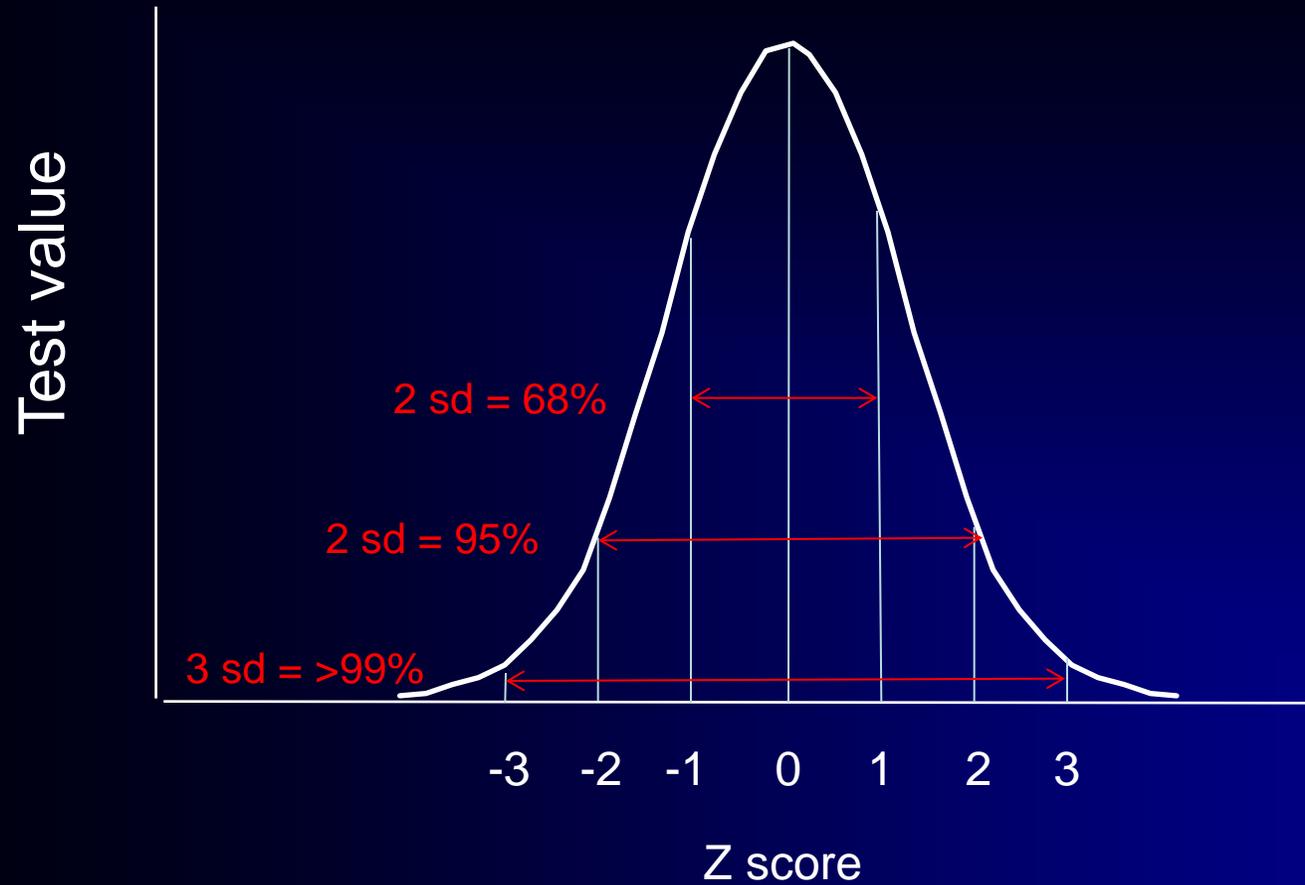


Whose test is right: yours or mine?

Julian H Barth,
Leeds UK

Julian.barth@nhs.net

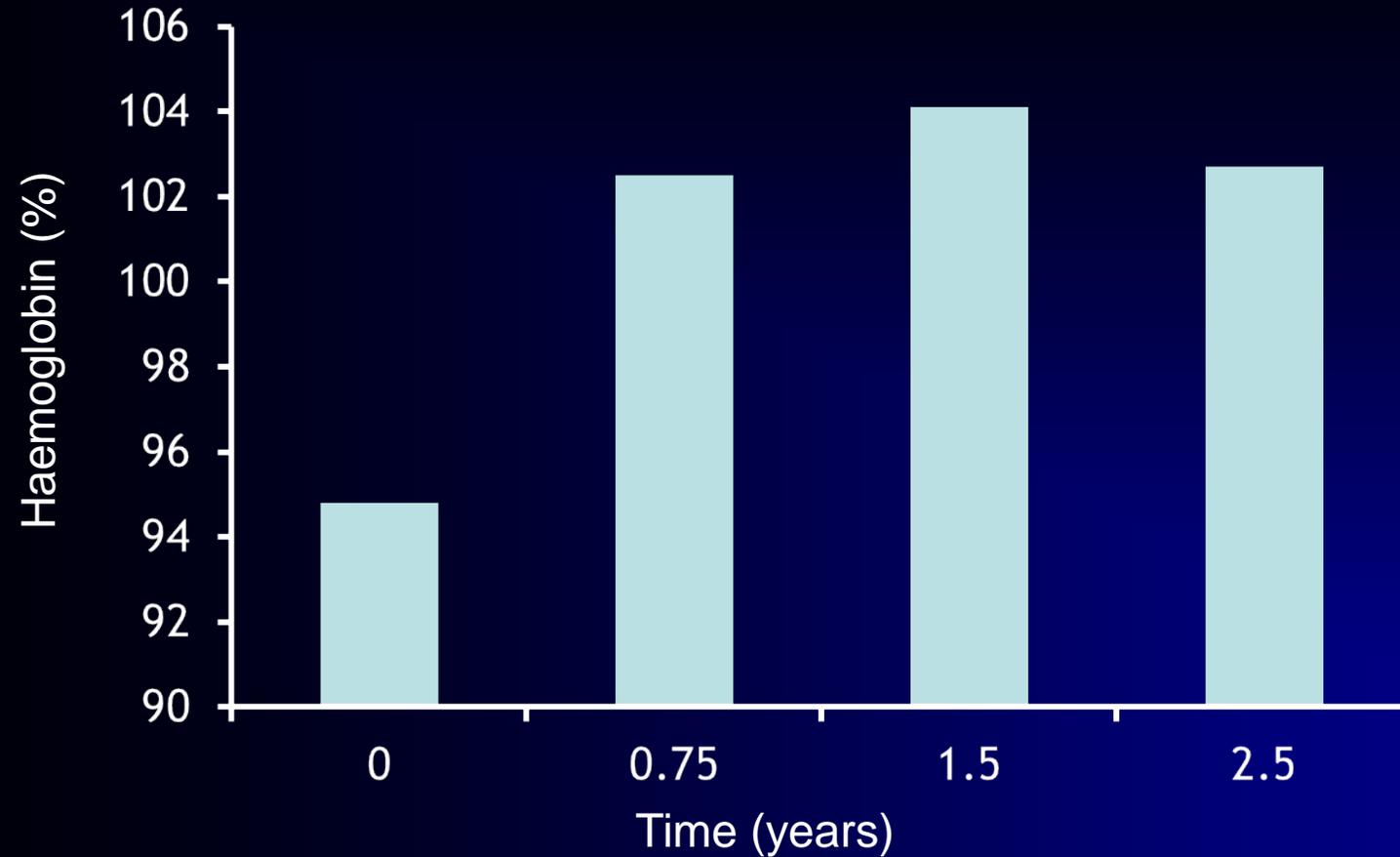
What is a reference interval



What is normal ?

- Gaussian
- Percentile
- Culturally desirable
- Risk factor
- Diagnostic
- Therapeutic
- Normal means "*typical*"
- Normal means not requiring further follow-up or intervention
- Normal means healthy ie absence of disease

What is normal: haemoglobin in WAAF



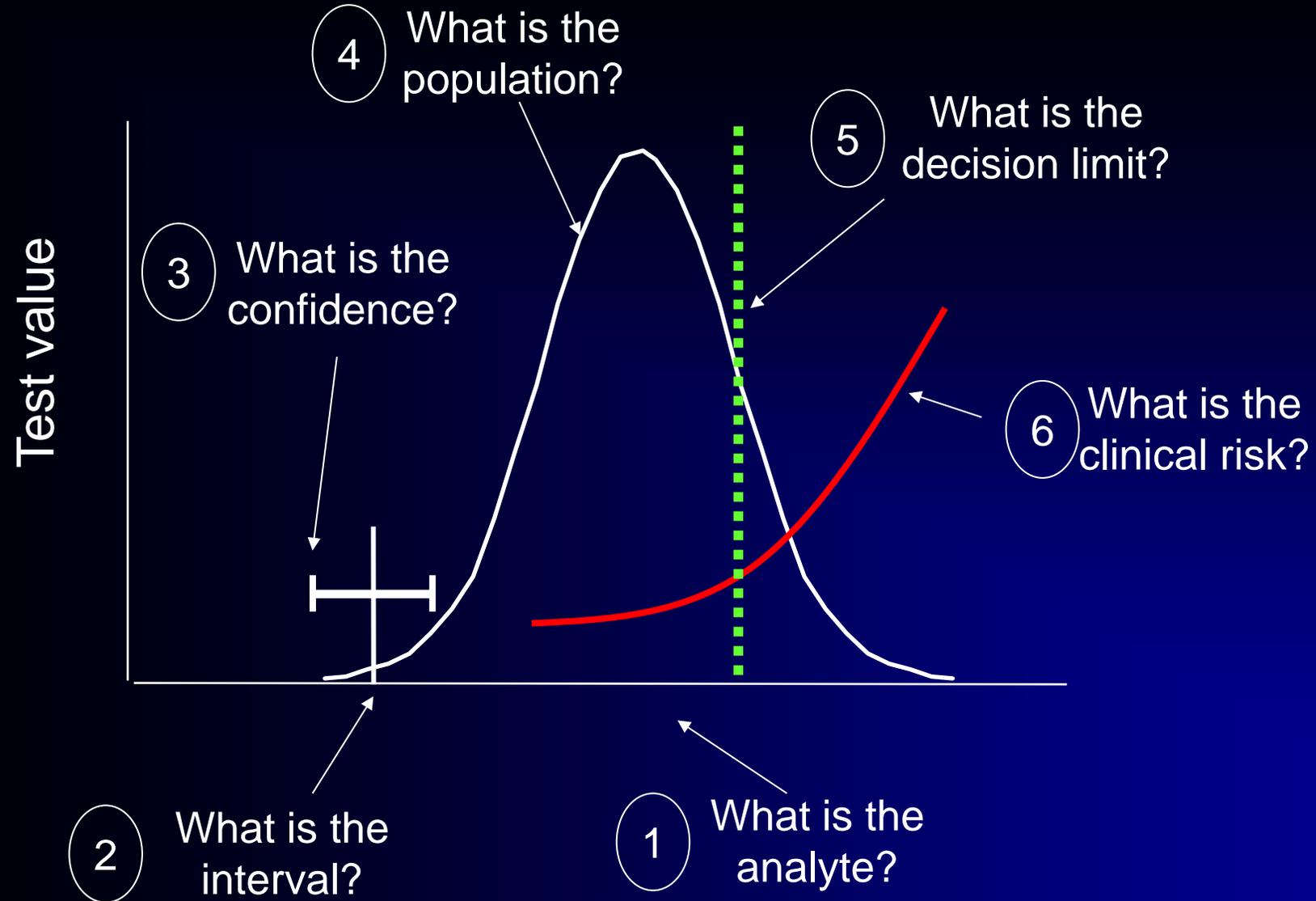
Why do Docs do too many tests ?

- To be complete
- “They say”
- We’ll get in trouble if we don’t
- If I don’t do it know it will be forgotten
- Since the patient is here, we might as well
- We are in an academic unit
- Malpractice
- Protocol
- If it were my relative
- How do I know he doesn’t have ... (the heroic search)
- The fishing expedition
- I would want to know if my tests were abnormal

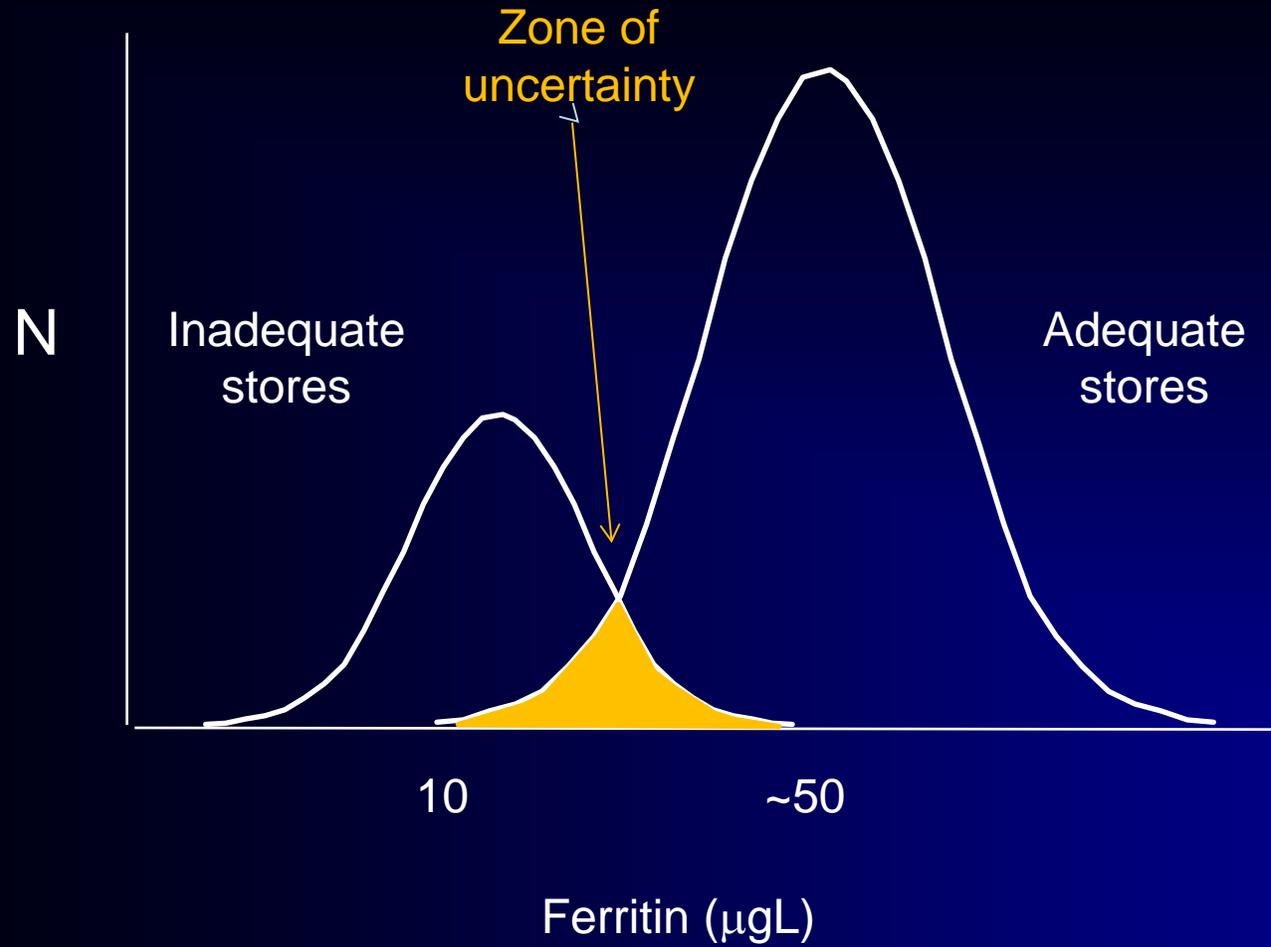
Why does primary care do blood tests ?

- Specific diagnosis 23%
- Screening 10%
- Monitoring diseases and treatments 38%
- Patient reassurance 16%
- Doctor reassurance 11%
- Uncertainty 14%

What is a reference interval



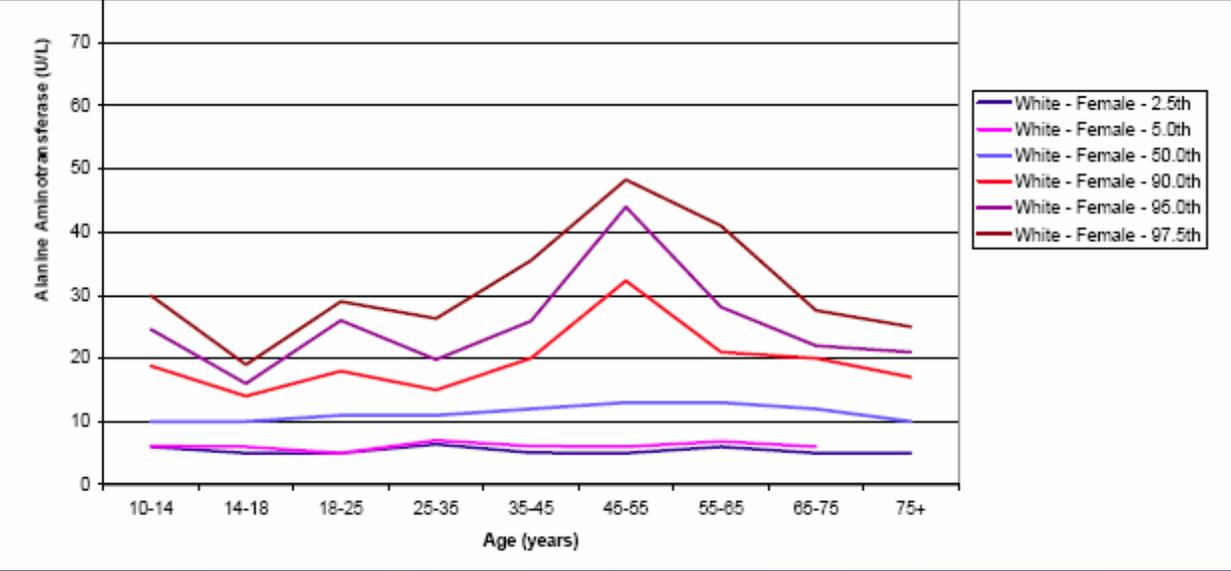
Uncertainty



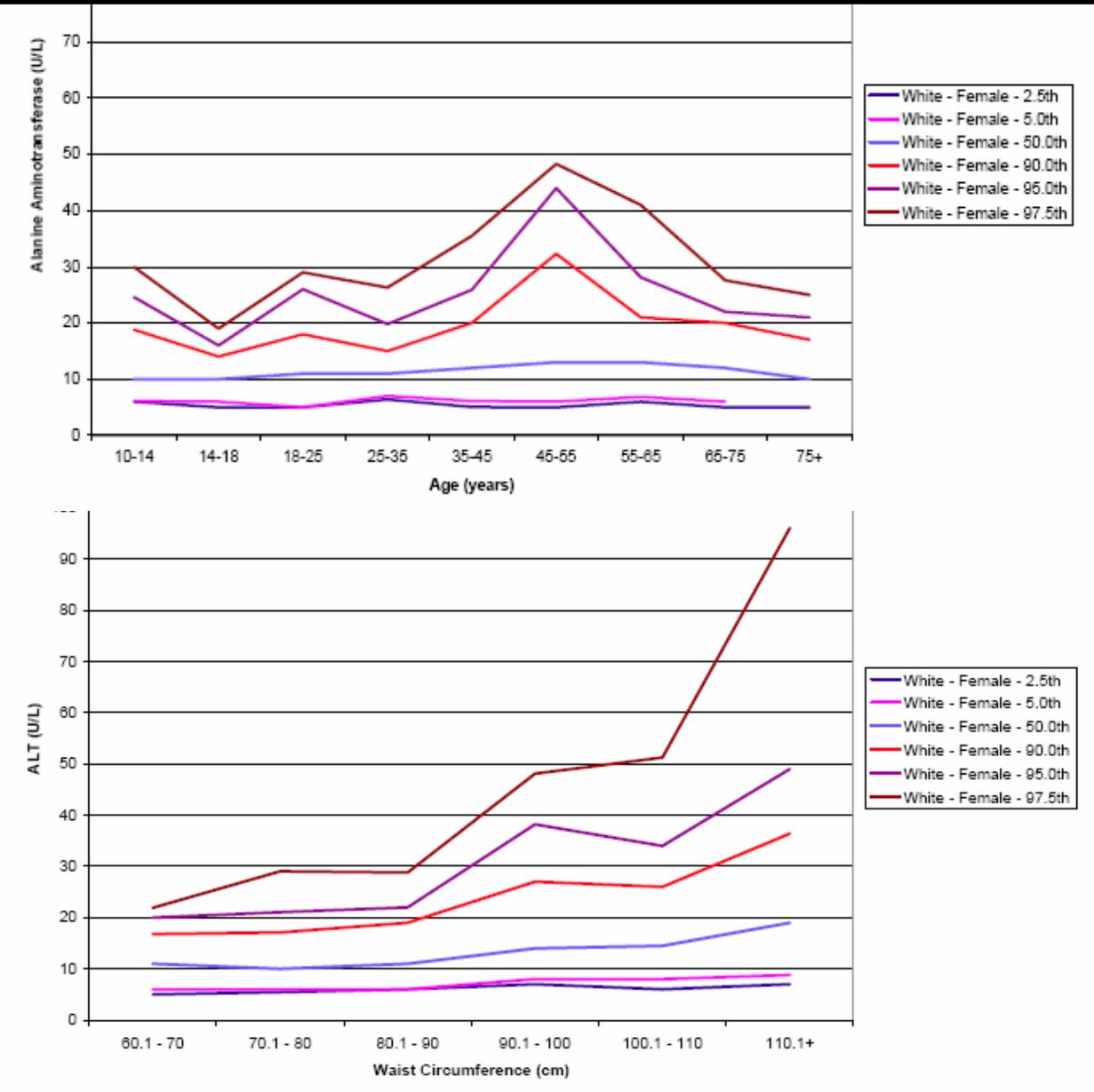
How much physiology do we know ?

- Sex
- Age
- Ethnicity
- Obesity
- Time day/season
- Diet
- Within person variation

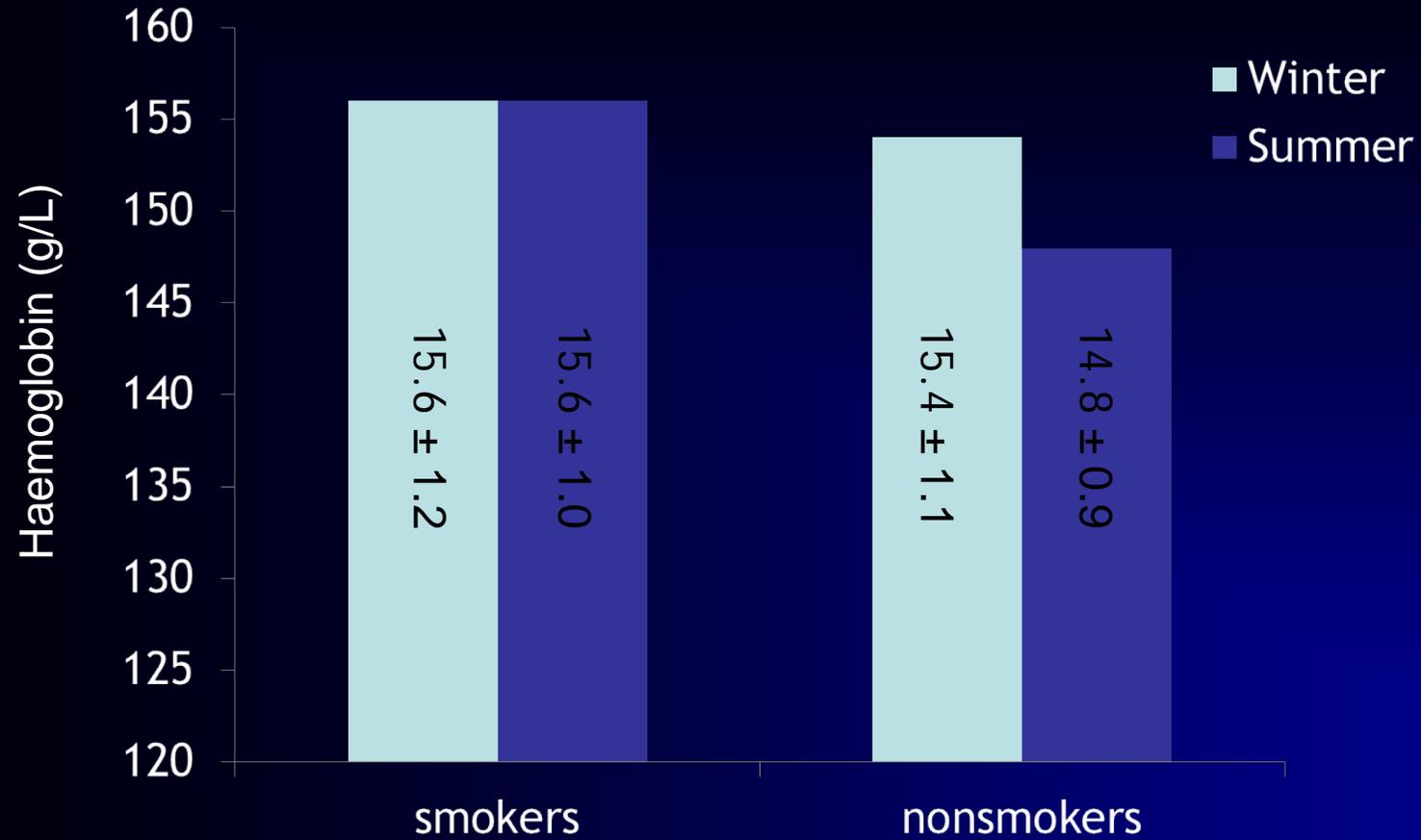
Alanine aminotransferase (NHANES III) - white females



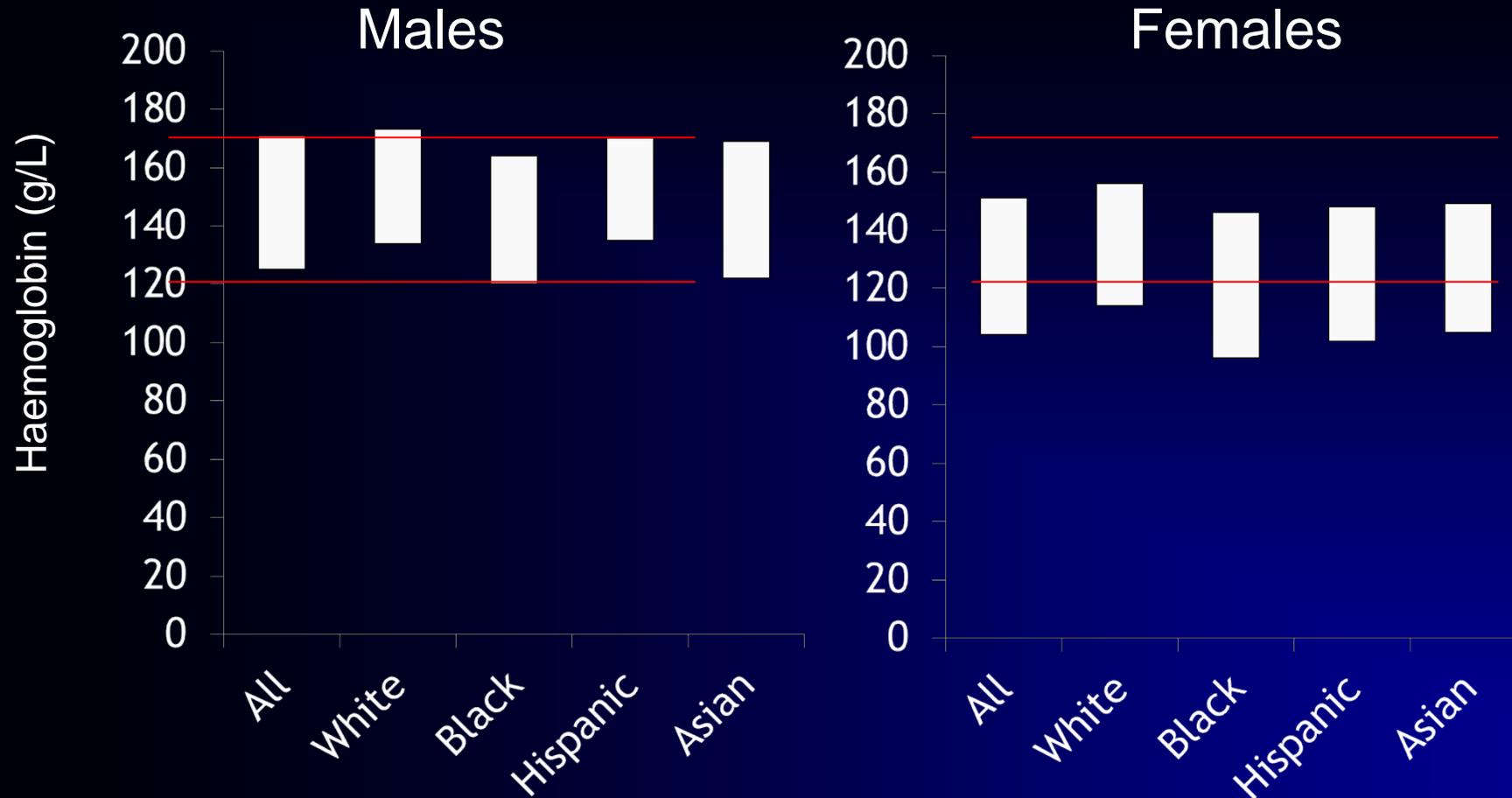
Alanine aminotransferase (NHANES III) - white females



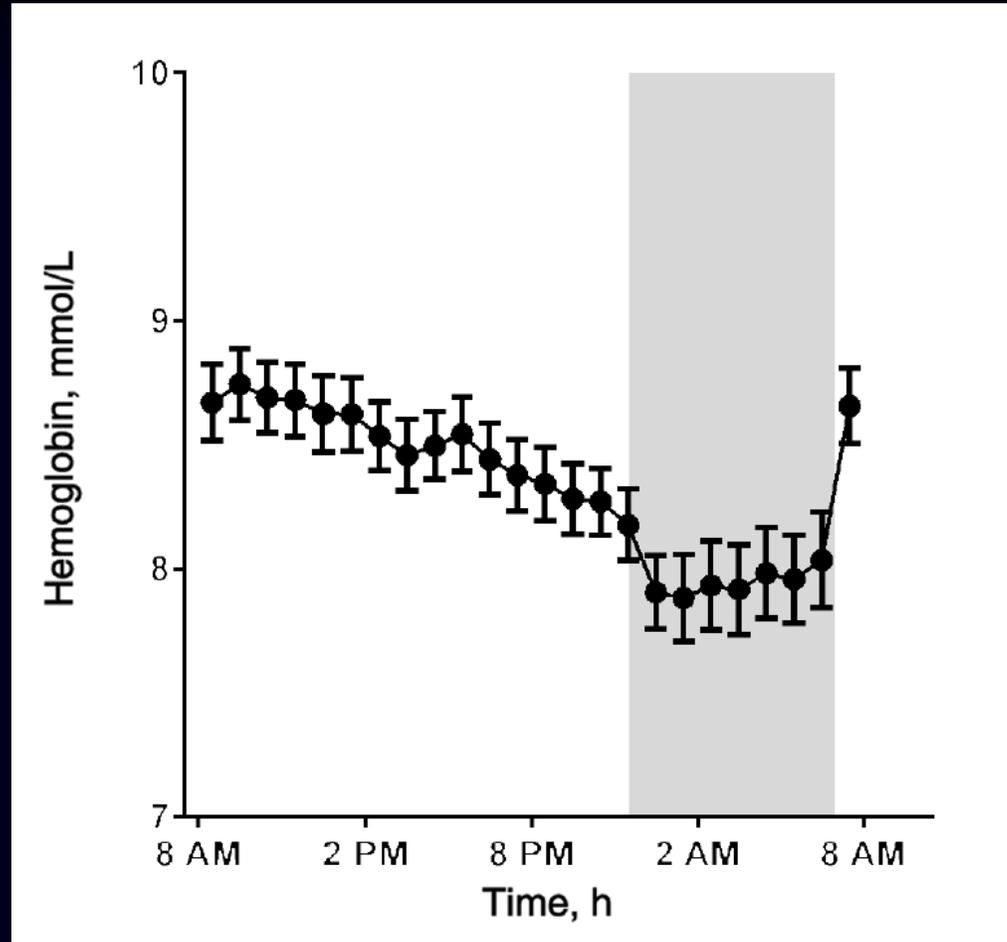
Effect of season



Ethnicity & Sex

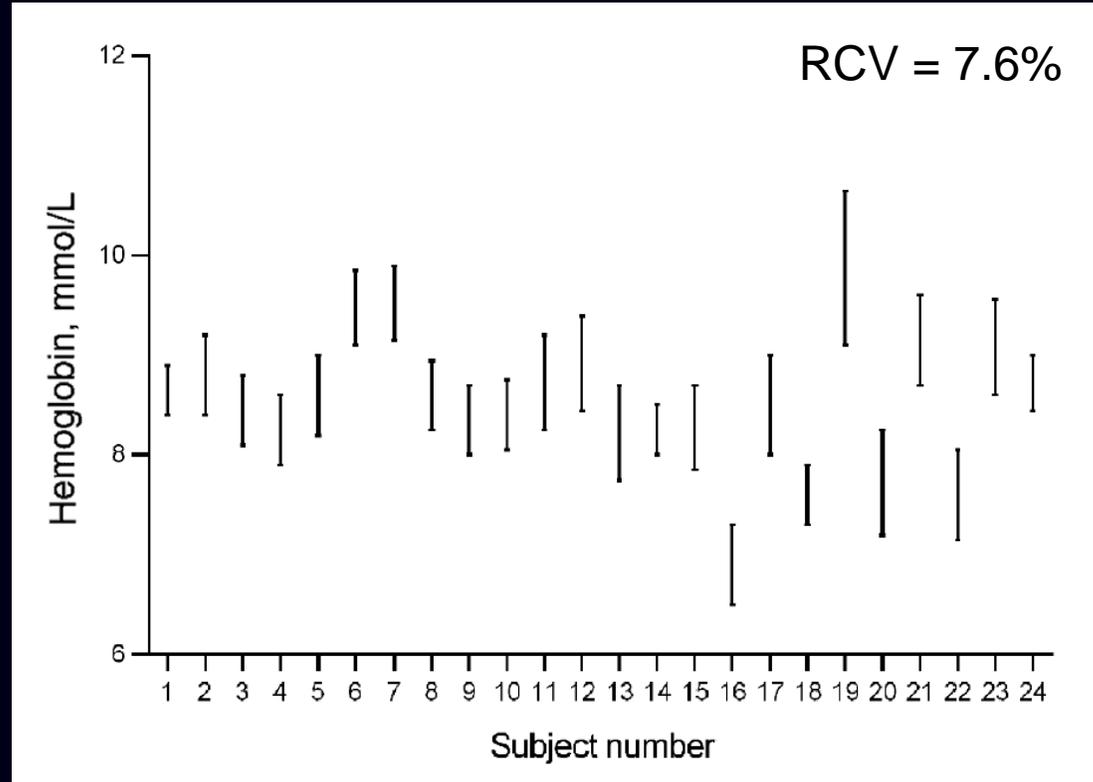


Time of day

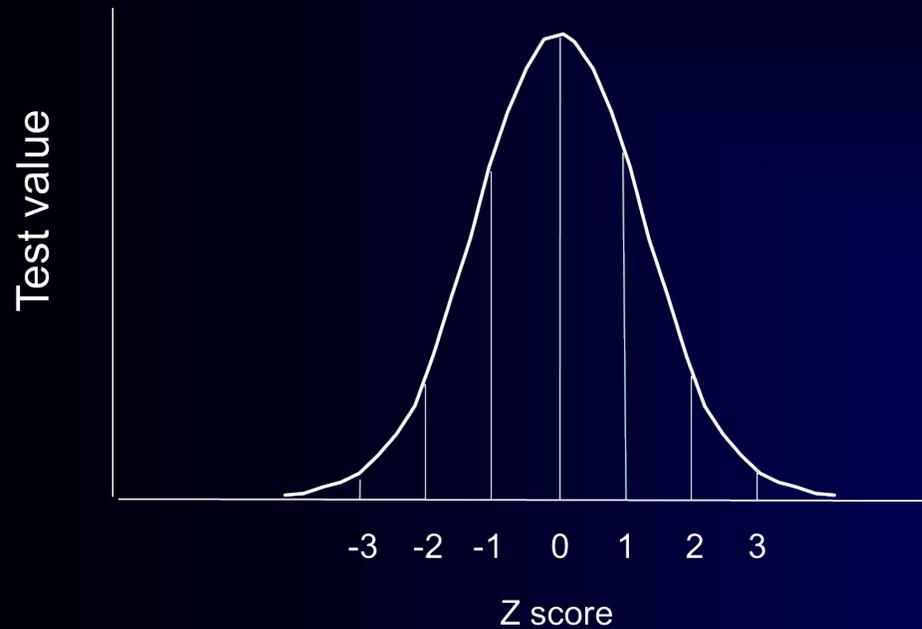


Within person variation

mmol/L * 16.1 = g/L



Reference limits or Decision limits



Cholesterol

Diabetes

PSA

CA125

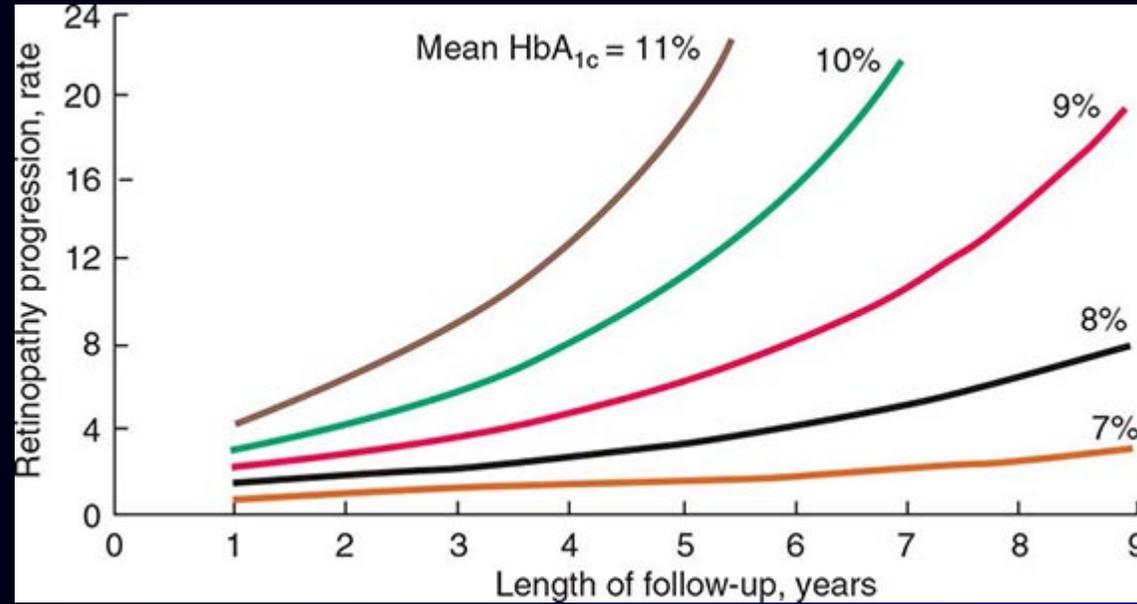
eGFR

Haemoglobin

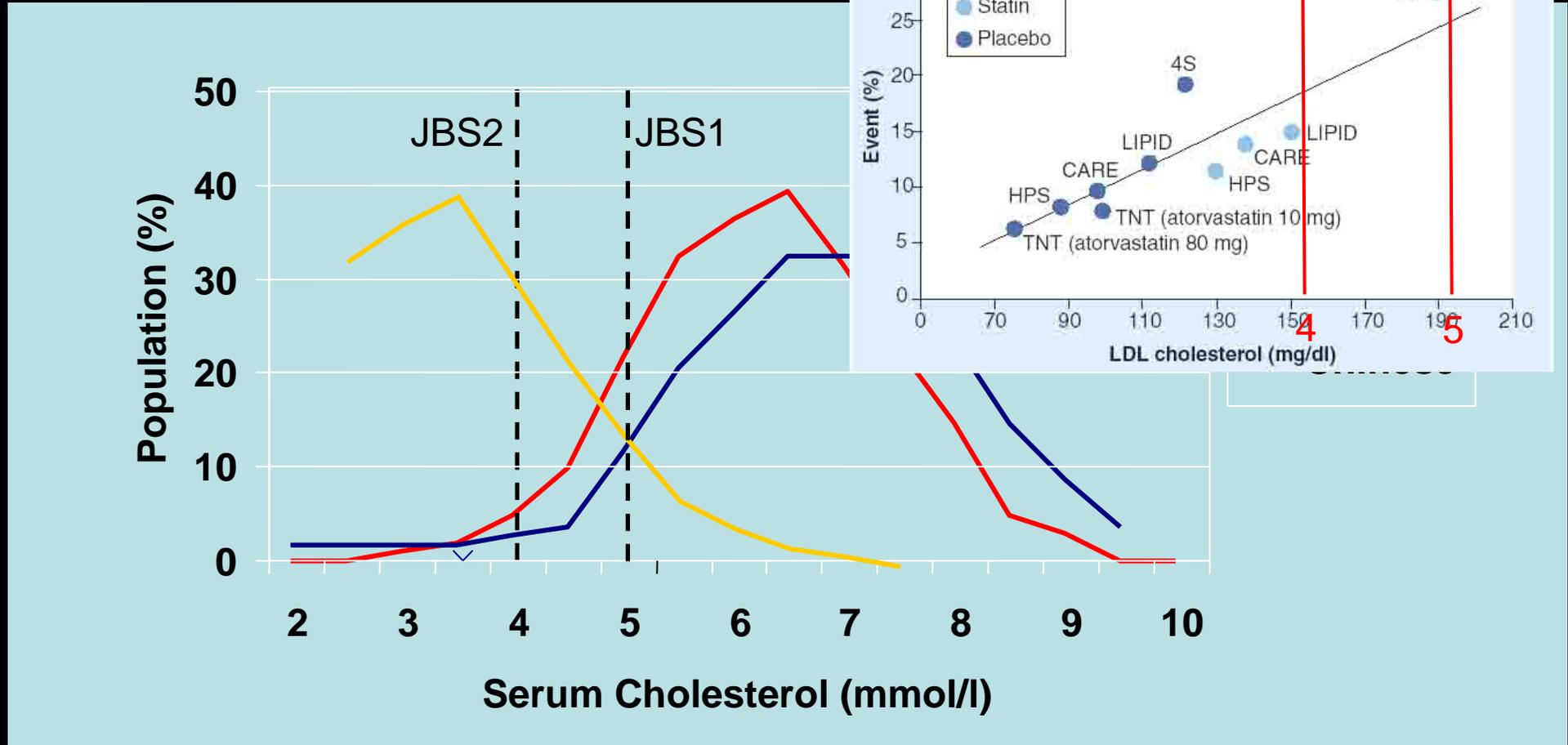
Variation in thyroid function within reference range and adverse outcomes

TSH > 2.0 mU/L	increased 20 year risk of hypothyroidism
TSH > 2.0 mU/L	increased frequency of thyroid autoantibodies
TSH 2.0-4.0 mU/L	Cholesterol values respond to thyroxine replacement
TSH > 4.0 mU/L	Increased risk of heart disease
TSH 0.2-5.5 mU/L	Decreased psychological wellbeing in patients on thyroid hormone compared with controls
TSH in normal range	Impaired psychomotor development of infant if occurs in first trimester

Decision limits



What is a normal cholesterol ?



This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES

No. 405

NUTRITIONAL ANAEMIAS

Report of a
WHO Scientific Group

WORLD HEALTH ORGANIZATION

GENEVA

1968

The definition of anemia: what *is* the lower limit of normal of the blood hemoglobin concentration?

Ernest Beutler and Jill Waalen

Blood 2006;107:1747



Critical Reviews in Oncology/Hematology 73 (2010) 1–9

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology
www.elsevier.com/locate/critrevonc

What is the evidence for gender differences in ferritin and haemoglobin?

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Accepted 25 March 2009

- Sexual dimorphism in humans only
- Iron deficiency is common in women worldwide except Bantu, Ethiopia and Australia Aborigines
- 25-30% US women have absent iron stores or low transferrin saturation
- Therapeutic iron raises Hb in women close to values in men
- Systematic review (1994)
 - ferritin 50 mg/L = 50% chance of absent marrow iron stores

WHO definition of anaemia and mortality

16334 apparently healthy subjects

Annual health checks

71200 examinations

11511 males

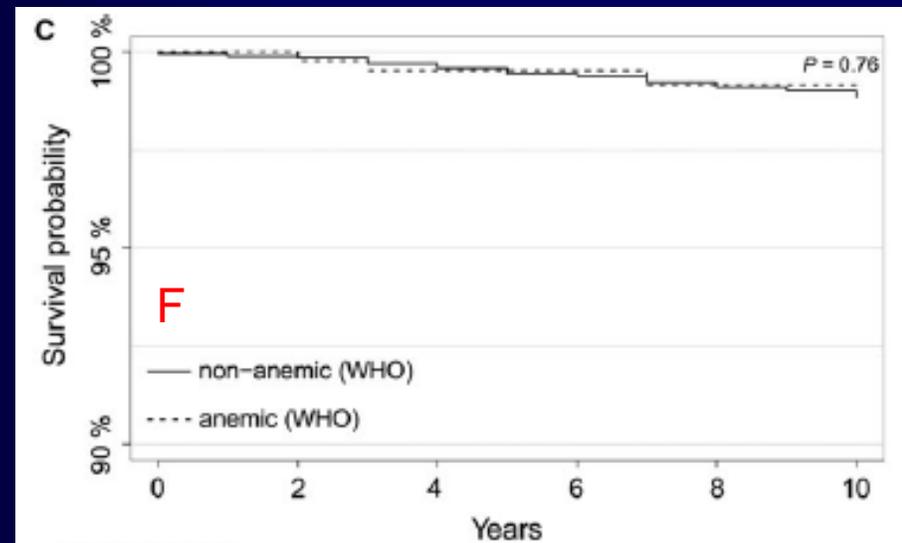
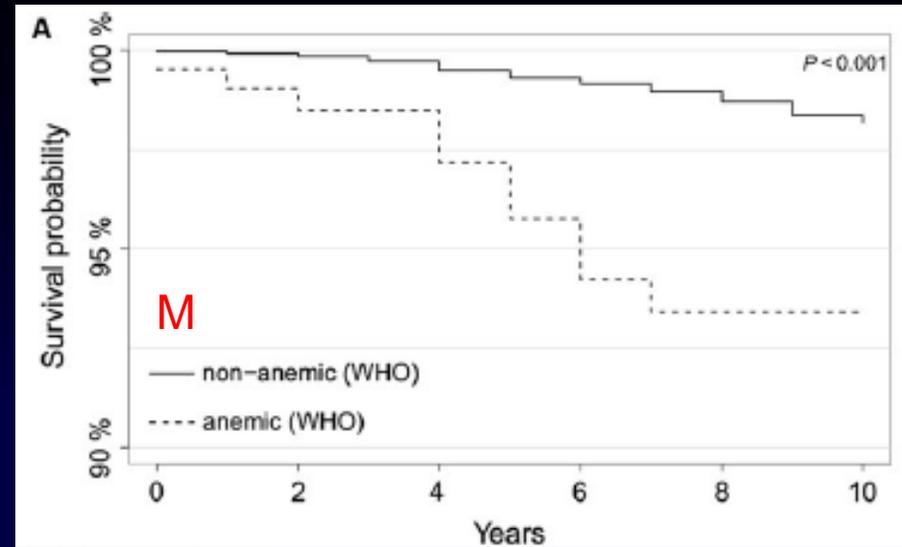
4823 females

WHO anaemia

Males <130 g/L

Females <120 g/L

Low fitness 29% M; 28% F





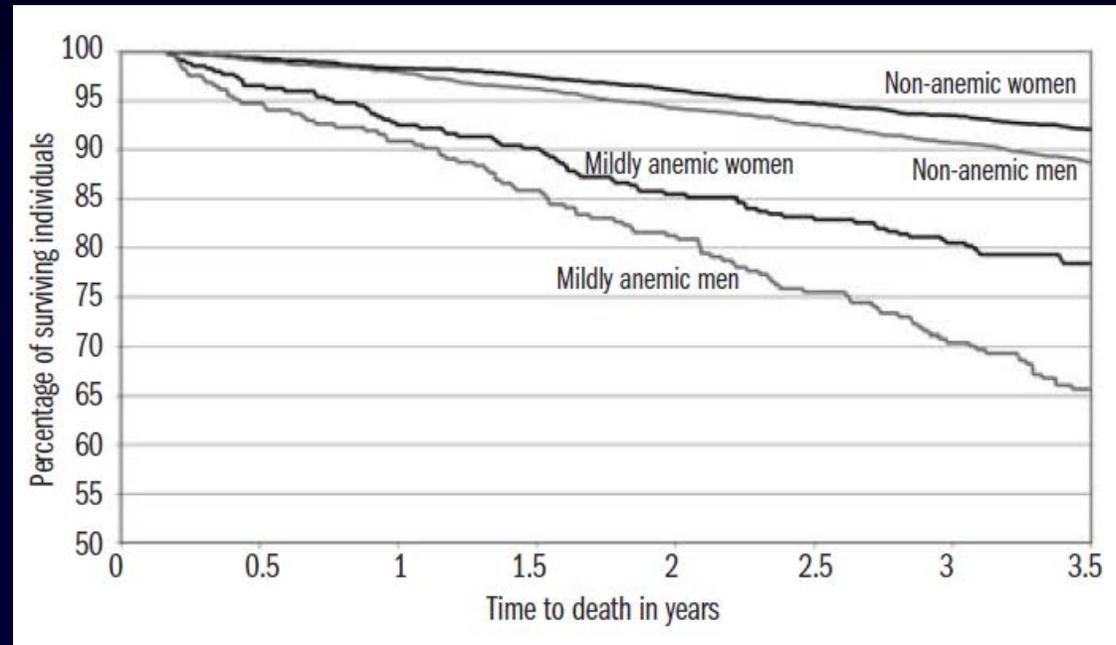
Anaemia & mortality in the elderly

Prospective
65-84 years
Blood tests 7536
Full data 4501

Anaemia defined as:

M 100-129

F 100-119

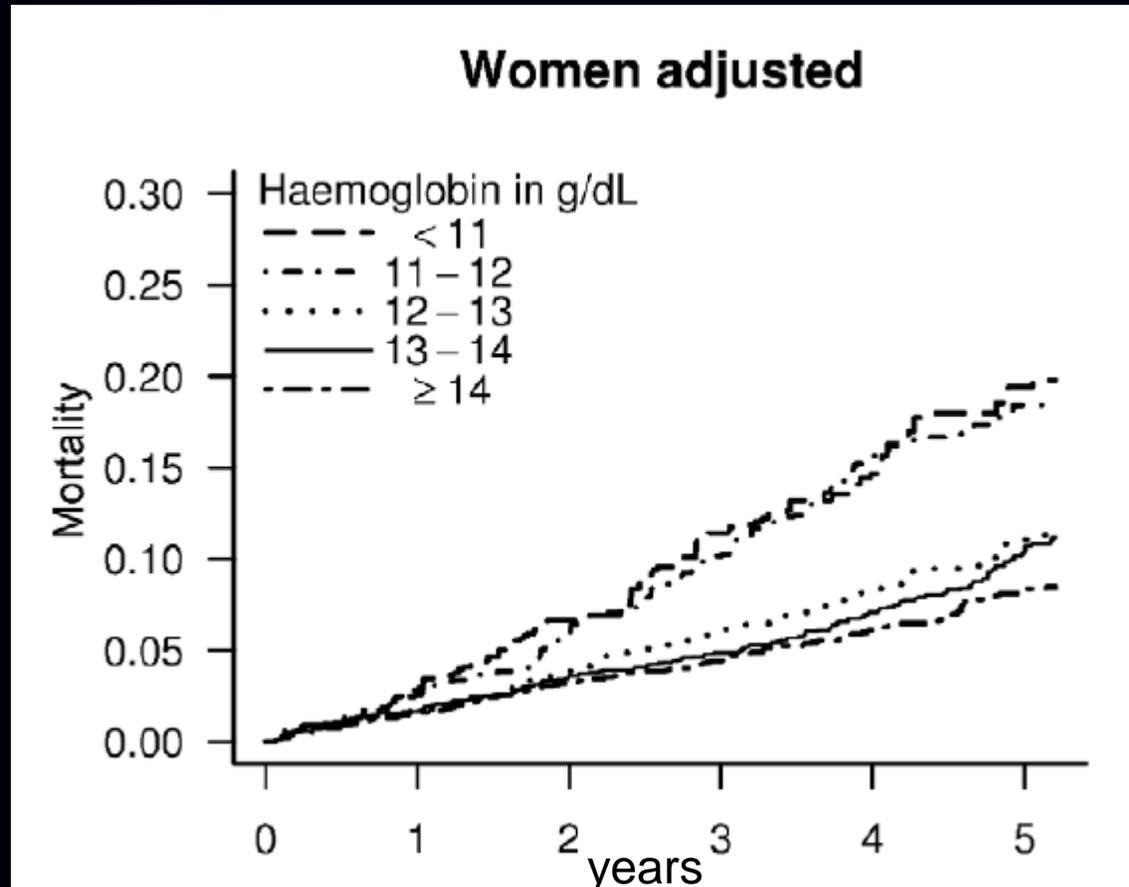


Age adjusted nadir for death is at

Males Hb 150 g/L

Females Hb 140 g/L

Threshold Haemoglobin Levels and the Prognosis of Stable Coronary Disease: Two New Cohorts and a Systematic Review and Meta-Analysis



20,131 new D
stable IHD

14,171 first MI
survival >7days

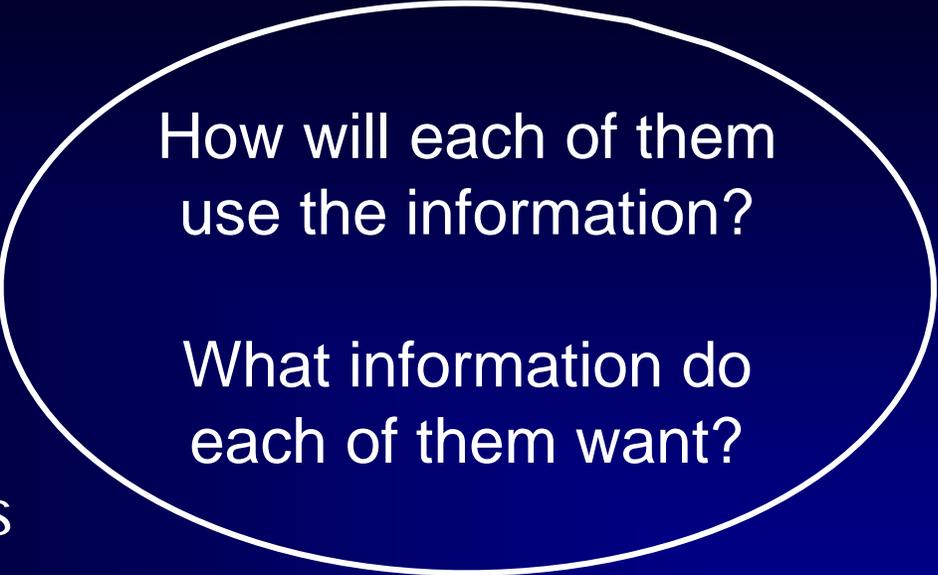
Challenges

- What is normal
- Accept kit inserts or determine local RI
- Who are appropriate reference individuals
- Are RI related to method bias
- How many variables are considered

- Tests with no reference data
- Assays with different standardisation
- What are RIs for analytes with decision limits
- Narrative reports
- Can we continue the current pretence in the era of EPR

Who will be using laboratory reports?

- Patients
- Pharmacists
- Physicians assistants
- Nurses
- Physicians
- Other AHP
- National disease registries
- Managers & commissioners
- Insurance companies



How will each of them
use the information?

What information do
each of them want?

What do patients and doctors want?

Patients

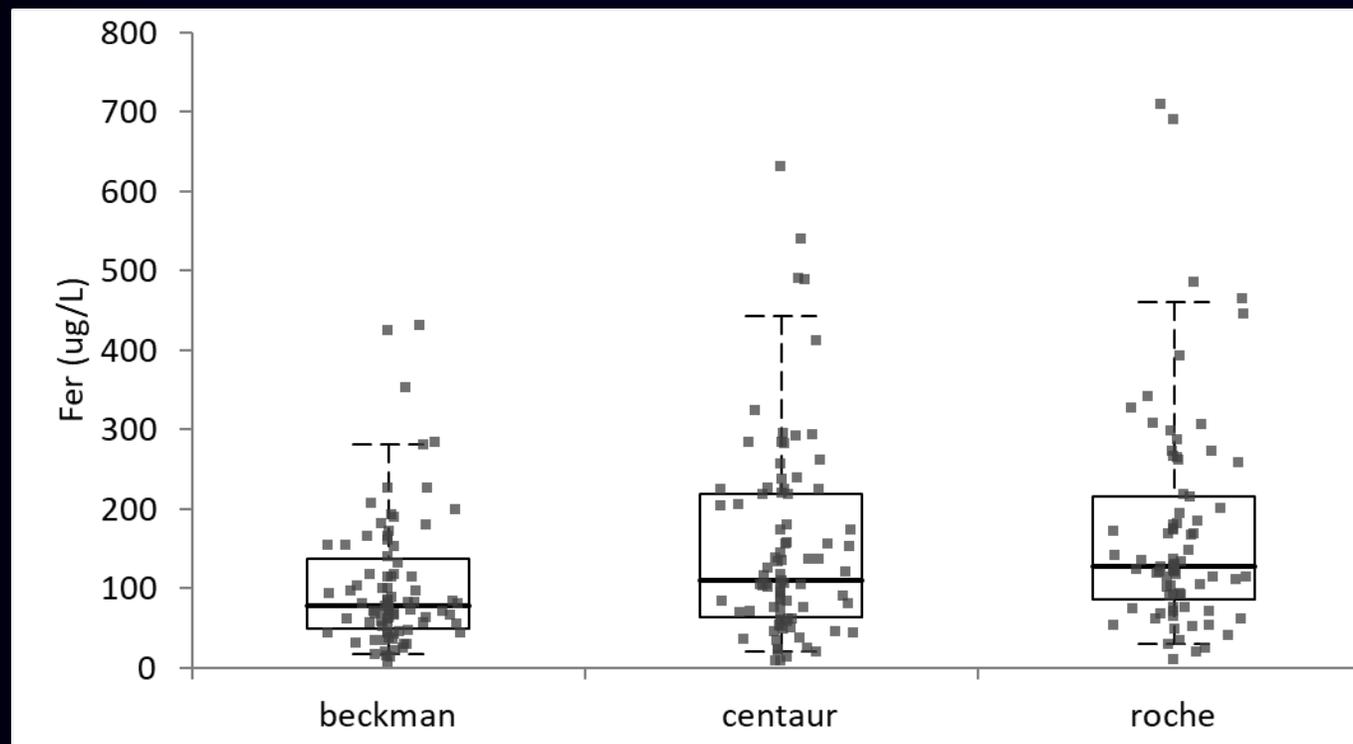
- All possible helpful information
- Available as soon as technically possible
- To make the best informed decision possible
- In order to reduce the risk of...
...morbidity, mortality, misdiagnosis, complications, depression, treatment failure, etc etc

Doctors

- *Help!*
- Fast and accurate results
- Understandable and useful information
- Direction on therapy
- Low costs - but this may not be important

What method ? - Ferritin

100 apparently healthy males
Normal MCV



Median Ferritin (µg/L)

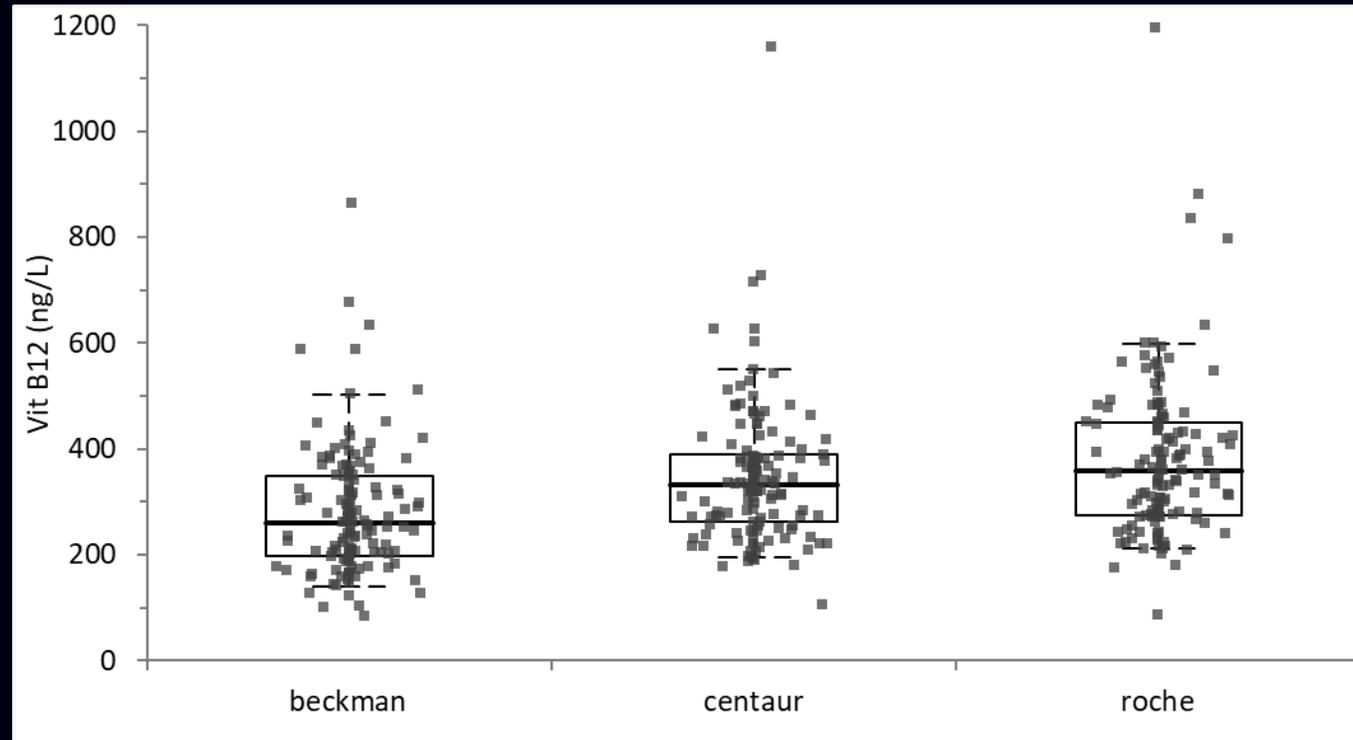
Beckman 79

Centaur 110

Roche 127

What method ? - Vitamin B12

100 apparently healthy females
Normal MCV



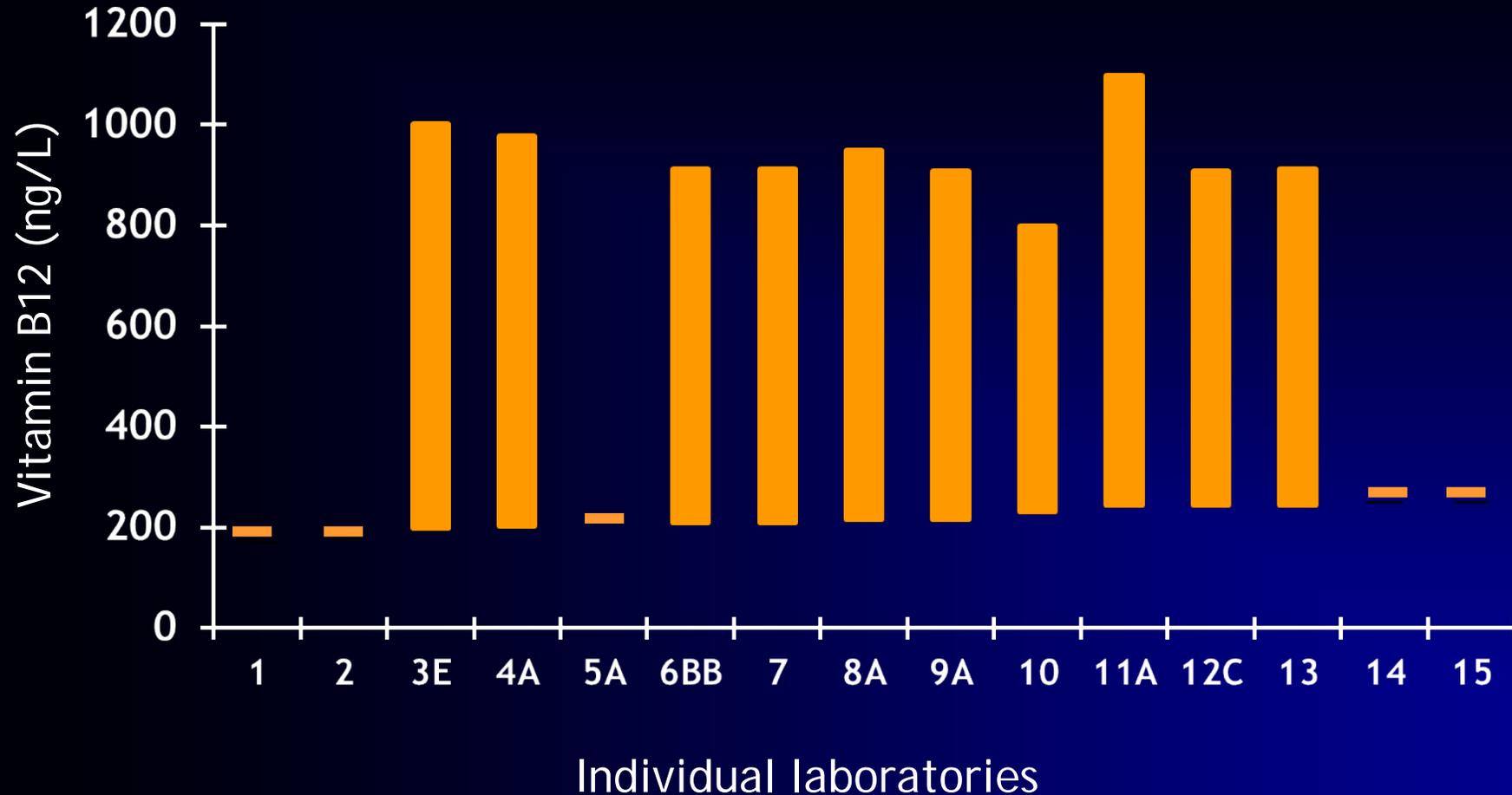
Median B12 (ng/L)

Beckman 261

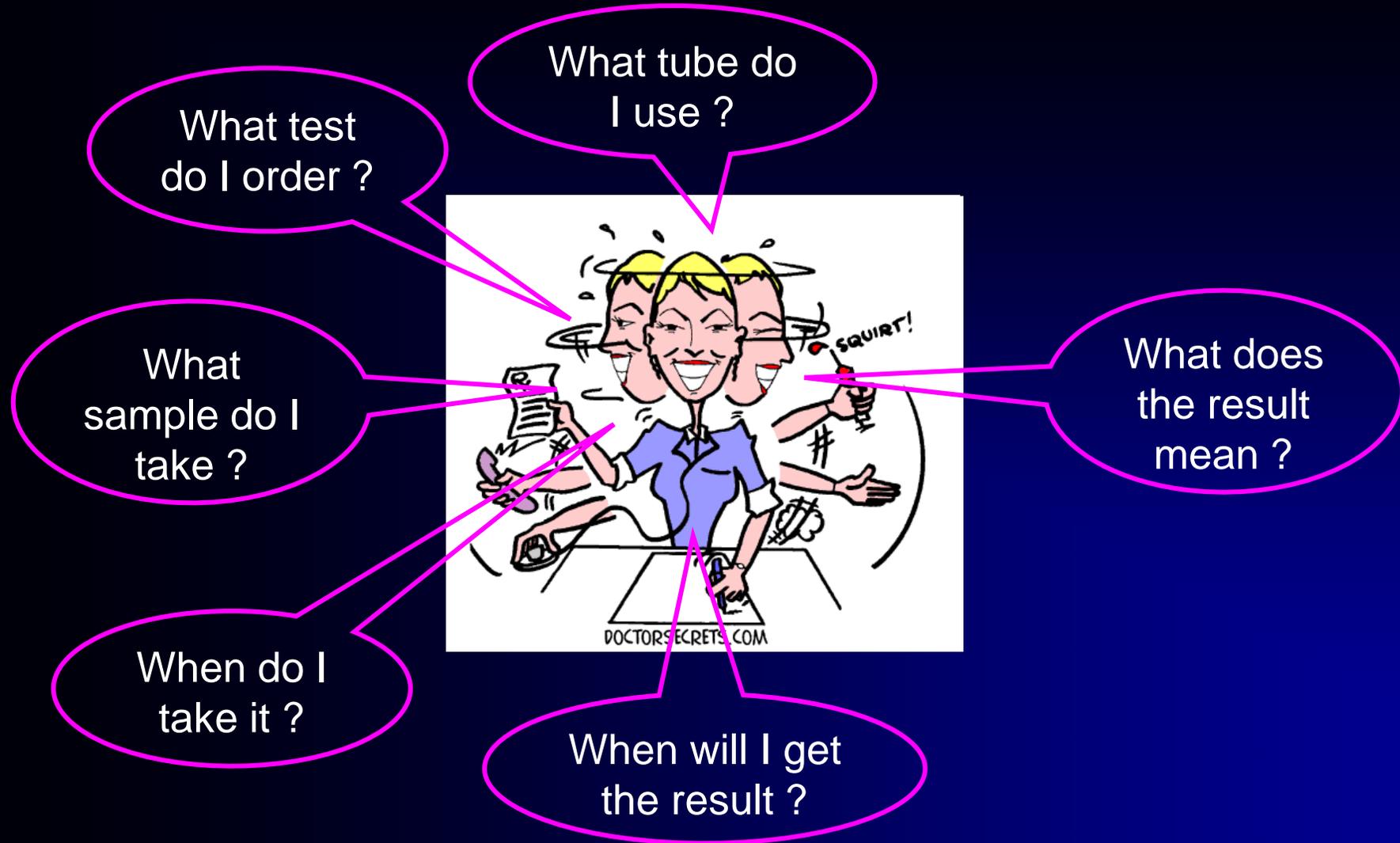
Centaur 389

Roche 451

RI for Bayer Vitamin B12 cited by clinical laboratories



What are we doing to help ?



Reference interval errors

- Errors in Laboratory reference limits as shown in a collaborative quality-assurance program
 - Clin Chem 1986;32:845
- ... IMEP-17 survey in Australia showed no relationship between method bias and reference limits ...
 - Clin Biochem Rev 2004;25:99
- Survey of reference ranges and clinical measurements for psychoactive drugs in serum
 - Ther Drug Monit 2003;25:243
- A survey of endocrine function testing by clinical biochemistry laboratories in the UK
 - Ann Clin Biochem 1995;32:442-449