AN INTRODUCTION TO THE ROLE AND USE OF PATHOLOGY LABORATORY TESTING IN CLINICAL PRACTICE

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RHH Pathology Services & UTas HLS

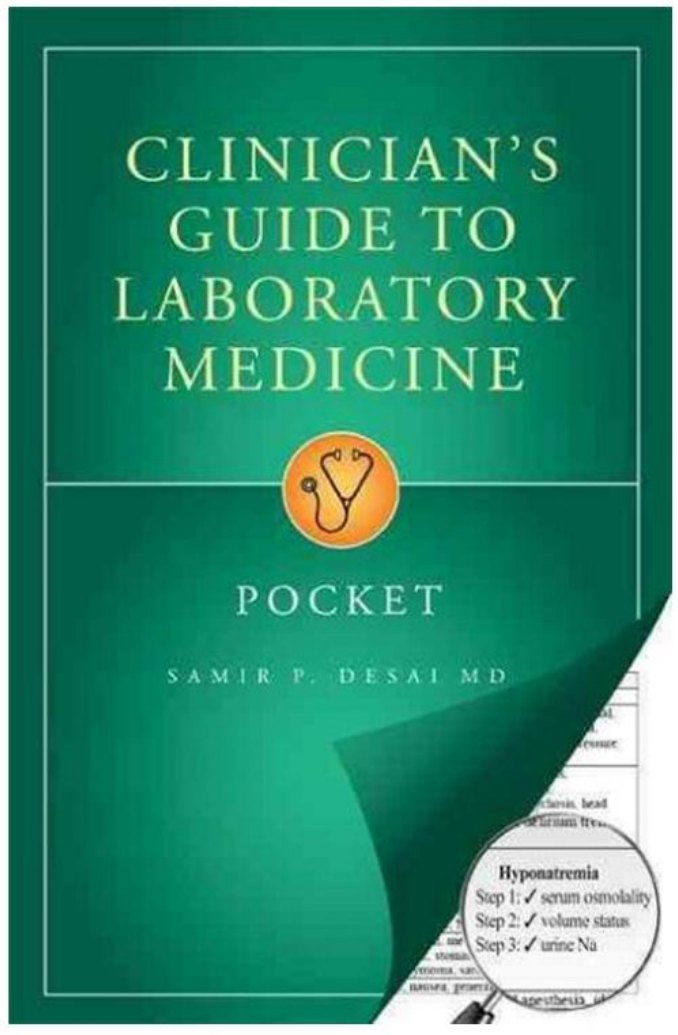
March 2013 **CAM 201**

SETTING THE SCENE : DIAGNOSTIC SERVICES

- Diagnostic Services – where does the Pathology Laboratory fit in ?
- Group One : Medical “Imaging” … X-Ray, CAT scan, Ultrasound, Angiography, Endoscopy, NMR, PET, Nuclear Medicine ….
- Group Two : Pathology “Testing” : 5 Main Disciplines across 13 Laboratories
  - **Anatomical Pathology**
  - **Clinical Biochemistry**
  - **Coagulation**
  - **Cytogenetics**
  - **Cytology**
  - **Endocrinology**
  - **Haematology**
  - **Infection Control**
  - **Microbiology**
  - **Molecular Medicine**
  - **Phlebotomy Service**
  - **Post Mortem**
  - **Transfusion Medicine**

TEXTBOOKS

You can’t get by without one ..



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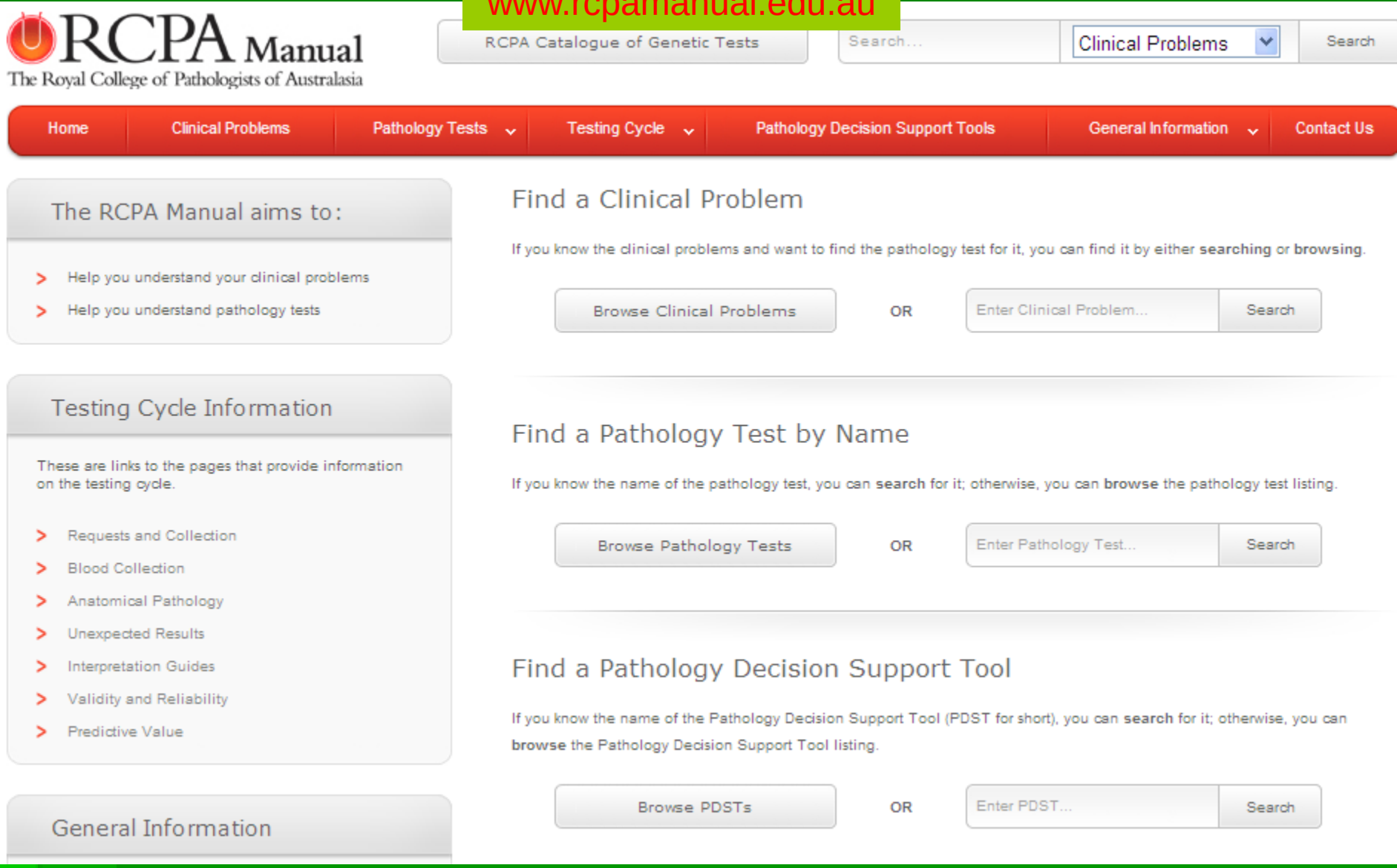


RCPA Manual
The Royal College of Pathologists of Australasia

RCPA Catalogue of Genetic Tests

Home | Clinical Problems | Pathology Tests | Testing Cycle | F

Pathology Decision Support Tools by Alphabetical Order

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

-

-♦♦♦♦♦ PDST Example ♦♦♦♦♦-

A

Anaphylaxis

Antenatal Screening

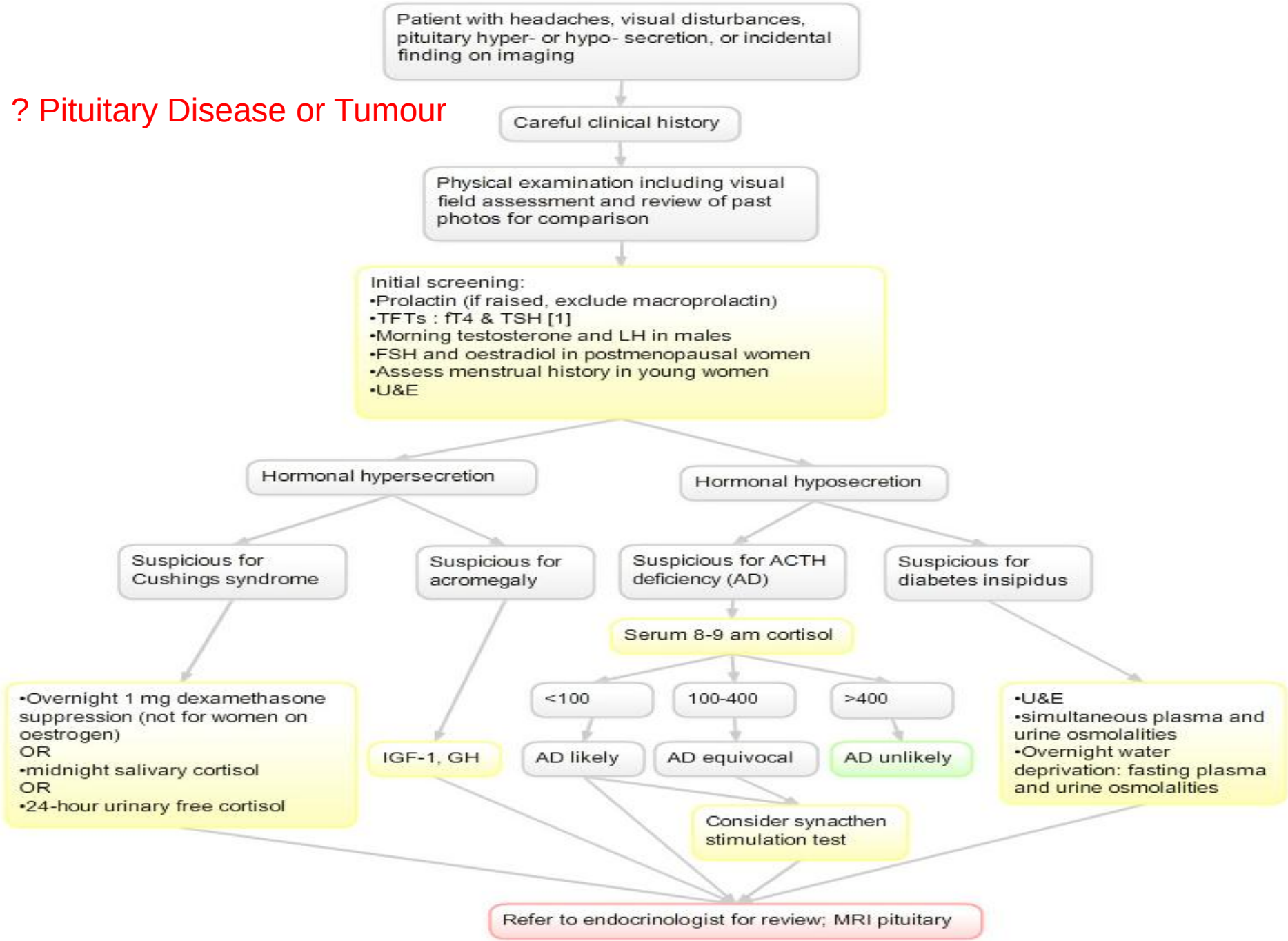
Arthritis

B

Bone pain in adults

Bowel Cancer Screening

? Pituitary Disease or Tumour



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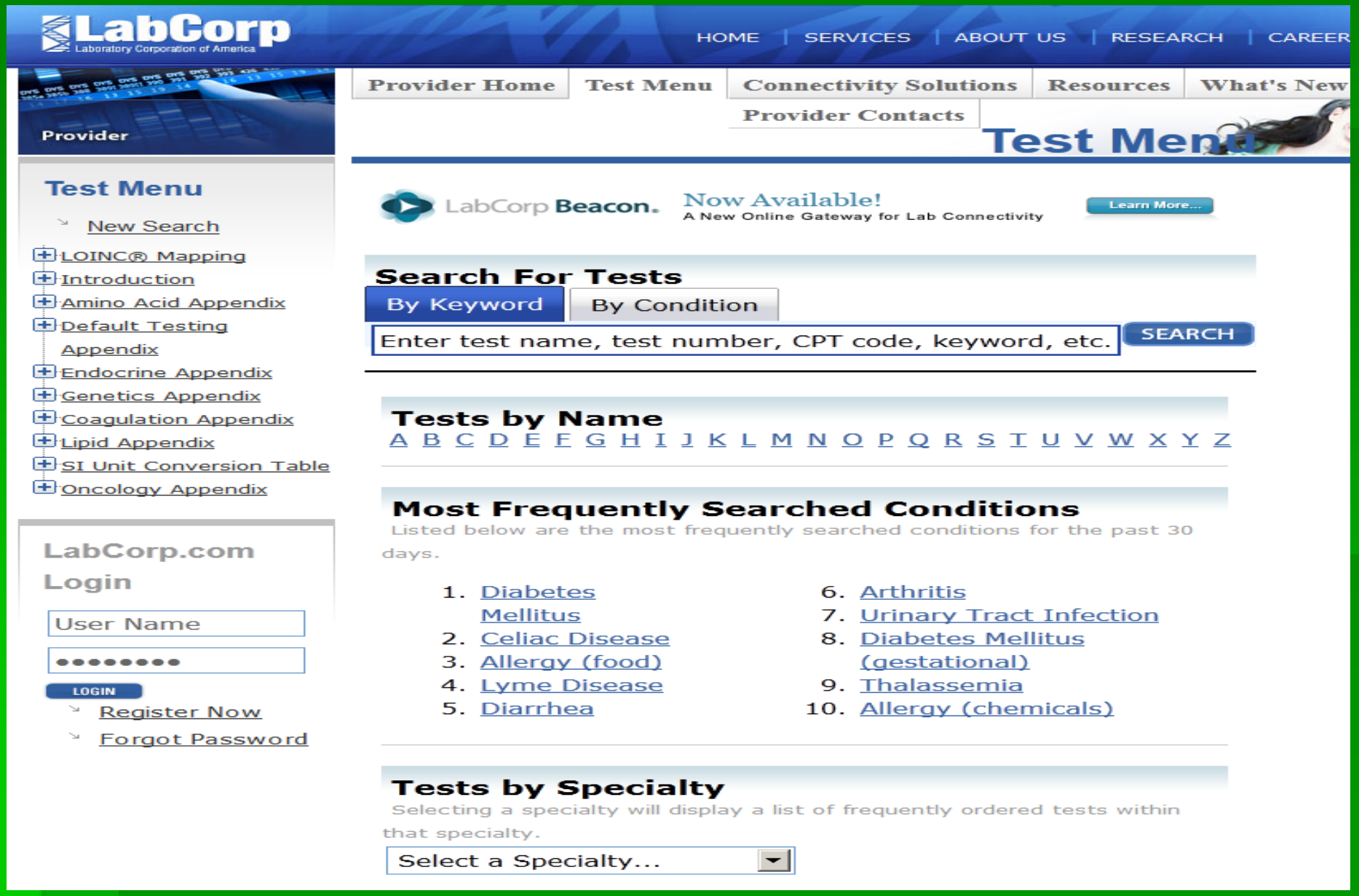


Specimen:	Serum (preferred) **or** plasma
Volume:	1 mL
Minimum Volume:	0.5 mL
Container:	Red-top tube, gel-barrier tube, green-top (heparin) tube, **or** lavender-top (EDTA) tube
Collection:	Separate serum or plasma from cells within 45 minutes of collection.
Storage Instructions:	Maintain specimen at room temperature.

Stability:

Temperature	Period
Room temperature	14 days
Refrigerated	14 days
Frozen	14 days
Freeze/thaw cycles	Stable x3

Causes for Rejection: Improper labeling

Reference Interval:

Age	Acceptable	Borderline	High
0–19 years	<170 (or 100–169)	170–199	≥200
20–24 years	<190 (or 100–189)	190–224	≥225
>24 years	<200 (or 100–199)	200–239	≥240

Use: Evaluate lipid status and metabolic disorders. High levels of cholesterol that reflect high levels of HPLs may be caused by an inherited defect in lipoprotein metabolism, by disease of the endocrine system, by liver disease, or by renal disease. Low levels of cholesterol in the plasma may reflect an inherited deficiency of either LDL or HDL, or they may reflect impairment of liver function. Various hormone conditions are also related to cholesterol levels. Increased serum cholesterol in hypothyroid persons shows an increased LDL and decreased HDL. Low cholesterols are found in cases of hyperthyroidism, severe liver disease, pernicious anemia, and with increased estrogens. Pregnancy is accompanied by a moderate increase. Cholesterol is increased in early hepatitis, obstructed bile ducts, primary biliary cirrhosis, nephrotic syndrome, and diabetic meningitis. Finally, through much controversy, it appears that cholesterol is implicated in atherosclerosis and heart disease. Evaluate risk of coronary arterial occlusion, atherosclerosis, myocardial infarction, and complications including the demise of the patient.

Australian & UK Labs Use SI Units

To Convert to SI units :

$$\frac{(\text{mg/dl} \times 10)}{\text{Molecular Weight}}$$

= mmol/L

http://dwjay.tripod.com/conversion.html

JAY CLINICAL SERVICES *Clinical Laboratory Software and Consulting*

Clinical Analyte Unit Conversion

(Requires JavaScript)

1. Select Analyte
2. Select Units
3. Enter number to be converted in Value box
4. Press Enter or click Calculate

Analyte

Cholesterol

Convert from	Convert to
mg/dL	mmol/L
Value	**Answer**
145	3.75

Factor

0.02586

Calculate

Reset

You can purchase your own executable version of this program which includes molecular structures, empirical formula and formula mass. Click on the image below to see a screenshot.

First question – what is the probability that this Test Result I have just got back from the Lab ...eg a serum albumin concentration ..... is abnormal ?

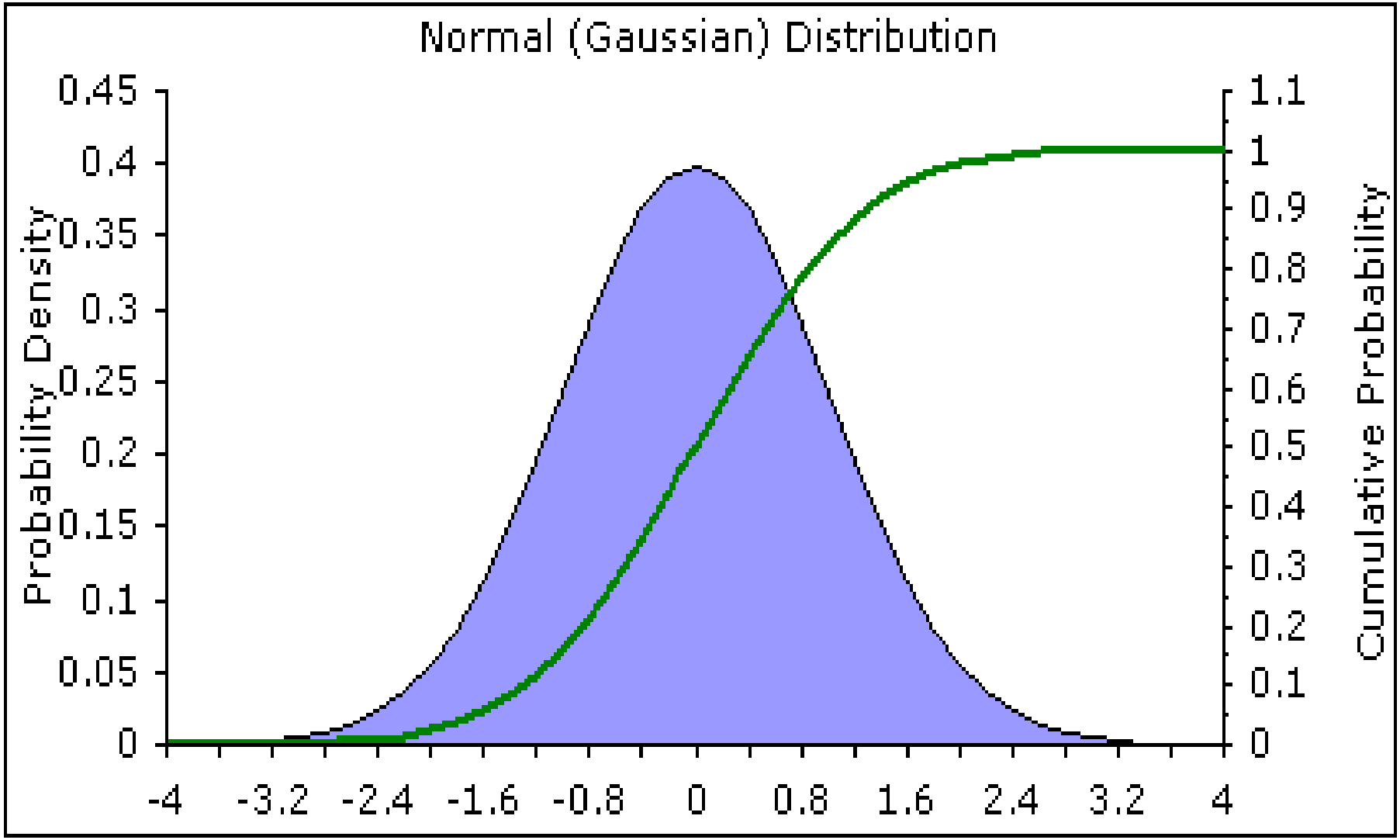
- To make this decision you need to know some basic probability and statistical theory …. And this puts a lot of people off thinking about their laboratory data critically

The Normal Range for a Laboratory Test Result

Conventionally laboratories report normal ranges that encompass the values for that test observed in 95% of healthy individuals.

So if we have a normal range for Serum Albumin 35 – 50 g/L then there is a 0.025 probability that a healthy person could have a serum albumin of less than 35. Equally there is a 0.025 probability that a healthy person could have a serum albumin of greater than 50.

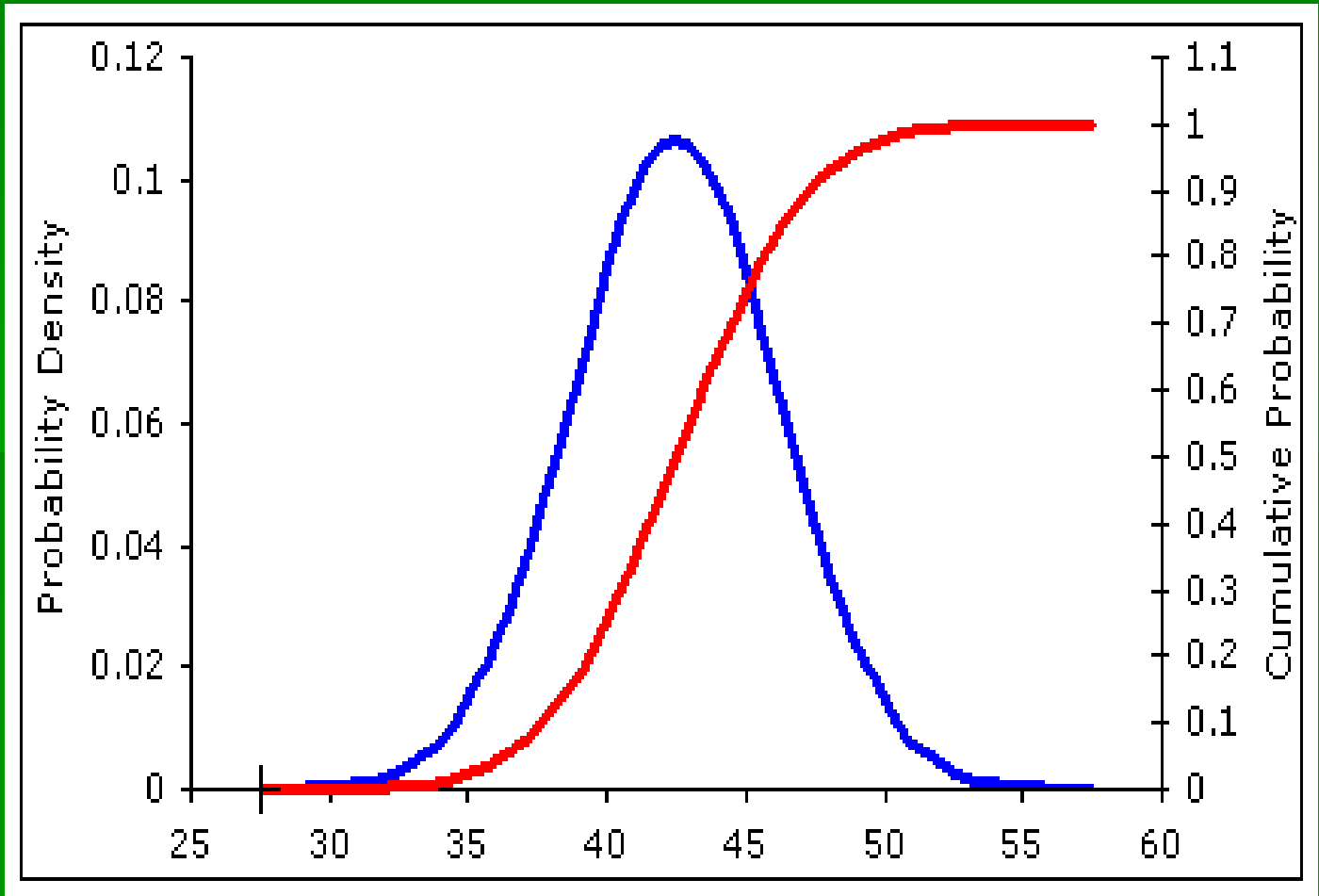
The Statistician's Normal Distribution Curve

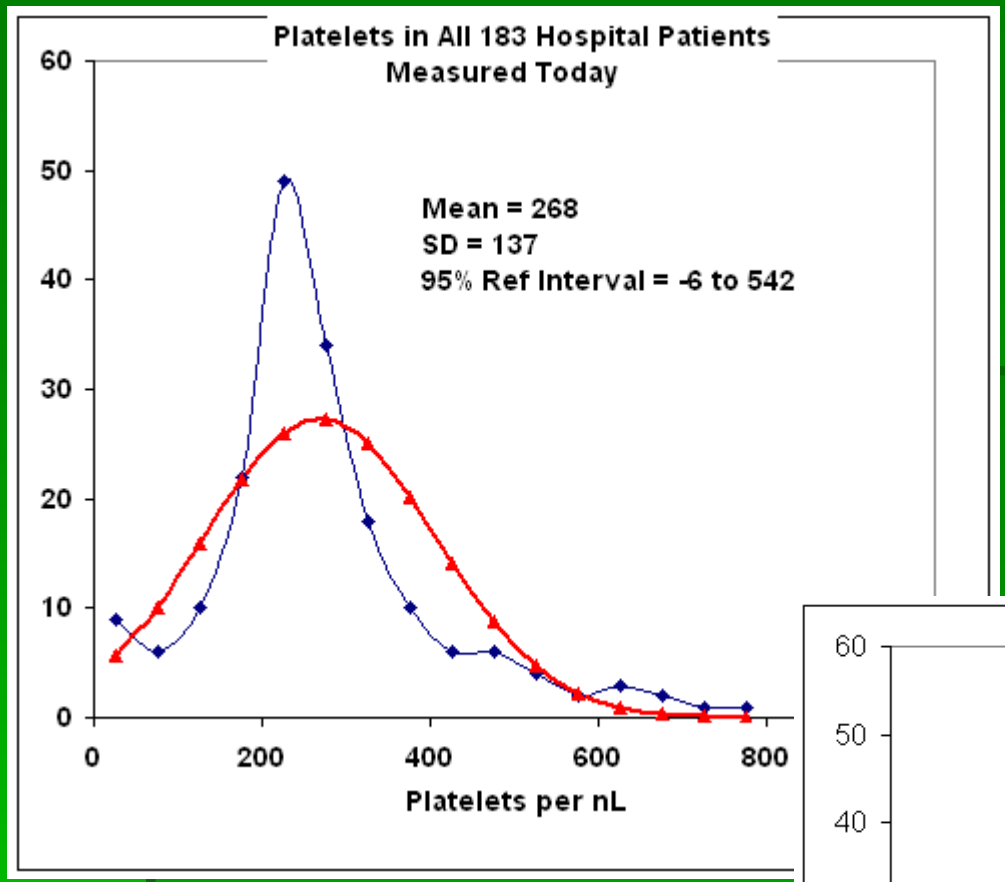


The Clinician's Normal Distribution Curve

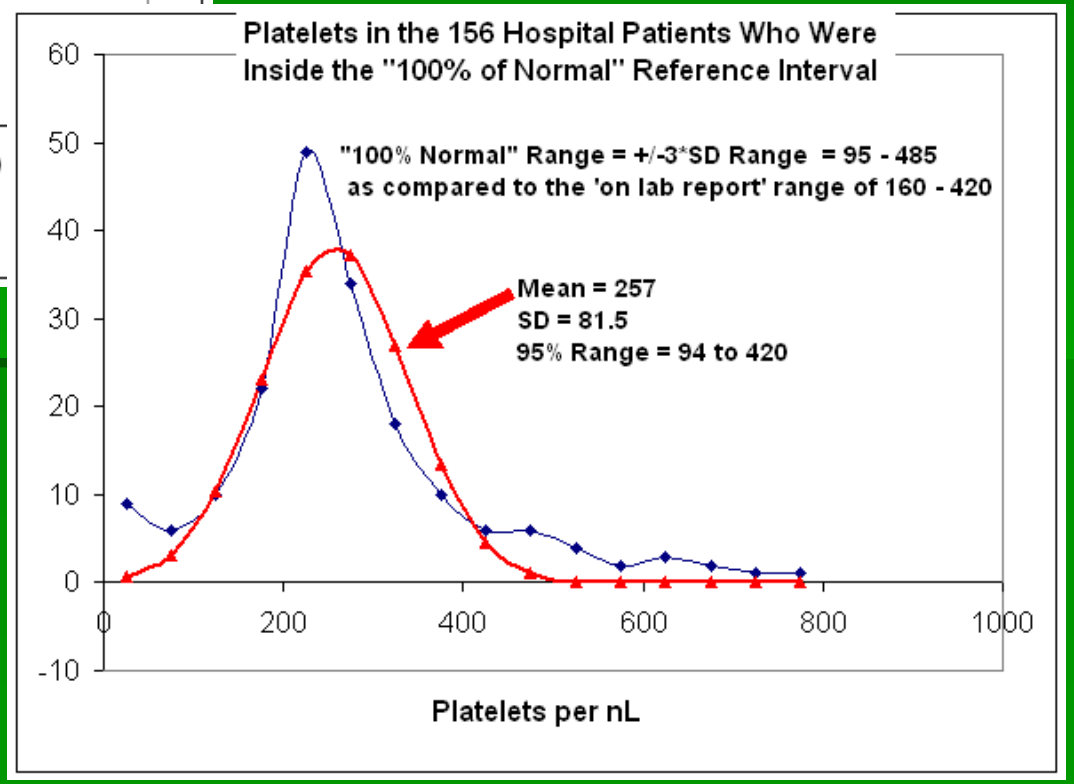
Serum Albumin : Reference Interval = 35 – 50 g/L

Therefore : Mean = 42.5 and SD = 3.75 and 2.5% of normal patients have a serum albumin less than 35 g/L and 100% of normal patients have serum albumins between 31.25 g/L and 53.75 g/L





But not all Laboratory data are normally distributed eg Platelets



So Laboratories should use Parametric and Non-Parametric Reference Intervals as appropriate to the distribution of results from normal individuals

Steps in getting a reliable Pathology Result

- Correct patient
- Correct patient preparation
- Correct Sample Container
- Correct Sampling Site
- Correct Sample Labelling
- Complete Pathology Request Form with Clinical Notes
- Correct Sample Storage and Transport
- Sent to the Correct Laboratory on the correct day

Second Question :
How can you diagnose a disease from a laboratory result ?

"How can I diagnose Gestational Diabetes from my patient's fasting blood glucose?"

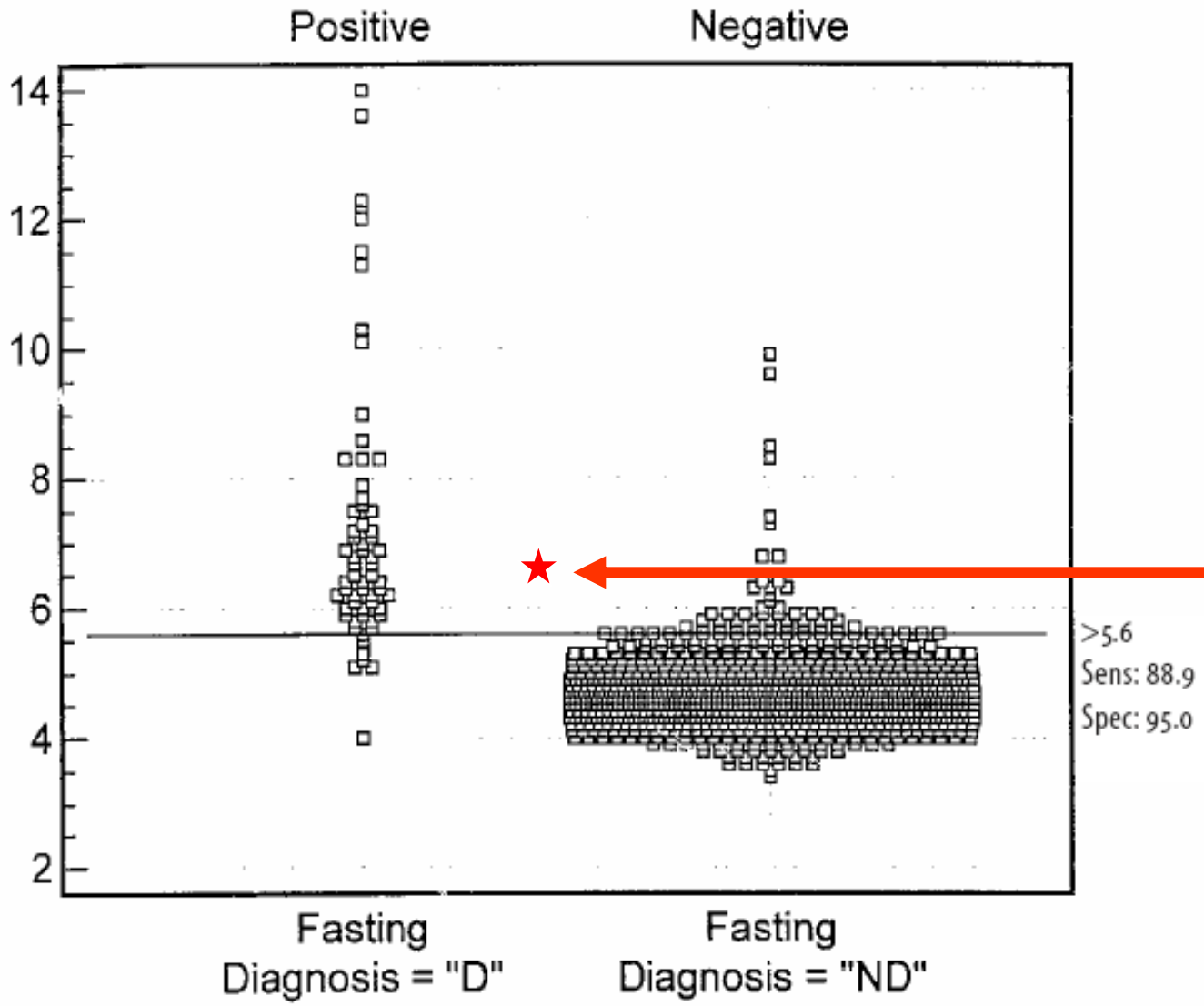


Figure 1. *Distribution of negative and positive GDMs using fasting blood sugar testing under the receiving operating characteristics curve*

Your direction of view when with a new patient

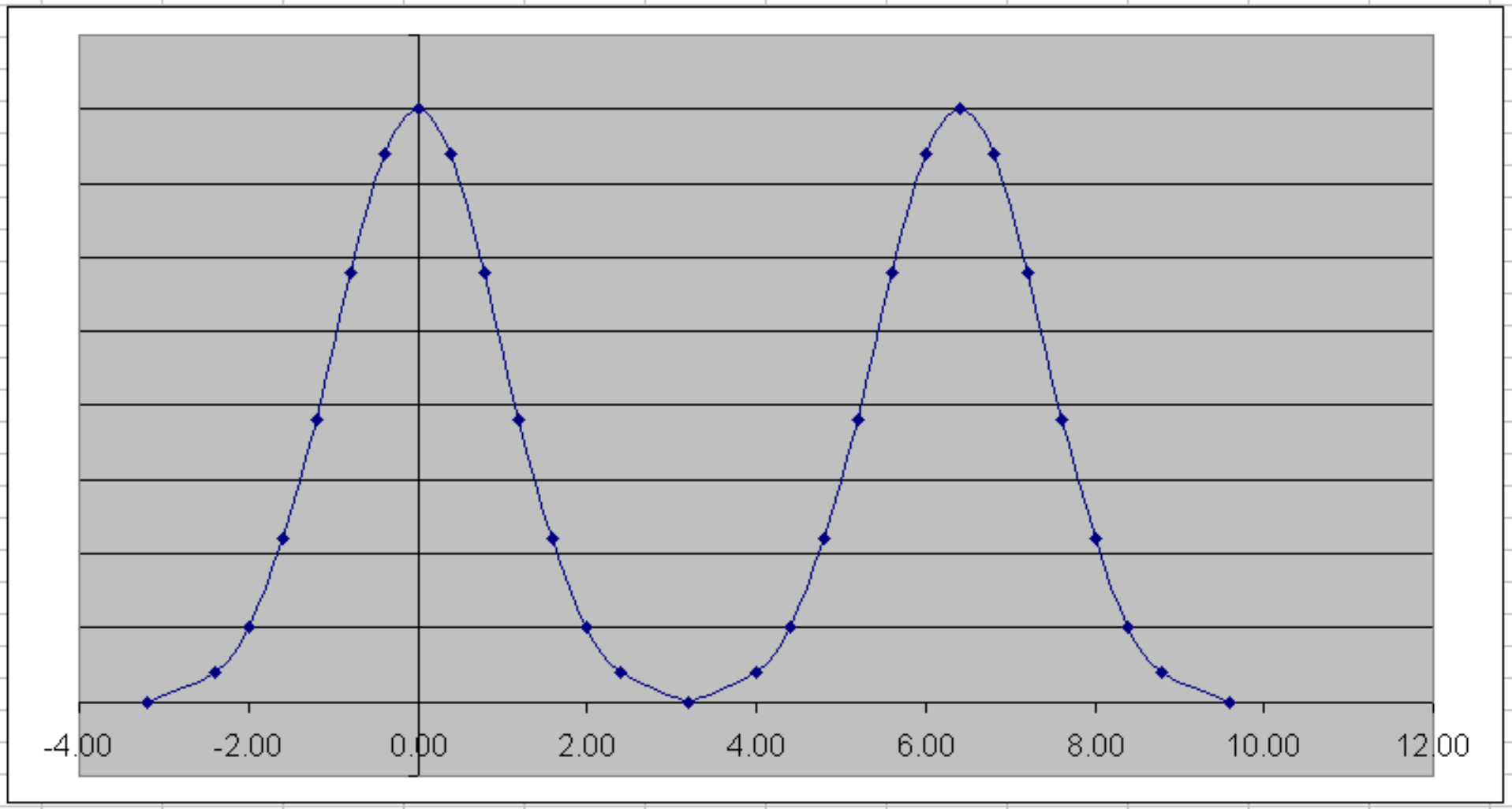
To answer this properly we need to talk about

- Test Specificity

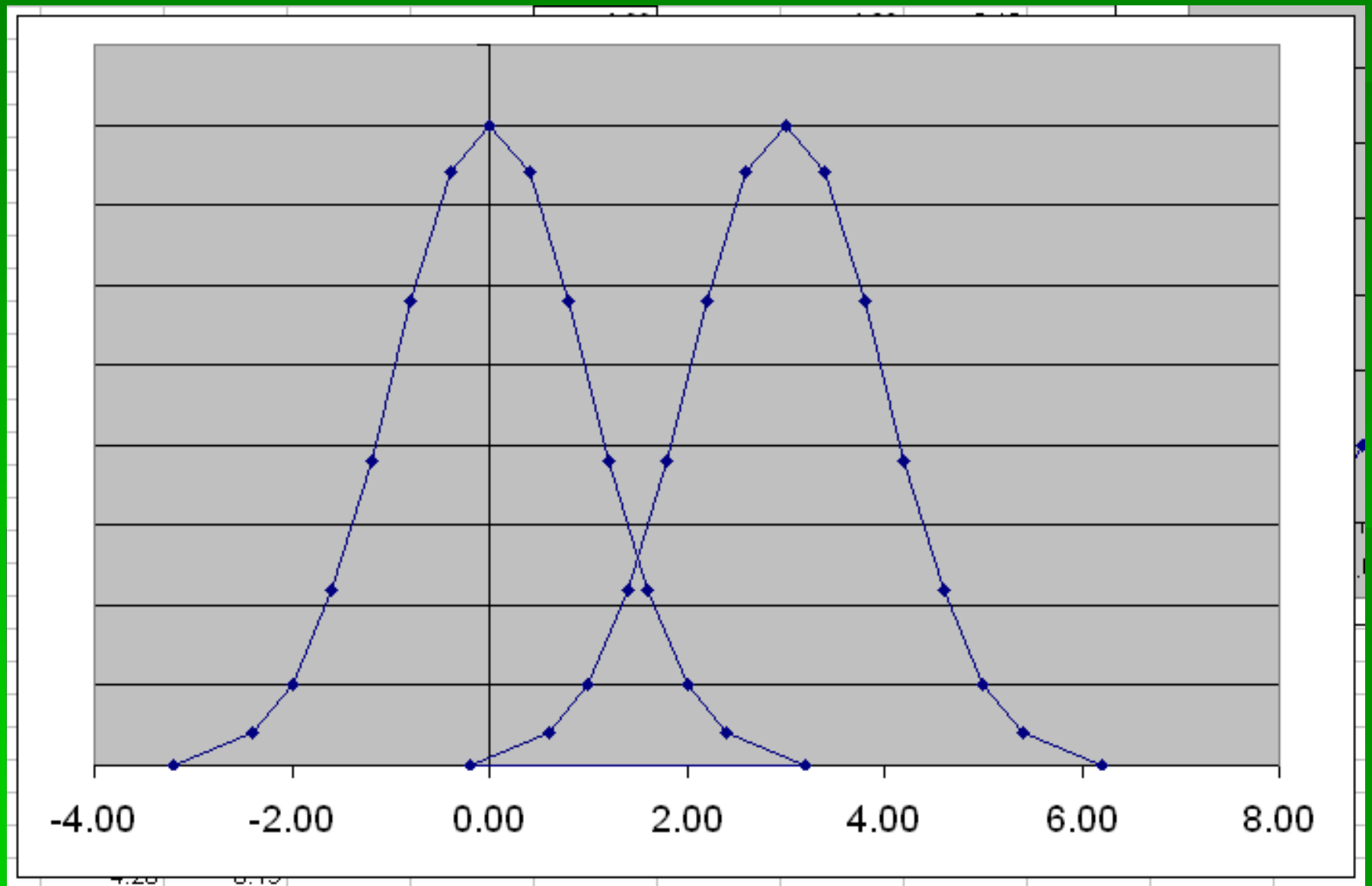
  and

- Test Sensitivity ……

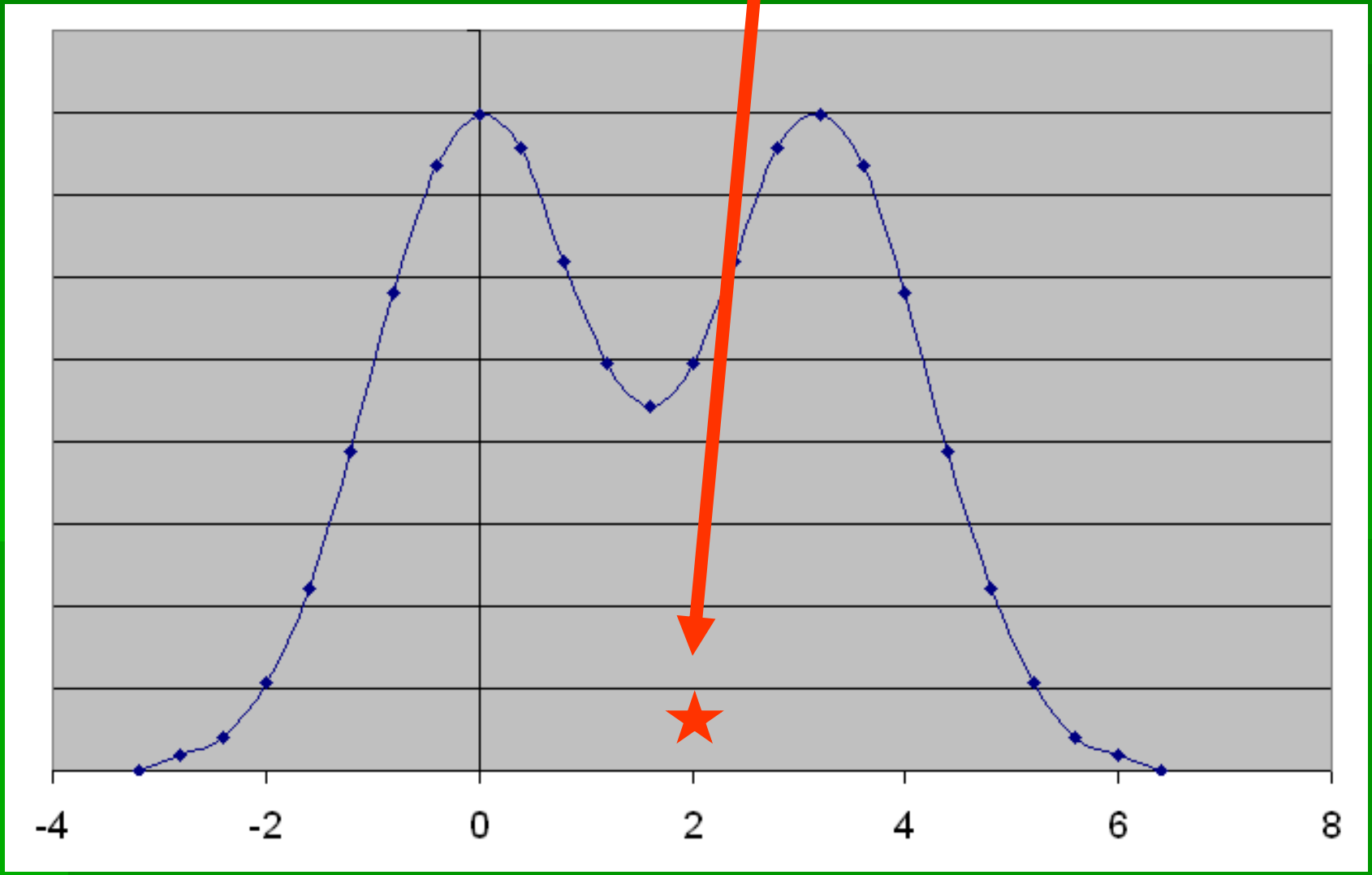
IDEAL SEPARATION OF NORMALS FROM PATIENTS

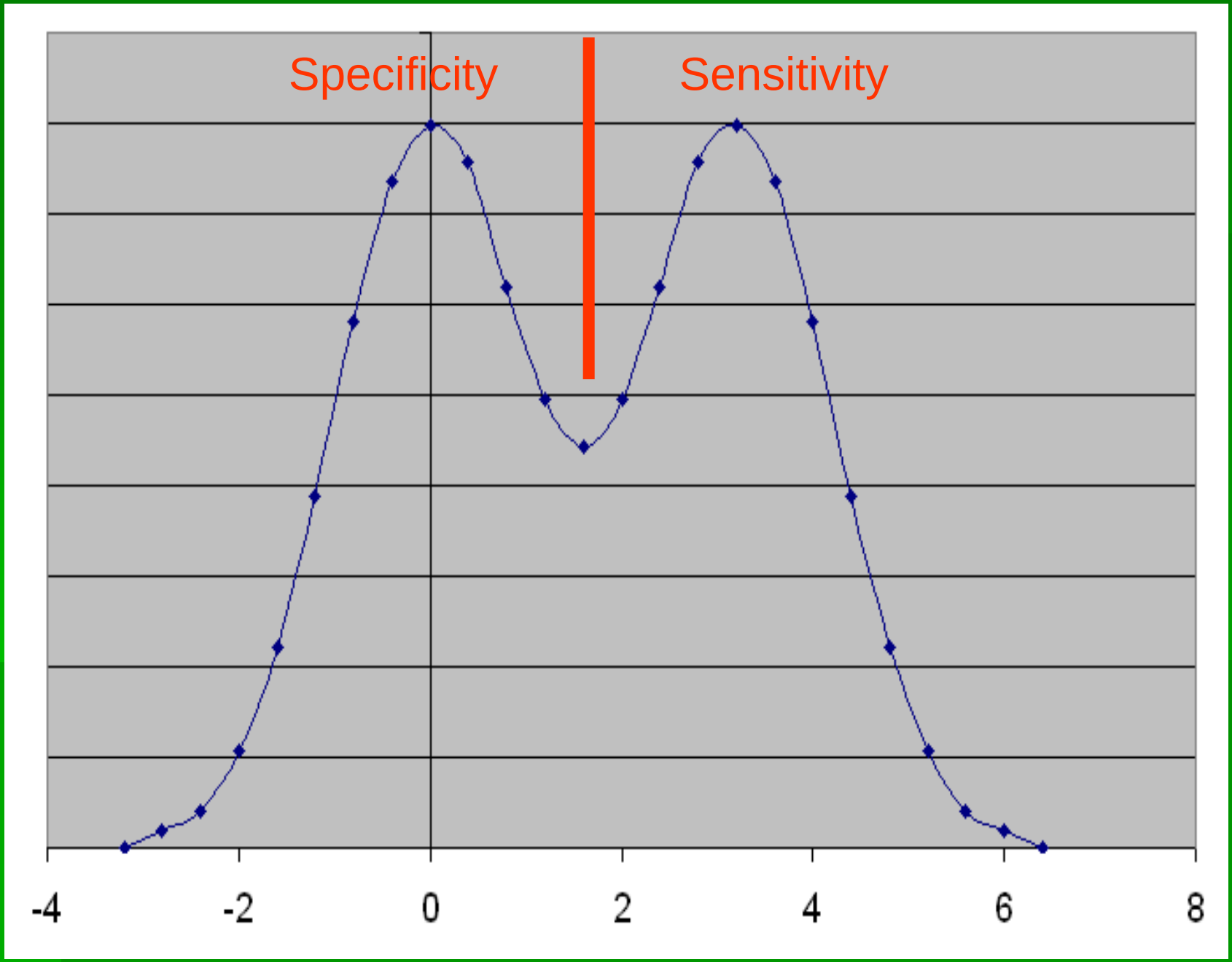


TYPICAL OVERLAP OF RESULTS FROM NORMALS AND RESULTS FROM PATIENTS



What does this result from a new patient mean ?

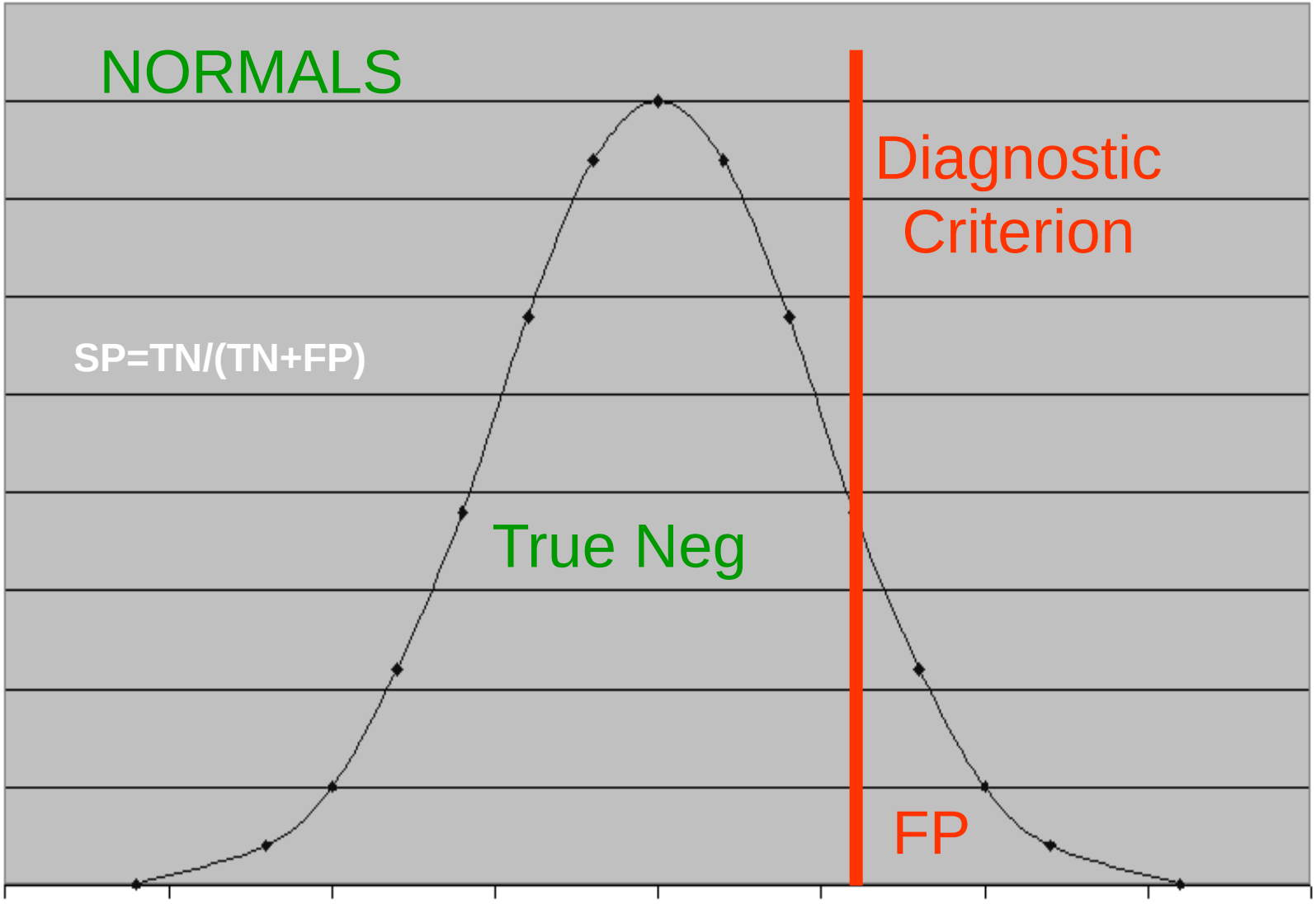



Specificity
Sensitivity
-4
-2
0
2
4
6
8

Specificity and Sensitivity of a Test

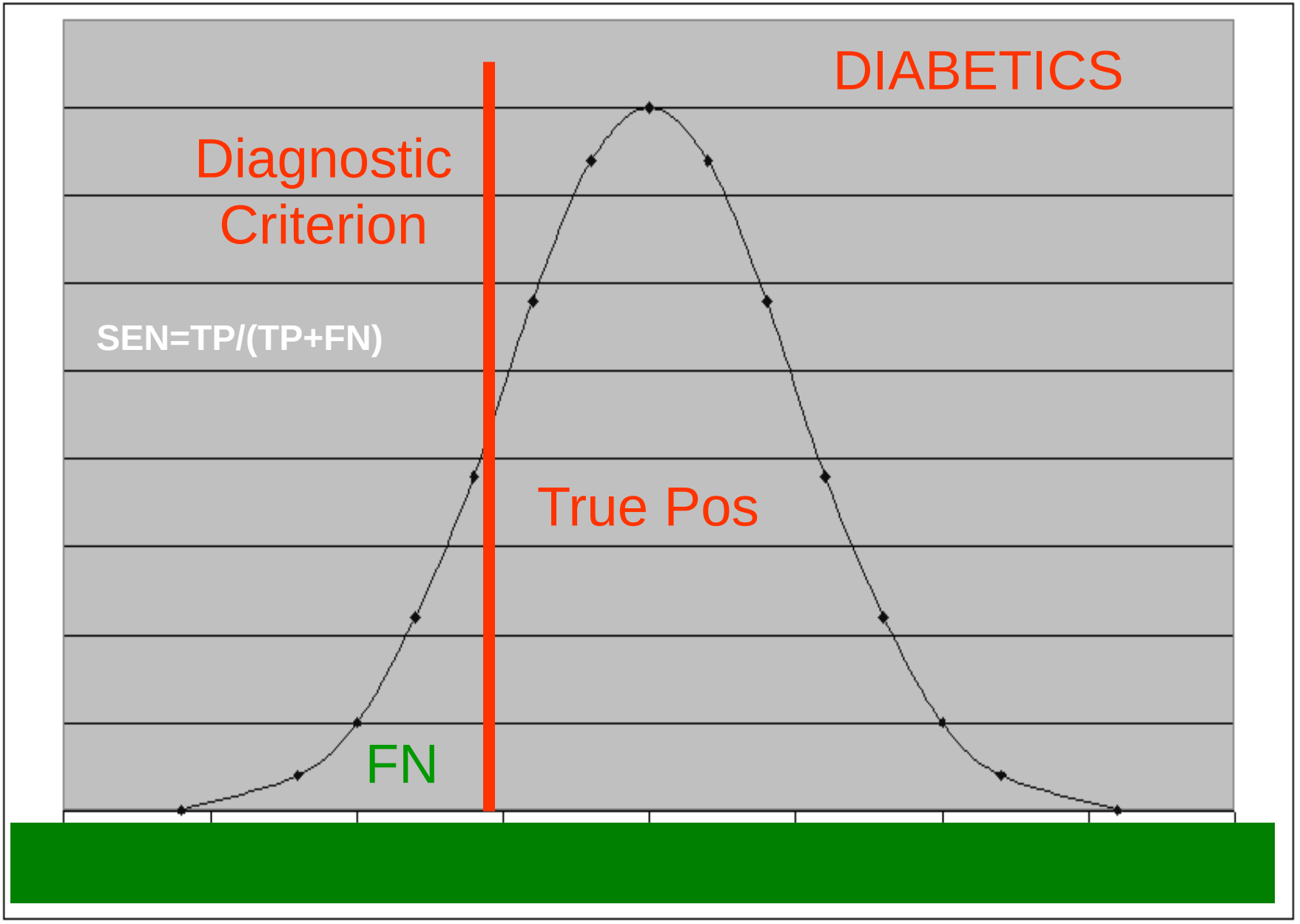
Specificity : the probability that a laboratory test will be negative in the absence of a disease

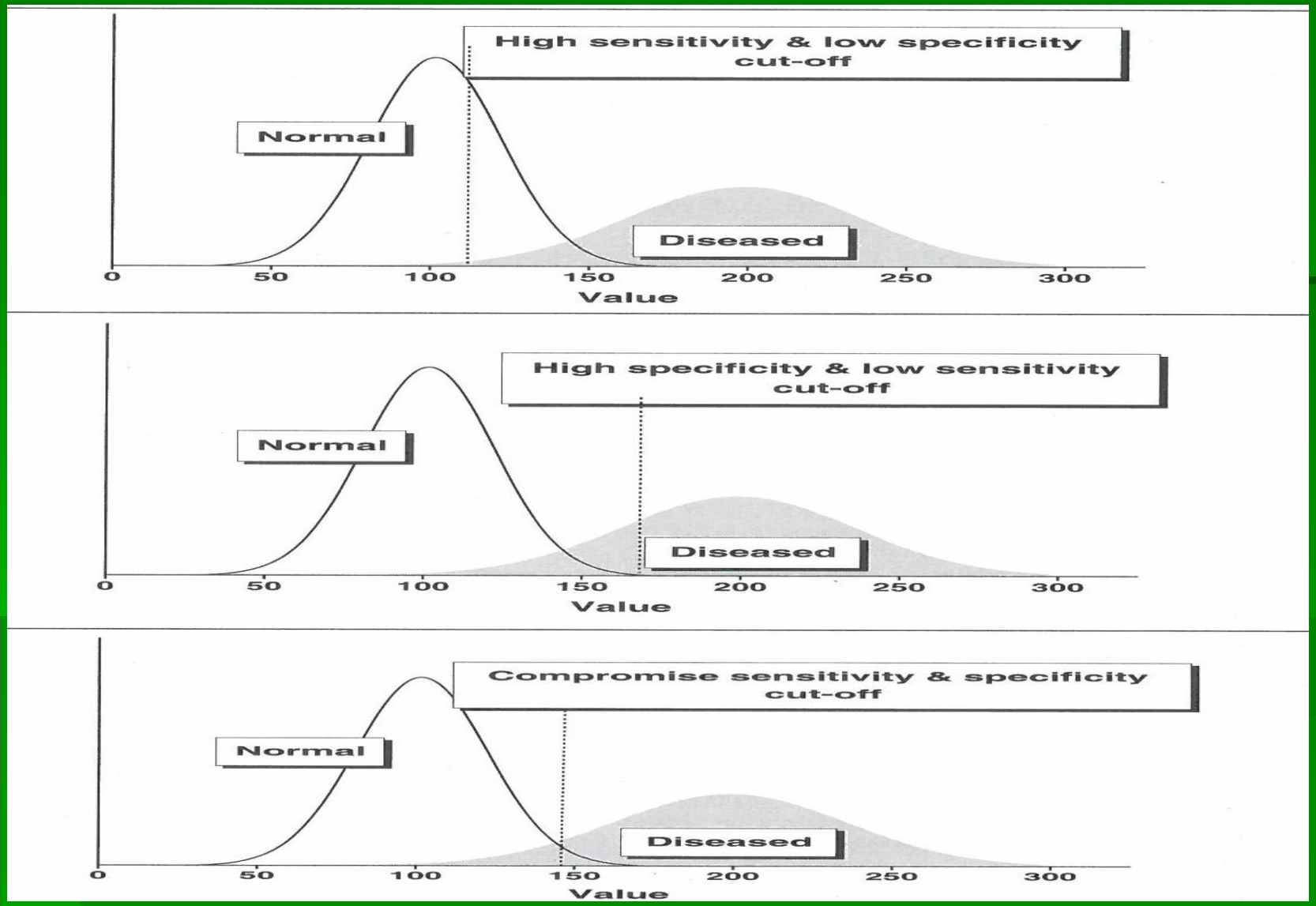
= # of true negatives divided by (# of true negative + # of false positives)


NORMALS
Diagnostic
Criterion
SP=TN/(TN+FP)
True Neg
FP

Sensitivity : the probability that a laboratory test is positive in the presence of disease

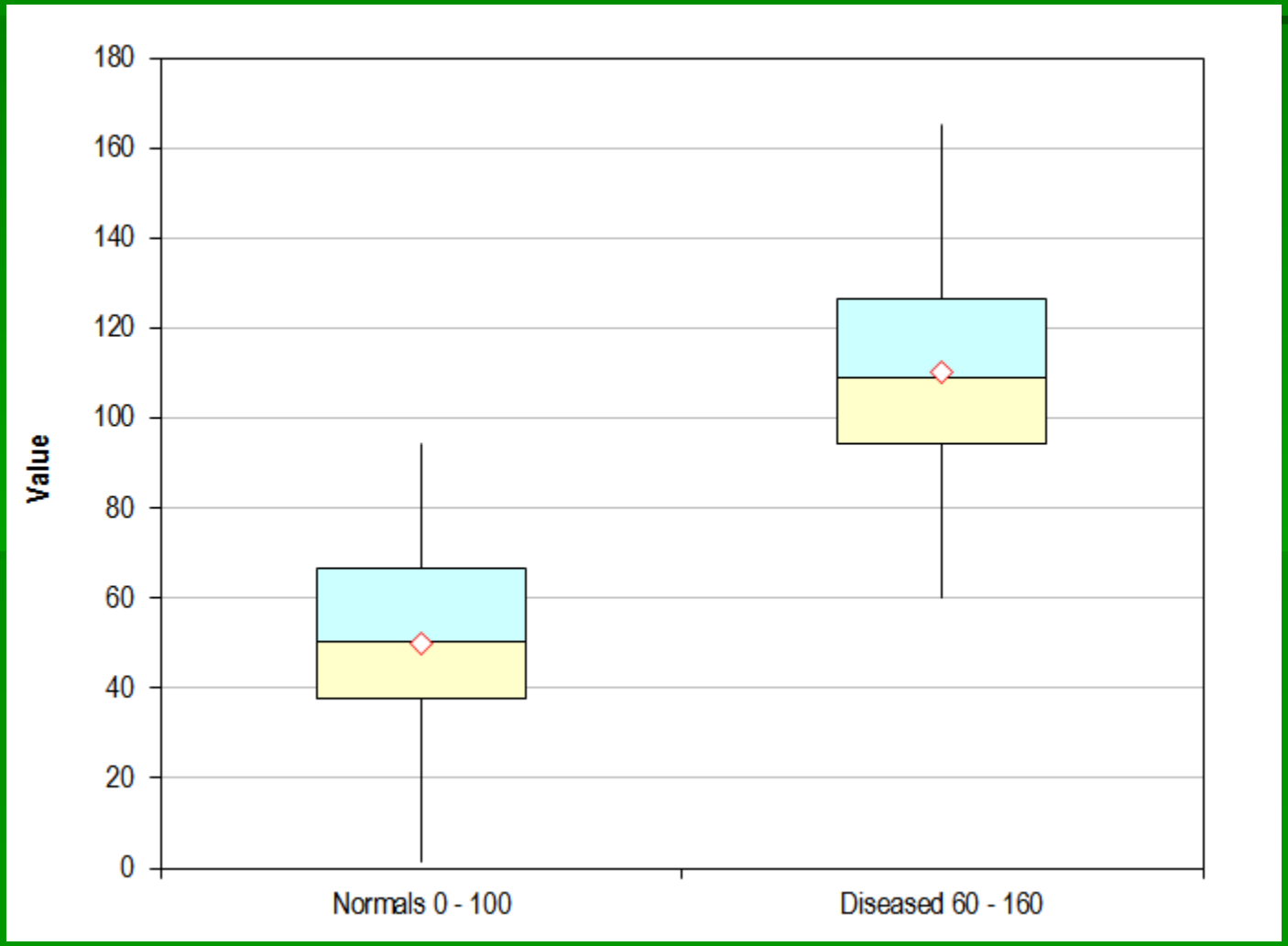
= # of true positives divided by (# of true positives and # of false negatives)


DIABETICS
Diagnostic Criterion
SEN=TP/(TP+FN)
True Pos
FN

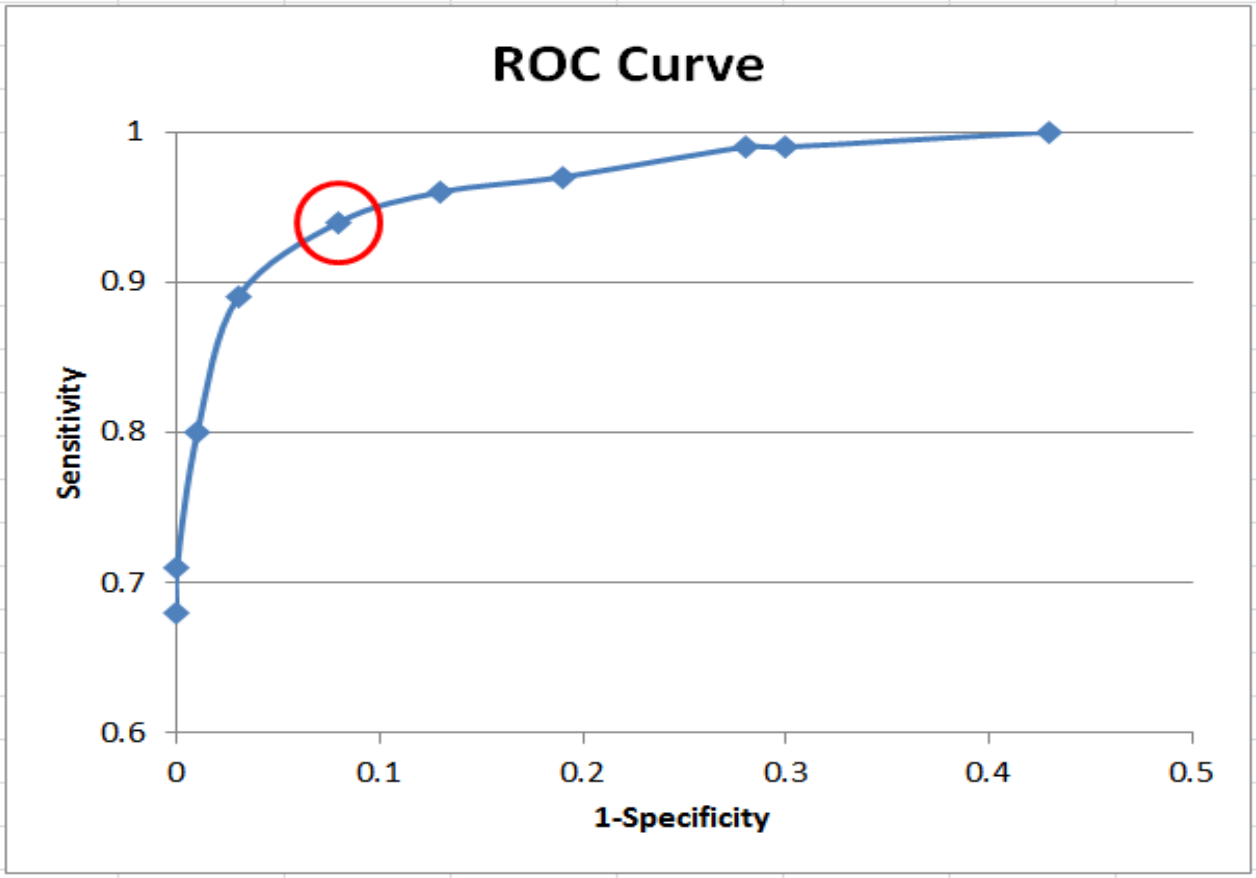


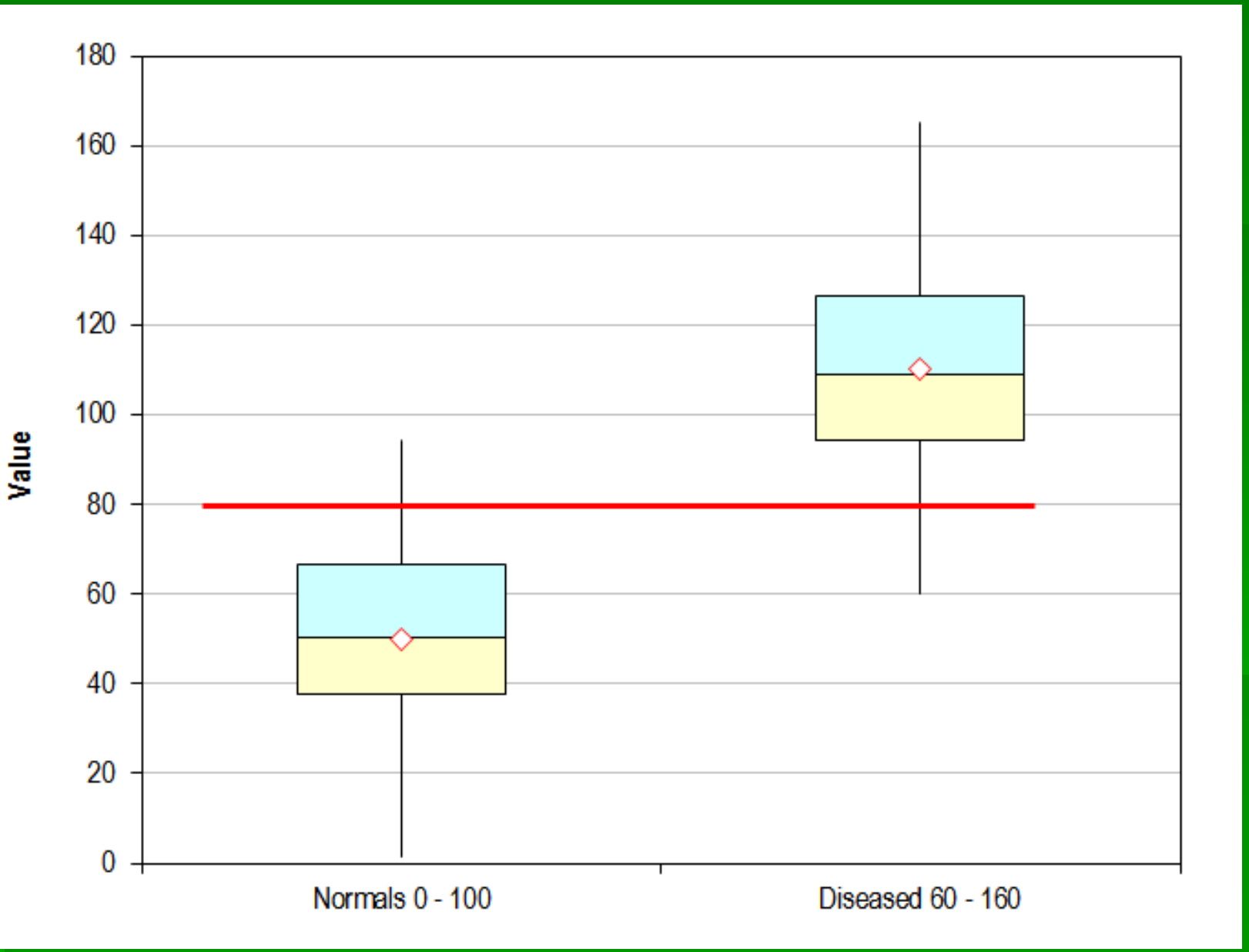
We can use a 'Receiver Operator Curve', which is a plot of (1-Specificity) on the x axis vs Sensitivity on the y axis, to visualise what happens when we move the 'diagnostic threshold'

ROC Simulation



Threshold	55	60	65	70	75	80	85	90
True Positives	100	99	99	97	96	94	89	80
False Positives	43	30	28	19	13	8	3	1
True Negatives	57	70	72	81	87	92	97	99
False Negatives	0	1	1	3	4	6	11	20
1 - Specificity	0.43	0.3	0.28	0.19	0.13	0.08	0.03	0.01
Sensitivity	1	0.99	0.99	0.97	0.96	0.94	0.89	0.8
Specificity	0.57	0.7	0.72	0.81	0.87	0.92	0.97	0.99
Checksum	200	200	200	200	200	200	200	200
sum	1.57	1.69	1.71	1.78	1.83	1.86	1.86	1.79




180
160
140
120
100
80
60
40
20
0
Value
Normals 0 - 100
Diseased 60 - 160

Third Question : How do I know that there has been a Significant change in my patient's Laboratory Result ?

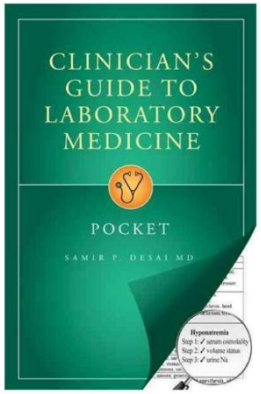
- When the difference between the previous result and today's result is greater than 2.77 times the Standard Deviation of the Laboratory's Analytical Method eg.
- 01/12/07 Cholesterol = 5.65
- 12/02/08 Cholesterol = 5.75
- Laboratory's SD of their analysis = 0.17 mmol/L
- Difference = 0.10 ….
- Diff/SD = 0.10/0.17 = 0.59 NOT SIGNIFICANT !
- A significant difference would be +/- 0.47 mmol/L !

Fourth Question : Why do you need Pathology Tests ??

To gather evidence to prove and/or disprove hypothetical diagnoses.

- This means you need hypotheses
- To make hypotheses you need to have a knowledge of the underlying physiology of your hypotheses
- The best way is to have a flow diagram of the pathophysiology which shows where you will START ‘pathology testing’ with decision points that show when you will STOP ‘pathology testing’ ..

HYPONATREMIA

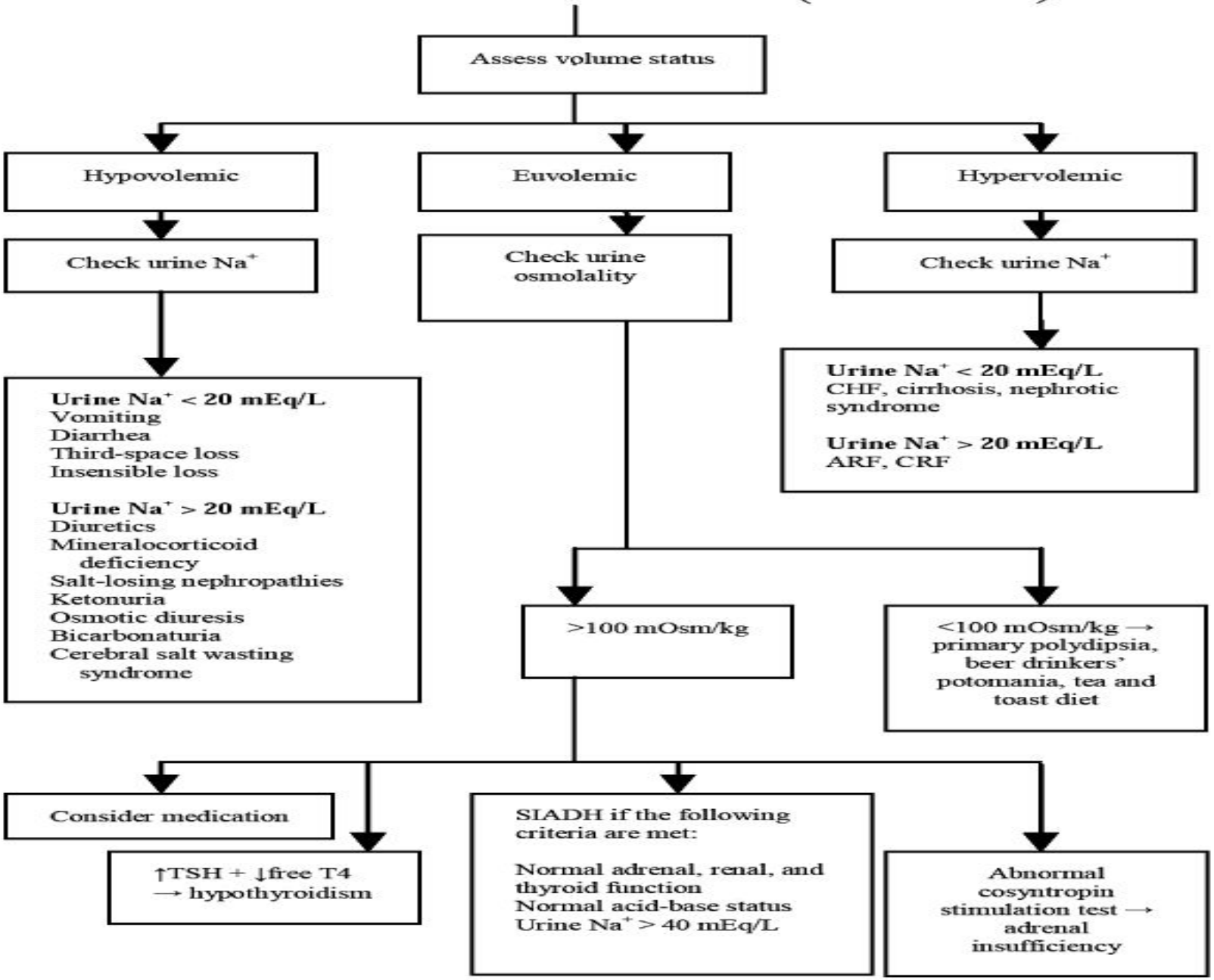


↓ serum Na^+

Check serum osmolality

>290 mOsm/kg	275-290 mOsm/kg	<275 mOsm/kg
Hypertonic hyponatremia	Isotonic hyponatremia (pseudohyponatremia)	Hypotonic hyponatremia
Consider: Hyperglycemia Mannitol Maltose	Consider: Hyperlipidemia Hyperproteinemia Bladder irrigation	Assess volume status
		See next page

HYPONATREMIA (*continued*)



More results than you need .... ?

Identifications

Accession No.	032295
Patient ID	[redacted]
Patient Last Name	[redacted]
Patient First Name	[redacted]
$FO_2(I)$	21.0 %
Sample type	Not specified
Operator	[redacted]

Blood Gas Values

pH	7.377	
pCO_2	43.9	mmHg
pO_2	56.9	mmHg
$cHCO_3^-(P)_c$	25.2	mmol/L
$cBase(B)_c$	0.4	mmol/L

Electrolyte Values

cNa^+	141	mmol/L
cK^+	4.1	mmol/L
cCa^{2+}	1.18	mmol/L
$cCa^{2+}(7.4)_c$	1.16	mmol/L
cCl^-	105	mmol/L

Metabolite Values

cLac	1.8	mmol/L
cGlu	6.0	mmol/L

Oximetry Values

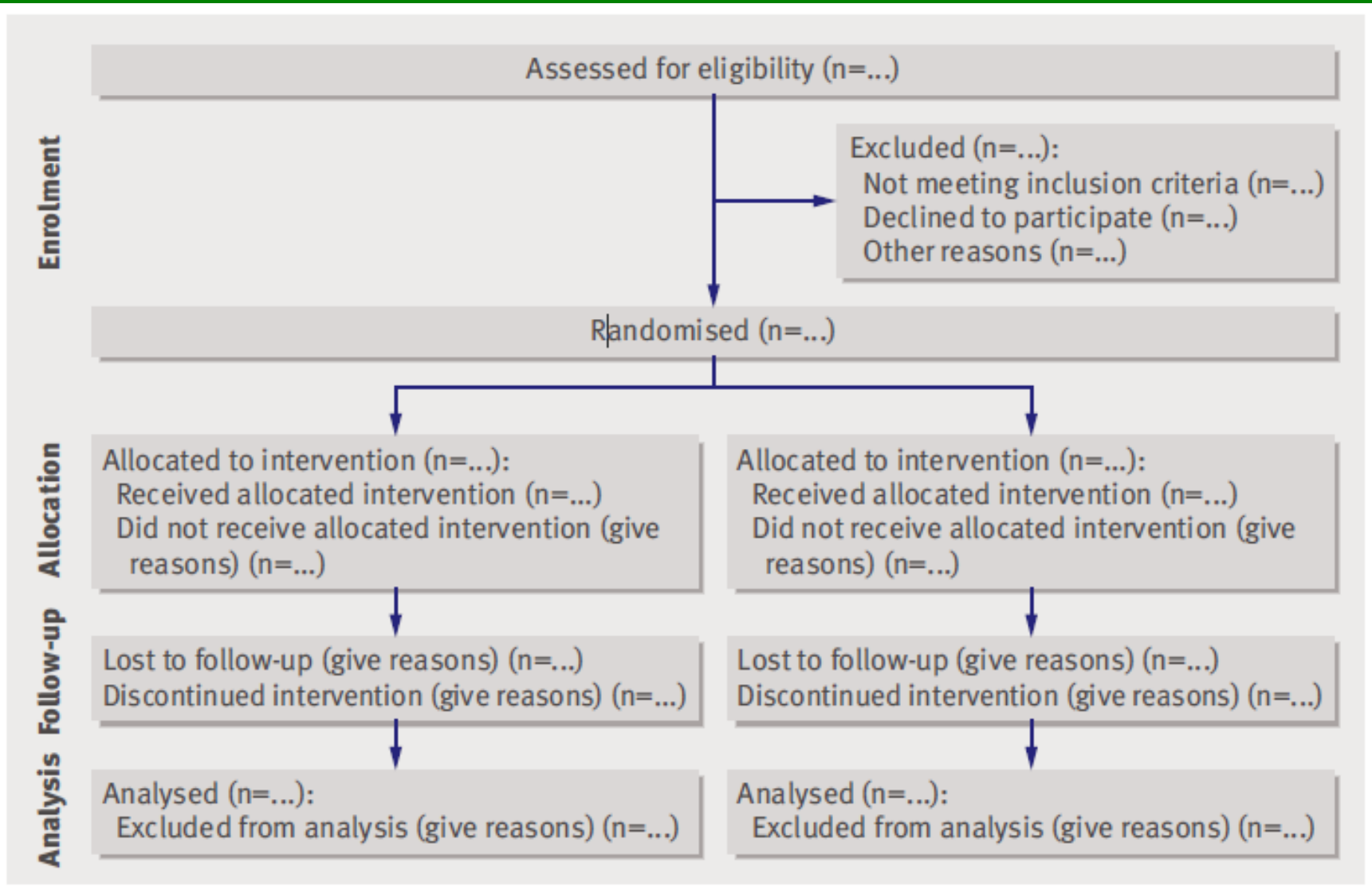
sO_2	86.6	%
ctHb	110	g/L
FCOHb	0.7	%
FMetHb	28.3	%
FO_2Hb	61.5	%

Clinical Trials : The majority are heavily reliant upon carefully controlled pathology testing performed by carefully chosen pathology laboratories.

CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

Kenneth F Schulz,[1] Douglas G Altman,[2] David Moher,[3] for the CONSORT Group

BMJ 2010;340:c332



Flow diagram of the progress through the phases of a parallel randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis)

Annals of Internal Medicine | ARTICLE

An Evaluation of D-Dimer in the Diagnosis of Pulmonary Embolism

A Randomized Trial

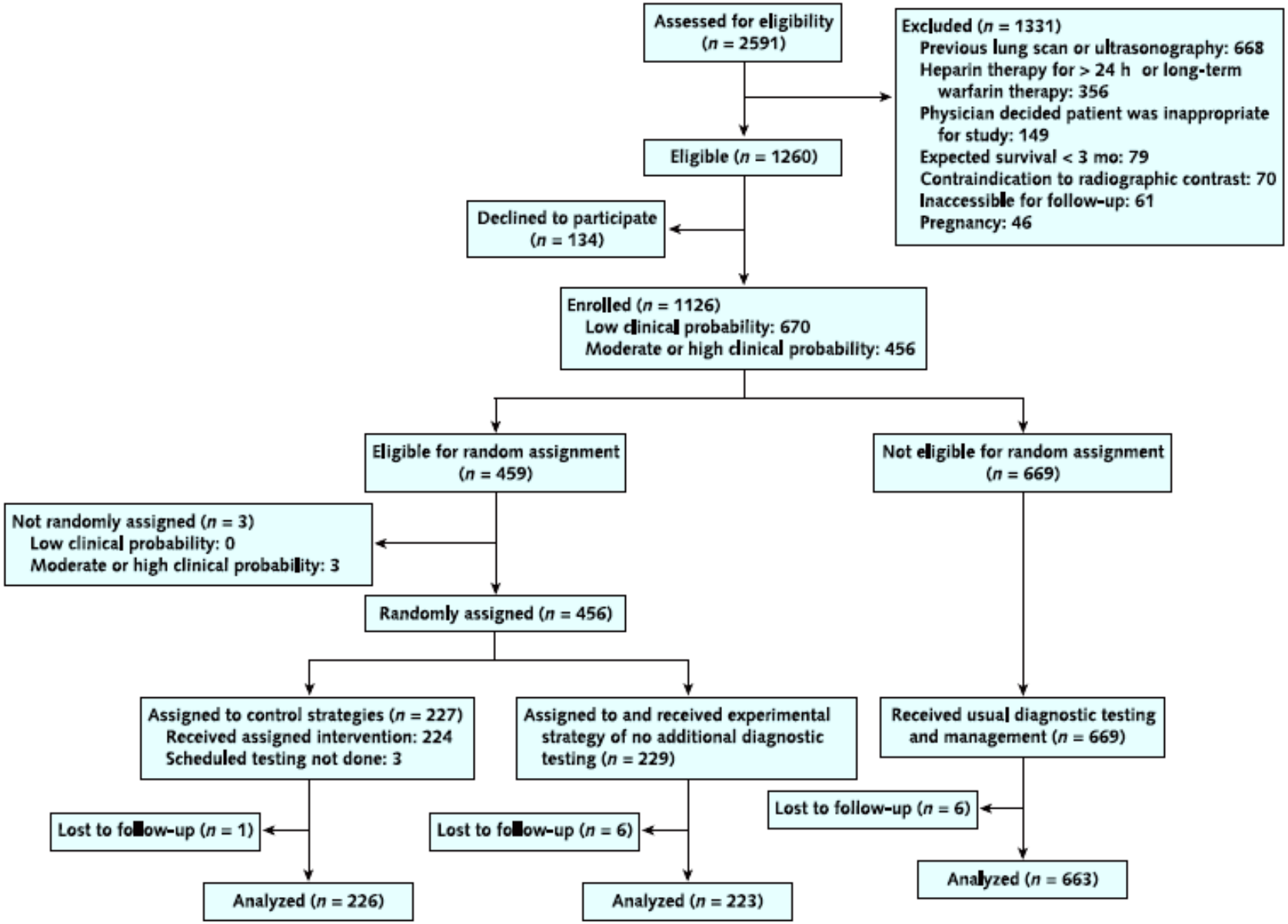
Clive Kearon, MB, PhD; Jeffrey S. Ginsberg, MD; James Douketis, MD; Alexander G. Turpie, MB; Shannon M. Bates, MDCM; Agnes Y. Lee, MD; Mark A. Crowther, MD; Jeffrey I. Weitz, MD; Patrick Brill-Edwards, MD; Philip Wells, MD; David R. Anderson, MD; Michael J. Kovacs, MD; Lori-Ann Linkins, MD; Jim A. Julian, MMath; Laura R. Bonilla, MSc; and Michael Gent, DSc, for the Canadian Pulmonary Embolism Diagnosis Study (CANPEDS) Group*

Background: It may be safe to omit additional diagnostic testing in selected patients with suspected pulmonary embolism (PE) who have a negative D-dimer test, but this approach has never been evaluated in a randomized, controlled trial.

Objective: To determine if additional diagnostic testing can be safely withheld in patients with suspected PE who have negative erythrocyte agglutination D-dimer test results.

Ann Intern Med. 2006;144:812-821.

Figure 1. Study flow diagram.



Conclusion: In patients with a low probability of PE who have negative D-dimer results, additional diagnostic testing can be withheld without increasing the frequency of VTE during follow-up. Low clinical probability and negative D-dimer results occur in 50% of outpatients and in 20% of inpatients with suspected PE.

Pathology Testing comes to the aid of the 21 most underdiagnosed diseases

http://www.wrongdiagnosis.com/

✔ Indicates conditions that are best diagnosed via pathology testing

1. Type 2 diabetes and Impaired glucose tolerance ✔
2. High cholesterol ✔
3. Hypertension
4. Osteoporosis ✔
5. Sexually transmitted diseases ✔
6. Hemochromatosis ✔
7. Chronic kidney disease ✔
8. Hypothyroidism including Hashimoto's thyroiditis ✔
9. Glaucoma
10. Depression

Pathology Testing comes to the aid of the 21 most underdiagnosed diseases

11. Infectious diarrhea ✔
12. Fecal incontinence
13. Lactose intolerance ✔
14. Polycystic ovary syndrome (PCOS) ✔
15. Flat feet
16. Attention deficit hyperactivity disorder and hyperactivity
17. Sleep disorders such as sleep apnoea ✔
18. Asthma ✔
19. Bipolar disorder
20. Celiac disease ✔
21. Whooping cough (or pertussis) ✔

SUMMARY

- Pathology testing is usually the most convenient ‘diagnostic’ for both patient and clinician
- Results need to be interpreted ‘statistically’ viz how abnormal, how ‘big’ is the change, what is the specificity and sensitivity of the test in the patient’s ‘suspected’ condition.
- Testing protocol needs to be designed to match the ‘suspected’ pathophysiology and/or rule out other ‘pathologies’. Negative results are often just as valuable as positives.
- There are good online resources as well as good ‘pocket’ guides…. You will not be able to get by without one.
- Pathology results are only as good as the specimen
- Pathology results are only “useful” if they have been requested because you have a diagnostic ‘hypothesis’ to prove or disprove.
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Lecture : AN INTRODUCTION TO THE ROLE AND USE OF PATHOLOGY LABORATORY TESTING IN CLINICAL PRACTICE : 2013

Background Reading : The CONSORT Statement

Background Reading : D-Dimer Testing and Pulmonary Embolus

Email comments and enquiries to *tom.hartley@dhhs.tas.gov.au* with the Subject = 'Lecture Notes : Pathology Testing'