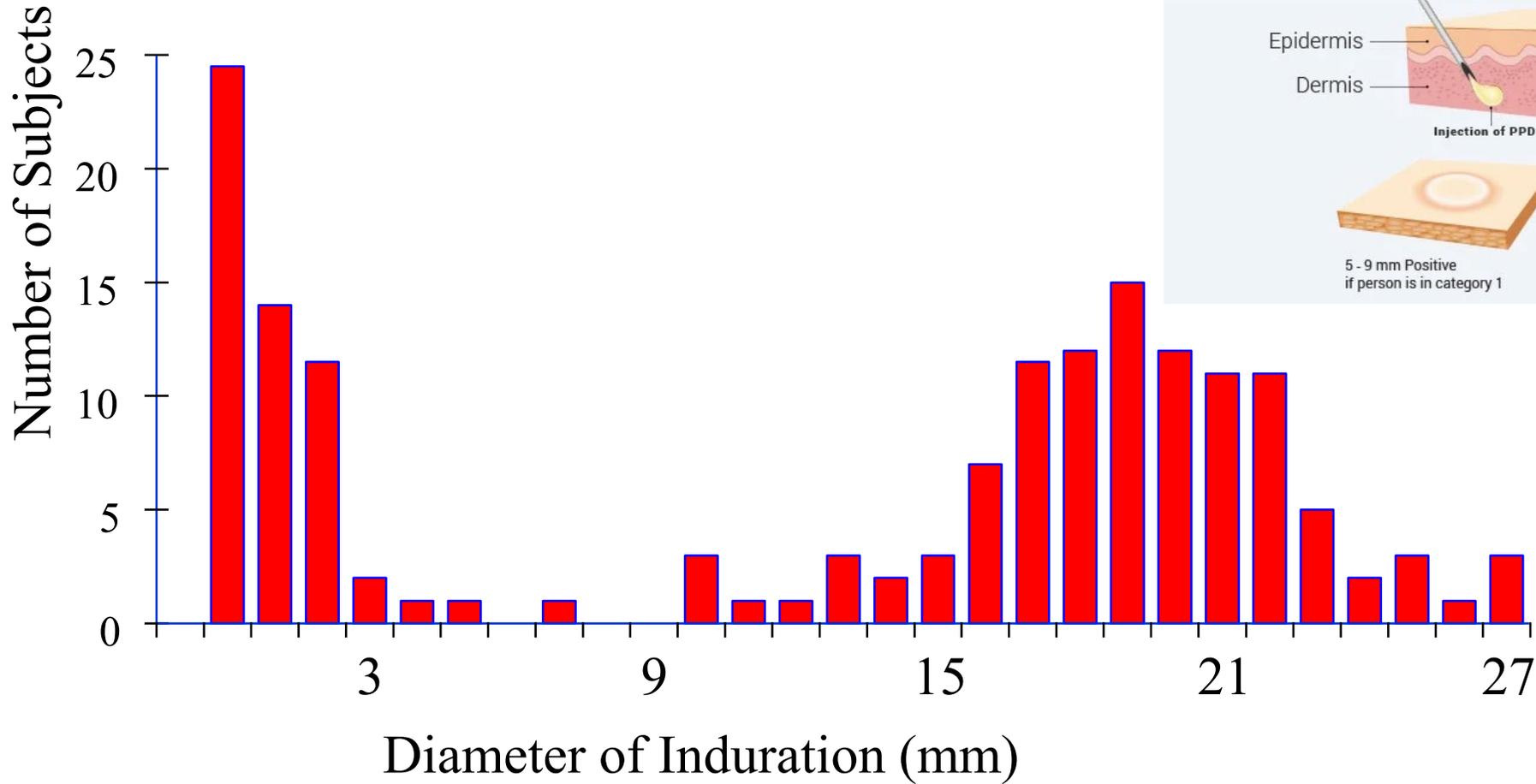
# Distribution of tuberculin reactions



Source: *Edwards et al, WHO Monograph 12, 1953 (L. Gordis, Epidemiology)*



# Distribution of tuberculin reactions



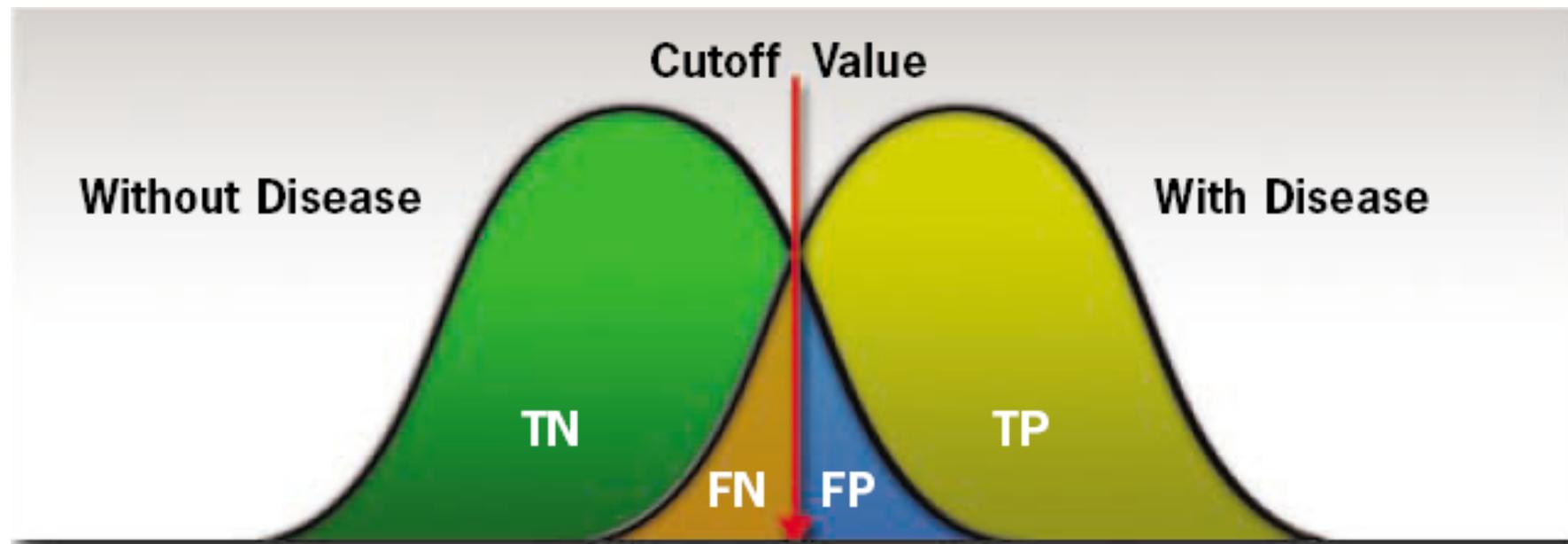
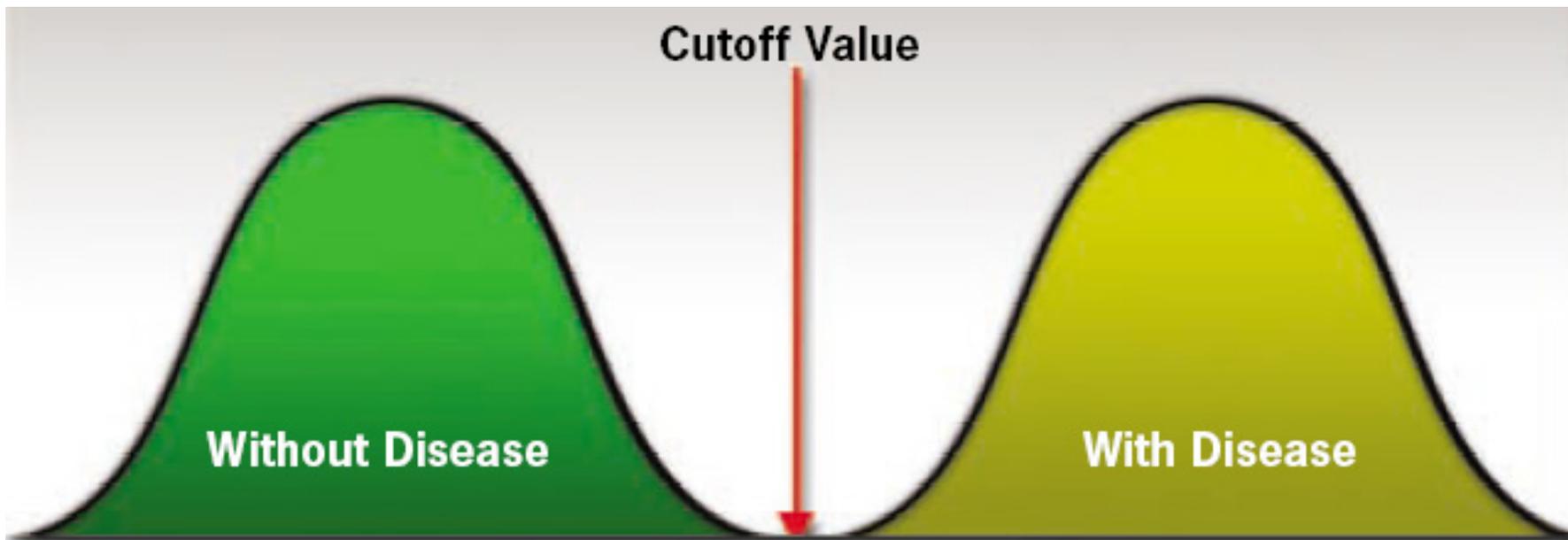
Source: Edwards et al, WHO Monograph 12, 1953 (L. Gordis, Epidemiology)



## Distribution of human characteristics

- Many human characteristics have a continuous scale: e.g., blood pressure, fasting glucose, 2-hour glucose, HbA1c, cholesterol, kidney function, hormones
- Distribution of biologic measurements in humans may not permit easy separation of diseased from non-diseased individuals based upon the value of the measurement





## Diagnostic cut-points

- Cut-points are necessary in clinical practice
  - Making a diagnosis is fundamental to care
  - Treatment, prognosis, use of health care resources



# **The Epidemiology of Biomarkers of Hyperglycemia:**

***Importance for Informing Diabetes  
Screening and Diagnostic Cut-points***

# How do we evaluate the validity of a diagnostic or screening test?

- **Compare to the “truth” or gold standard test.**



## Issues in deciding on diagnostic cut-points

- Imperfect “gold standard” tests for defining diabetes
- Type 2 diabetes has a gradual onset; glucose levels rise over time
- Complications or long-term prognosis are also useful “gold standards”
  - Microvascular disease (more specific to diabetes)
  - Macrovascular disease (less specific but more common)



## **Retinopathy is an important 'gold standard' in diabetes**

- Early studies showed high prevalence of microvascular complications in diabetes before the onset of symptoms (Keen et al 1970s)
- Levels of glycemia below which there is little prevalent retinopathy and above which retinopathy increases in a linear fashion (1990s)
  - Supplanted the notion that progression to overt, symptomatic diabetes should be the basis for diagnosis.



# 1997 Diagnostic Criteria for Type 2 Diabetes

Table 2—Criteria for the diagnosis of diabetes

- |    |   |
|----|---|
| 1. | FPG $\geq$ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*   |
| OR |   |
| 2. | Symptoms of hyperglycemia and a casual plasma glucose $\geq$ 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss. |
| OR |   |
| 3. | 2-h plasma glucose $\geq$ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*                         |

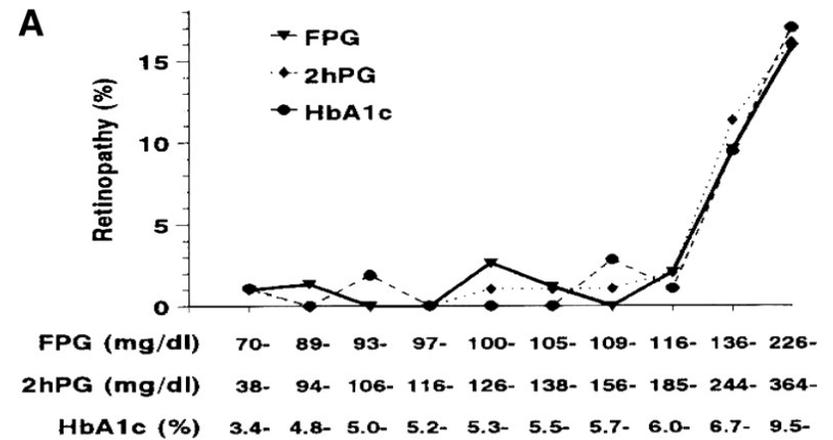
\*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.



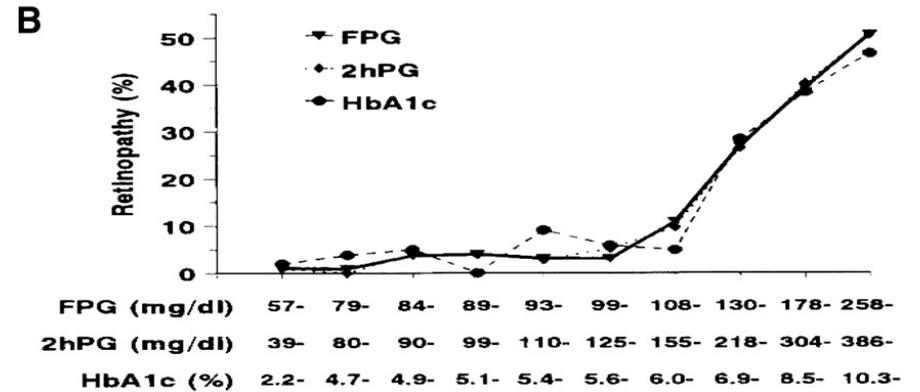
# Tests of Hyperglycemia and Retinopathy

- Retinopathy is highly specific to diabetes
- Diagnostic cut-points largely based on associations with retinopathy

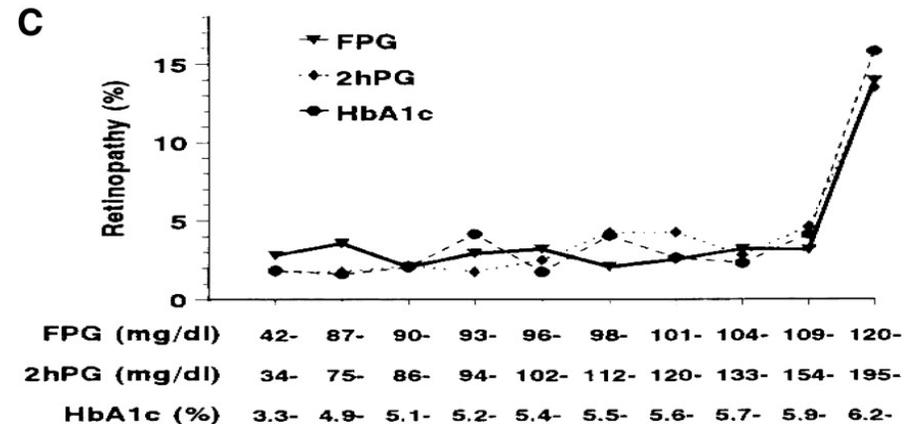
Pima Indians  
N=960



Egyptians  
N=1,018



USA general population  
(NHANES III)  
N=2,821



## Glycemia and long-term outcomes

- In cross-sectional studies, HbA1C is strongly linked to **retinopathy**
- We know from **clinical trials that** lowering **HbA1c** (glucose control) prevents microvascular (small vessel) disease in persons with diabetes
  - Evidence-base for the use of **HbA1c** for monitoring and guiding treatment in diabetes



## What about the use of HbA1c for diagnosis?

- For decades, fasting glucose has been the standard used to diagnose diabetes in the U.S.
- Historically, HbA1c has been recommended **only** for determination of glucose control among persons with diagnosed diabetes.
- By 2005 or so, assay standardization no longer an issue – HbA1c assays are now well standardized.
  - National Glycohemoglobin Standardization Program: [ngsp.org](http://ngsp.org)



**Old Paradigm: *Glucose is best for diagnosis of diabetes; HbA1c should not be used for diagnosis (only for monitoring of glycemic control)***

**New paradigm: *HbA1c is a powerful diagnostic test and can have advantages over glucose.***



## **Advantages of HbA1c for diagnosis of diabetes?**

- Much less biologic variability (vs fasting or 2-hr glucose)
- Better index of overall glycemic exposure
- Better or as well-standardized as glucose
- No need for fasting or timed samples
- Relatively unaffected by acute factors
- Already used to guide and adjust treatment

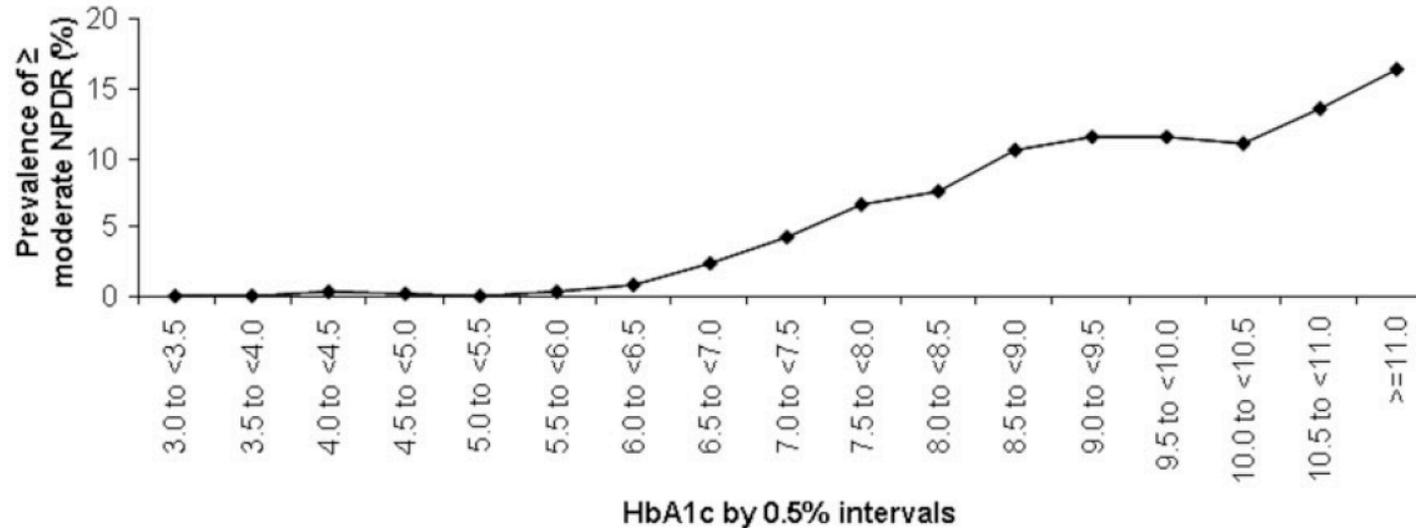


# June 2009 International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes

THE INTERNATIONAL EXPERT COMMITTEE\*

*Role of the A1C assay in the diagnosis of diabetes*

HbA1c  $\geq 6.5\%$  represents an  
“optimal” cut-point for defining  
diabetes



**Figure 2**—Prevalence of retinopathy by 0.5% intervals and severity of retinopathy in participants aged 20–79 years. NPDR, nonproliferative diabetic retinopathy. Adapted with permission from (S. Colagiuri, personal communication).



# Diagnosis of Diabetes – January 2010

## AMERICAN DIABETES ASSOCIATION

Table 2—*Criteria for the diagnosis of diabetes*

1. A1C  $\geq$ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.\*  
OR
2. FPG  $\geq$ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.\*  
OR
3. Two-hour plasma glucose  $\geq$ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.\*  
OR
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose  $\geq$ 200 mg/dl (11.1 mmol/l).

\*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.



# Hyperglycemia and Retinopathy

- Epidemiologic data can inform how glycemic measures relate to health outcomes among initially non-diabetic individuals
- Is **retinopathy** the optimal “gold standard” for defining diabetes?
  - What are some other relevant “gold standards”?



# HbA1c and Cardiovascular Outcomes?

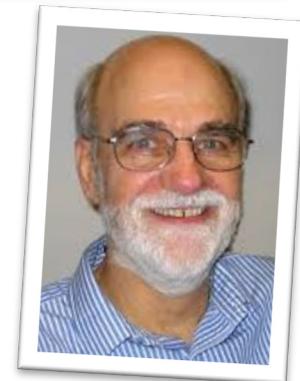
- The vast majority of deaths and hospitalizations in diabetes are from cardiovascular disease
  - **~70% of deaths in diabetes are from cardiovascular causes**
- Long-term prognostic data for major causes of morbidity and mortality are useful for informing diagnostic cut-points
  - **Few data on HbA1c and long-term outcomes in persons without a prior diagnosis of diabetes**



ORIGINAL ARTICLE

# Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults

Elizabeth Selvin, Ph.D., M.P.H., Michael W. Steffes, M.D., Ph.D., Hong Zhu, B.S.,  
Kunihiro Matsushita, M.D., Ph.D., Lynne Wagenknecht, Dr.P.H.,  
James Pankow, Ph.D., M.P.H., Josef Coresh, M.D., Ph.D.,  
and Frederick L. Brancati, M.D., M.H.S.



- Persons with HbA1c  $\geq 6.0\%$  are at high risk for the development of diabetes, cardiovascular outcomes, and death
  - HbA1c is useful marker to identify persons at risk for not only diabetes but also cardiovascular disease and death
- HbA1c is superior to fasting glucose for assessment of long-term prognosis
- Established the link between HbA1c and future vascular risk in an initially non-diabetic population
  - Evidence supporting the use of HbA1c as a diagnostic test

## **Advantages of HbA1c for diagnosis of diabetes?**

- Much less biologic variability (vs fasting or 2-hr glucose)
- Better index of overall glycemic exposure
- Better or as well-standardized as glucose
- No need for fasting or timed samples
- Relatively unaffected by acute factors
- Already used to guide and adjust treatment
- **Associated with major clinical outcomes including cardiovascular disease and death; with stronger associations than fasting glucose**



# **Variability In Measures Of Hyperglycemia:**

***Implications for Diagnosis***

**Old Paradigm: *A second blood draw is required for confirmatory testing for diabetes***

**New paradigm: *Using a combination of fasting glucose and HbA1c in a single blood sample is an efficient approach for diagnosis of diabetes.***



# Old Paradigm: Diagnosis of Diabetes – January 2010

## AMERICAN DIABETES ASSOCIATION

Table 2—Criteria for the diagnosis of diabetes

1. A1C  $\geq 6.5\%$ . The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.\*  
OR
2. FPG  $\geq 126$  mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.\*  
OR
3. Two-hour plasma glucose  $\geq 200$  mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.\*  
OR
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose  $\geq 200$  mg/dl (11.1 mmol/l)

\*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.



# Single-sample confirmatory definition of diabetes based on A1C and glucose

- Until 2019, current clinical practice guidelines recommended repeat testing of the same test in a new blood sample at a second time point
  - Reduce the possibility of a false-positive diagnosis
  - But requires a second visit and a second blood draw (high burden)
- It is common two different tests (e.g. HbA1c and fasting glucose) to be measured in the same blood sample
- Unclear if a combination of HbA1c and fasting glucose at a single time point provides adequate confirmation for diagnosis of diabetes





# Prognostic Implications of Single-Sample Confirmatory Testing for Undiagnosed Diabetes

## A Prospective Cohort Study

Elizabeth Selvin, PhD, MPH; Dan Wang, MS; Kunihiro Matsushita, MD, PhD; Morgan E. Grams, MD, PhD, MHS; and Josef Coresh, MD, PhD, MHS

**Background:** Current clinical definitions of diabetes require repeated blood work to confirm elevated levels of glucose or hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) to reduce the possibility of a false-positive diagnosis. Whether 2 different tests from a single blood sample provide adequate confirmation is uncertain.

**Objective:** To examine the prognostic performance of a single-sample confirmatory definition of undiagnosed diabetes.

**Design:** Cohort study.

**Setting:** The ARIC (Atherosclerosis Risk in Communities) study.

**Participants:** 13 346 ARIC participants (12 268 without diagnosed diabetes) with 25 years of follow-up for incident diabetes, cardiovascular outcomes, kidney disease, and mortality.

**Measurements:** Confirmed undiagnosed diabetes was defined as elevated levels of fasting glucose ( $\geq 7.0$  mmol/L [ $\geq 126$  mg/dL]) and HbA<sub>1c</sub> ( $\geq 6.5\%$ ) from a single blood sample.

**Results:** Among 12 268 participants without diagnosed diabetes, 978 had elevated levels of fasting glucose or HbA<sub>1c</sub> at baseline (1990 to 1992). Among these, 39% had both (confirmed undiagnosed diabetes), whereas 61% had only 1 elevated measure (unconfirmed undiagnosed diabetes). The confirmatory

definition had moderate sensitivity (54.9%) but high specificity (98.1%) for identification of diabetes cases diagnosed during the first 5 years of follow-up, with specificity increasing to 99.6% by 15 years. The 15-year positive predictive value was 88.7% compared with 71.1% for unconfirmed cases. Confirmed undiagnosed diabetes was significantly associated with cardiovascular and kidney disease and mortality, with stronger associations than unconfirmed diabetes.

**Limitation:** Lack of repeated measurements of fasting glucose and HbA<sub>1c</sub>.

**Conclusion:** A single-sample confirmatory definition of diabetes had a high positive predictive value for subsequent diagnosis and was strongly associated with clinical end points. Our results support the clinical utility of using a combination of elevated fasting glucose and HbA<sub>1c</sub> levels from a single blood sample to identify undiagnosed diabetes in the population.

**Primary Funding Source:** National Institute of Diabetes and Digestive and Kidney Diseases and National Heart, Lung, and Blood Institute.

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For author affiliations, see end of text.

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# Single-sample confirmatory testing for diagnosis of diabetes

- Two tests (HbA1c and fasting glucose) from the same blood sample provide adequate confirmation for diagnosis
  - High positive predictive value for future diagnosis of diabetes
  - Strongly associated with complications (heart disease, kidney disease, death)
- Streamlined process for diagnosis of diabetes
  - HbA1c test is used to guide treatment decisions
  - Single elevations in HbA1c or fasting glucose (“unconfirmed cases”) should have tests repeated at a second time point per guidelines
- If tests have sizable discordance, this suggests a processing problem or co-existing medication condition that may be interfering with either test



# Diagnosis of Diabetes – 2020

## AMERICAN DIABETES ASSOCIATION

**Table 2.2—Criteria for the diagnosis of diabetes**

FPG  $\geq$ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.\*

OR

2-h PG  $\geq$ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.\*

OR

A1C  $\geq$ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.\*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose  $\geq$ 200 mg/dL (11.1 mmol/L).

\*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.



# 2020 ADA Guidelines - Criteria for the Diagnosis of Diabetes

*“Unless there is a clear clinical diagnosis.... a second test is required for confirmation. ...*

*If two different tests (such as A1C and FPG) are both above the diagnostic threshold, this also confirms the diagnosis....”*

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# **Variability In Measures Of Hyperglycemia:**

***Implications for Prevalence***

**Old Paradigm: *Over one third of diabetes cases in the in the U.S. are undiagnosed.***

**New Paradigm: *Conventional prevalence estimates of undiagnosed diabetes are inaccurate; only a small proportion (~11%) of persons with diabetes are undiagnosed.***



# Implications of Variability on Prevalence

- High variability in 2-hour glucose and fasting glucose, especially relative to HbA1c
  - E.g., ~30% of persons with elevated fasting glucose will re-test negative (below threshold for diagnosis) if re-tested at a second visit
- Guidelines for diagnosis of diabetes are to use two measurements to confirm the diagnosis
  - Want to make sure we are not capturing false positive cases
- If only a single measurement is used to define diabetes, prevalence estimates will be inflated



# Impact of Variability on Defining Diabetes?

- Using conventional definitions from prior epidemiologic studies, prevalence of undiagnosed diabetes is substantially overestimated (3-4 times higher estimates)
- Implications for estimating the % of cases that are undiagnosed is substantial
  - Critical measure for monitoring how we are doing with screening and diagnosis
- Solutions?
  - Repeat measurements to confirm cases of diabetes
  - Use definitions that more closely approximate those used in clinical practice



# Epidemiologic Definitions of Diabetes

## Non-confirmatory definitions (in widespread use)

- Fasting glucose  $\geq 126$  mg/dL
- HbA1c  $\geq 6.5\%$
- 2-hour glucose  $\geq 200$  mg/dL
- Fasting glucose  $\geq 126$  mg/dL **OR** HbA1c  $\geq 6.5\%$  **OR** 2-hour glucose  $\geq 200$  mg/dL

## Confirmatory definitions (not used in prior studies)

- Fasting glucose  $\geq 126$  mg/dL **AND** HbA1c  $\geq 6.5\%$
- Fasting glucose  $\geq 126$  mg/dL at two separate time points
- HbA1c  $\geq 6.5\%$  at two separate time points



# Identifying Trends in Undiagnosed Diabetes in U.S. Adults by Using a Confirmatory Definition

## A Cross-sectional Study

Elizabeth Selvin, PhD, MPH; Dan Wang, MS; Alexandra K. Lee, PhD, MSPH; Richard M. Bergenstal, MD; and Josef Coresh, MD, PhD

**Background:** A common belief is that one quarter to one third of all diabetes cases remain undiagnosed. However, such prevalence estimates may be overstated by epidemiologic studies that do not use confirmatory testing, as recommended by clinical diagnostic criteria.

**Objective:** To provide national estimates of undiagnosed diabetes by using a confirmatory testing strategy, in line with clinical practice guidelines.

**Design:** Cross-sectional study.

**Setting:** National Health and Nutrition Examination Survey results from 1988 to 1994 and 1999 to 2014.

**Participants:** U.S. adults aged 20 years and older.

**Measurements:** Confirmed undiagnosed diabetes was defined as elevated levels of fasting glucose ( $\geq 7.0$  mmol/L [ $\geq 126$  mg/dL]) and hemoglobin A<sub>1c</sub> ( $\geq 6.5\%$ ) in persons without diagnosed diabetes.

**Results:** The prevalence of total (diagnosed plus confirmed undiagnosed) diabetes increased from 5.5% (9.7 million adults) in 1988 to 1994 to 10.8% (25.5 million adults) in 2011 to 2014. Confirmed undiagnosed diabetes increased during the past 2

decades (from 0.89% in 1988 to 1994 to 1.2% in 2011 to 2014) but has decreased over time as a proportion of total diabetes cases. In 1988 to 1994, the percentage of total diabetes cases that were undiagnosed was 16.3%; by 2011 to 2014, this estimate had decreased to 10.9%. Undiagnosed diabetes was more common in overweight or obese adults, older adults, racial/ethnic minorities (including Asian Americans), and persons lacking health insurance or access to health care.

**Limitation:** Cross-sectional design.

**Conclusion:** Establishing the burden of undiagnosed diabetes is critical to monitoring public health efforts related to screening and diagnosis. When a confirmatory definition is used, undiagnosed diabetes is a relatively small fraction of the total diabetes population; most U.S. adults with diabetes (about 90%) have received a diagnosis of the condition.

**Primary Funding Sources:** National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases and National Heart, Lung, and Blood Institute.

*Ann Intern Med.* doi:10.7326/M17-1272

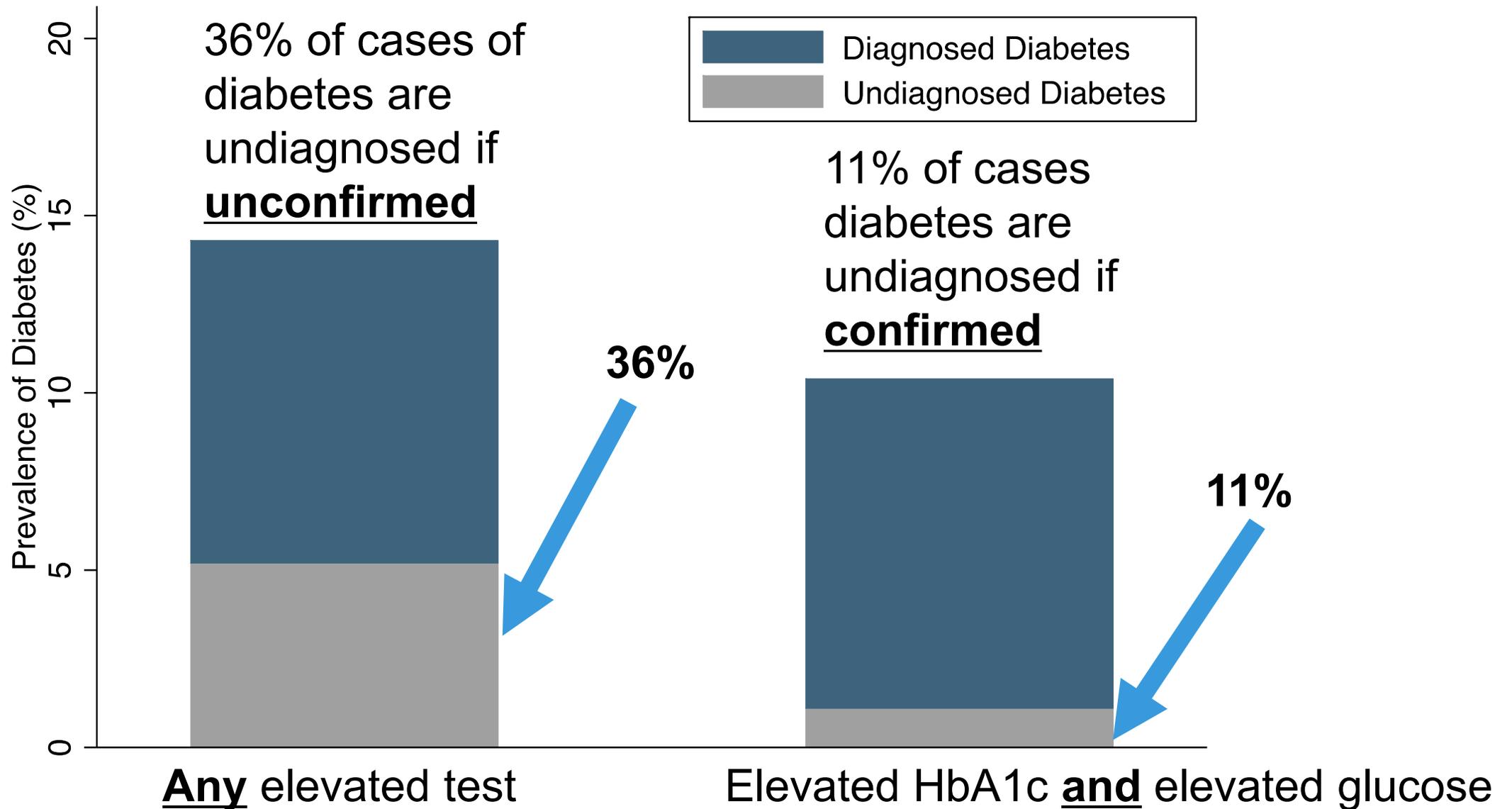
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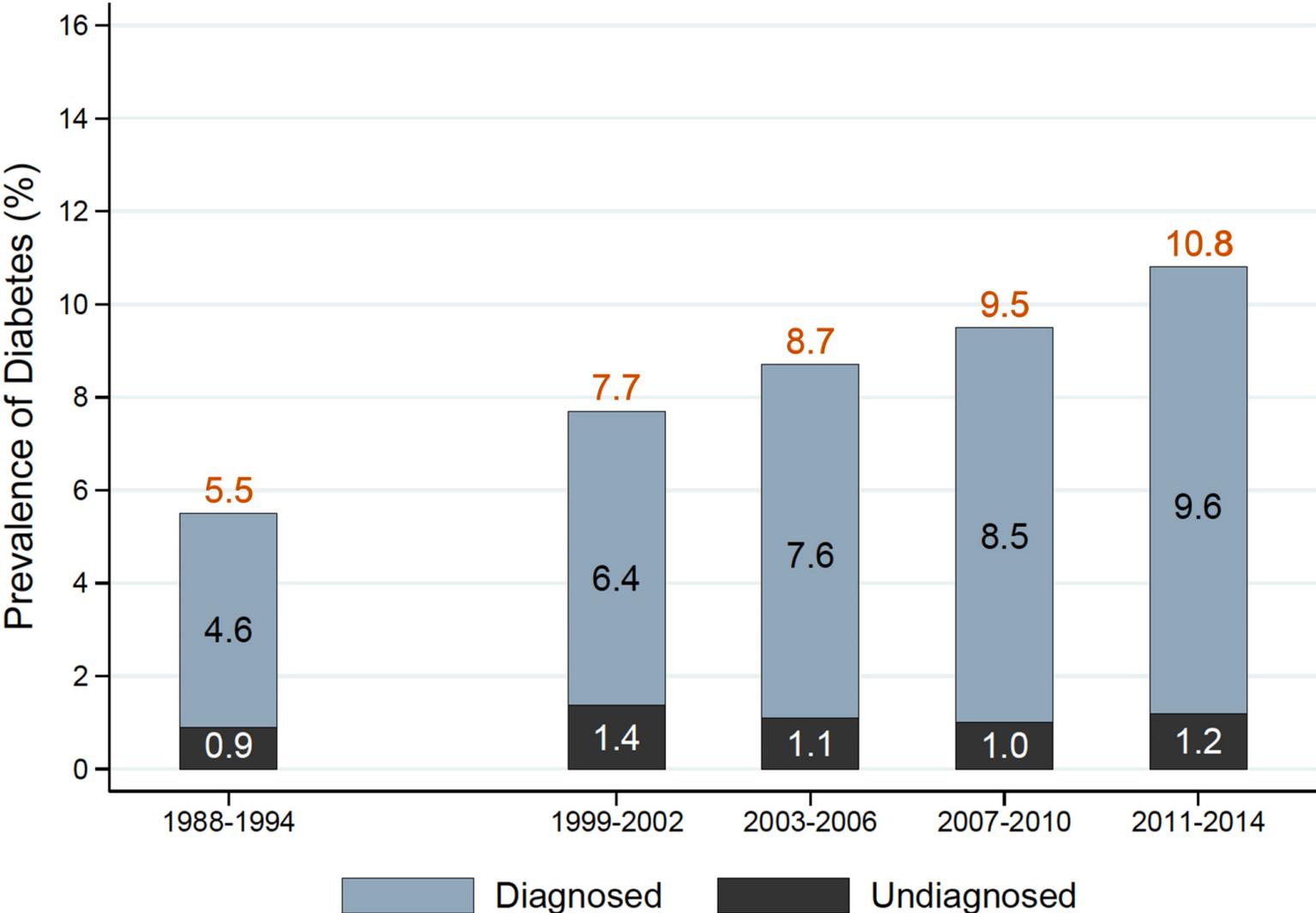
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# Estimating % of diabetes that is undiagnosed



# Prevalence **Total Diabetes** (**Diagnosed + Confirmed Undiagnosed**) in the U.S.



Source: Selvin et al, Ann Int Med 2017



## Summary

- 25.5 million adults in the U.S. have diabetes and only ~11% of this population is undiagnosed
- This reflects the strict application of clinical guidelines to NHANES data to most accurately estimate the proportion of persons with undiagnosed diabetes in the U.S.
- Our findings are in stark contrast to previously published national estimates which state that that 25 to 35% of cases of diabetes are undiagnosed



# ***Implications and Conclusions***

# Deciding on Screening and Diagnostic Cut-points: The Importance of Epidemiology

- Using the ARIC Study cohort, we established:
  - The link between HbA1c and future vascular risk in an initially non-diabetic population, informing the use of HbA1c for diagnosis  
**(2010 ADA guidelines)**
  - That two tests (HbA1c and fasting glucose) from the same blood sample provide adequate confirmation for diagnosis of diabetes  
**(2020 ADA guidelines)**



# Understanding the Effect of Variability on Prevalence: The Importance of Epidemiology

- Using data from NHANES, we demonstrated:
  - Problem: Conventional diabetes definitions in epidemiologic studies do not conform to clinical practice
  - Solution: Use definitions that more closely approximate clinical practice, i.e. “confirmed” definitions of diabetes
    - E.g., combination of HbA1c + fasting glucose in a single sample
- Using more accurate definitions demonstrates we are doing a good job of screening and diagnosing diabetes in the U.S.



# Deciding on Screening and Diagnostic Cut-points: The Importance of Epidemiology

- For risk factors along a continuum, separation of diseased from non-diseased is:
  - Inherently arbitrary
  - Intensely political
- But should be informed by the best available evidence, especially epidemiologic studies



# Acknowledgements

- Many, many co-authors and collaborators on these projects
- Faculty, staff, and trainees at the Welch Center for Prevention, Epidemiology and Clinical Research at Johns Hopkins
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- A special thank you to all the ARIC Study staff and participants for their important contributions
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# Questions?

