Professional Practice in Clinical Chemistry

Laboratory calculations I

Patti Jones, PhD
Professor of Pathology
UT Southwestern Medical Center
Director of Chemistry
Children's Medical Center Dallas

Presented by AACC and NACB

Learning Objectives

- Understand and be able to use the following types of calculations
  - Reference interval
  - How to work up Proficiency Testing results
  - Sensitivity/specificity
  - ROC curve
  - Student t test
  - Volume of distribution

Case 1: Reference intervals

- Validating a reference interval?
- Transferring a reference interval?
- Establishing a reference interval
  – On a test with well-defined inclusion/exclusion criteria? - a priori sampling
  – On a new analyte? – a posteriori sampling

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Case 1: Reference intervals

- Validating a reference interval?
  - 20 – 60 reference individuals
- Transferring a reference interval?
  - Method comparison and bias evaluation
- Establishing a reference interval
  - On a test with well-defined inclusion/exclusion criteria? - a priori sampling – 120 healthy individuals to get 90% C.I. at 95th percentile
  - On a new analyte? – a posteriori sampling – as many as you can analyze

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Case 1: Reference intervals

- Establishing a reference interval
- Look at data distribution! – why?

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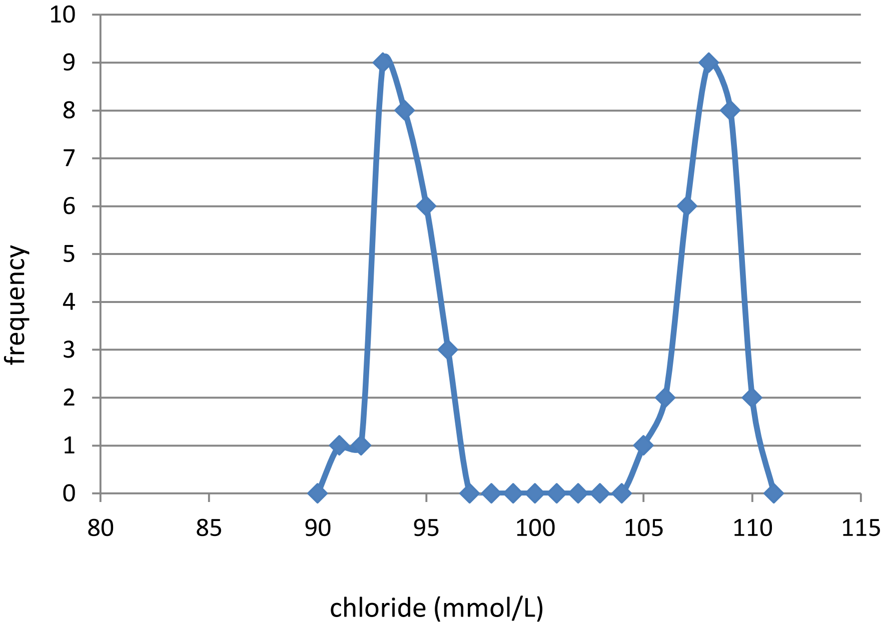
Reference intervals

- Chloride on CAVH fluid
  - N = 56
  - Mean = 101
  - Median 100
  - SD = 7

Reference intervals

- Chloride on CAVH fluid
  - N = 56
  - Mean = 101
  - Median 100
  - SD = 7



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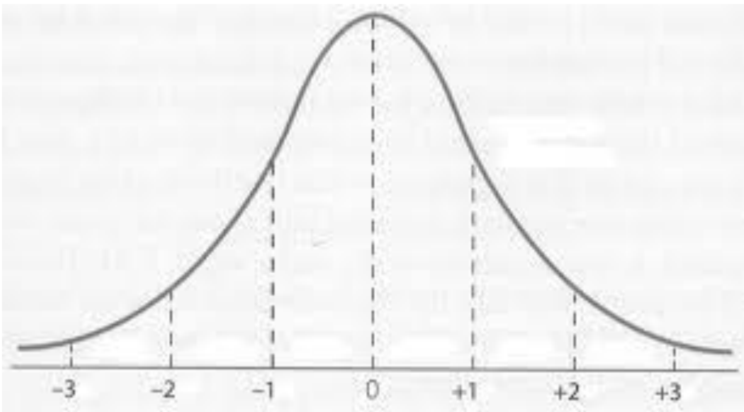
Reference intervals

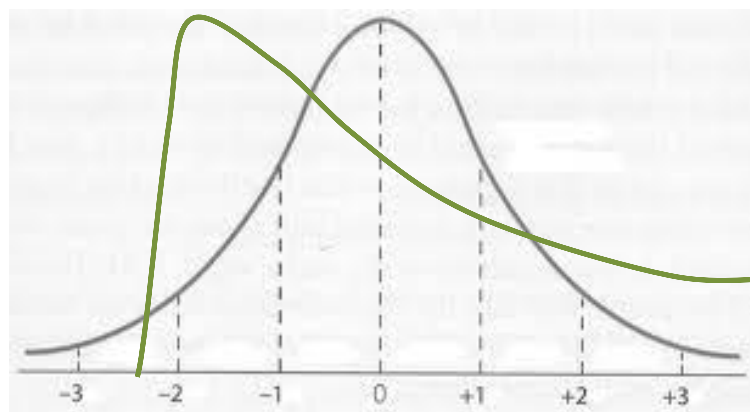


Normally distributed data:
use parametric statistics

mean ± 2SD to get 95%

NOT normally distributed data:
use **non-parametric statistics**

2.5th and 97.5th percentiles



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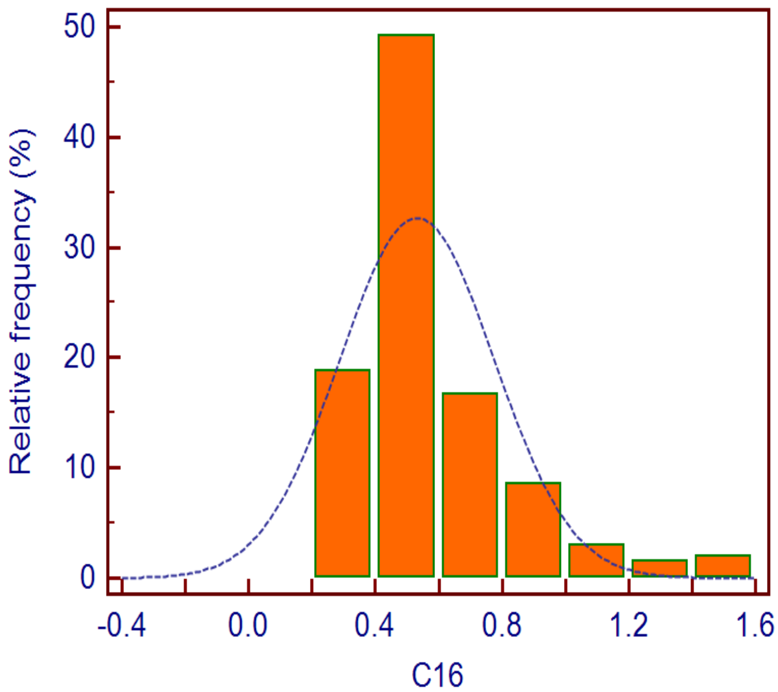
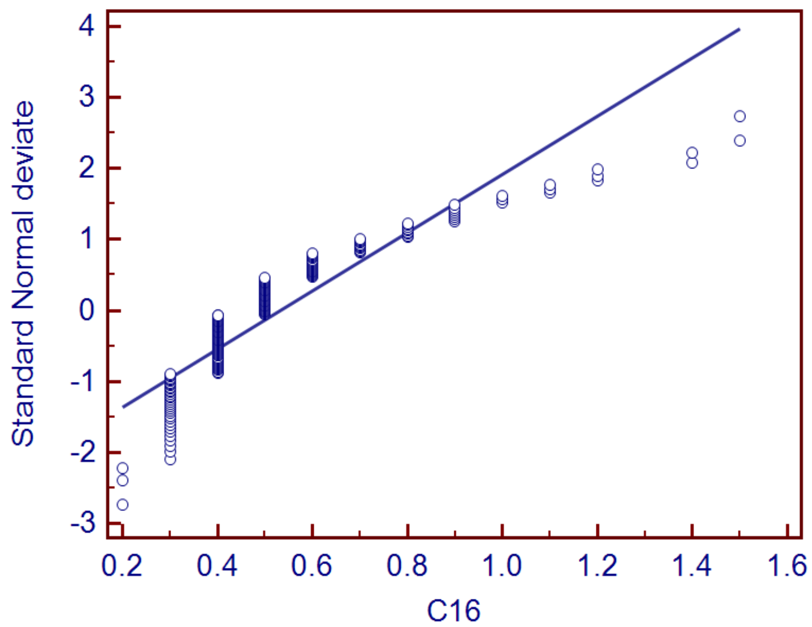
Case 1: reference interval for 3-OH-C16



Frequency histogram

Normal plot



Case 1: reference interval for 3-OH-C16

- Non-parametric analysis:
  - Rank the values in order, lowest to highest, and number them (1 = lowest value)
  - Determine 2.5th percentile and 97.5th percentile value
    - 2.5th = 0.025 (n+1)   97.5th = 0.975(n + 1)

3-OH-C16 reference interval

- N = 197
- Range = 0.2 – 1.5
- Mean = 0.53; median = 0.50

- Non-parametric 95% reference interval:
  - 2.5^{th} = 0.025(198) = 4.95 = 5^{th} value
  - 97.5^{th} = 0.975(198) = 193^{rd} value

0.3 – 1.2

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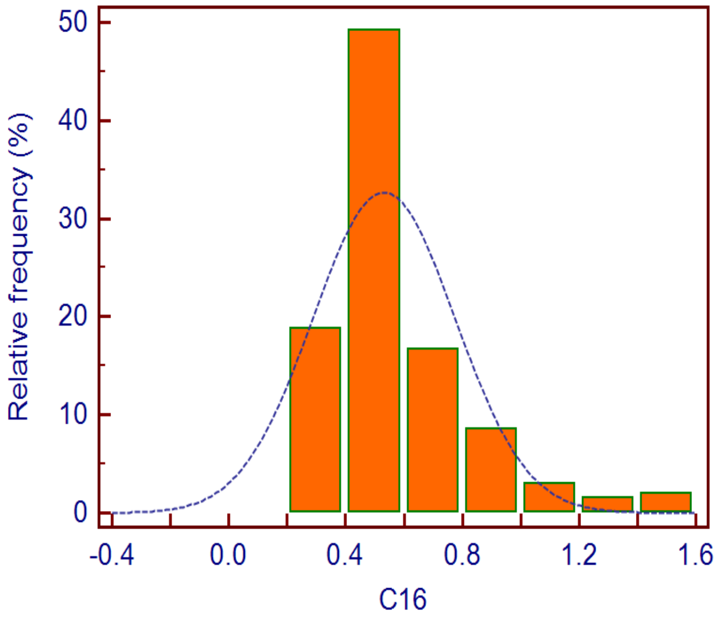
3-OH-C16 reference interval

- Non-parametric 95% reference interval:
  - 2.5th = 0.025(198) = 4.95 = 5th value
  - 97.5th = 0.975(198) = 193rd value

0.3 – 1.2

- Gaussian 95% reference interval

0.05 – 1.01



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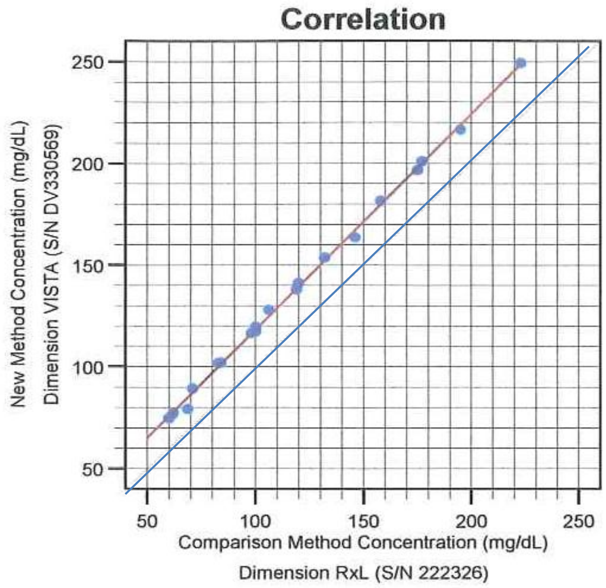
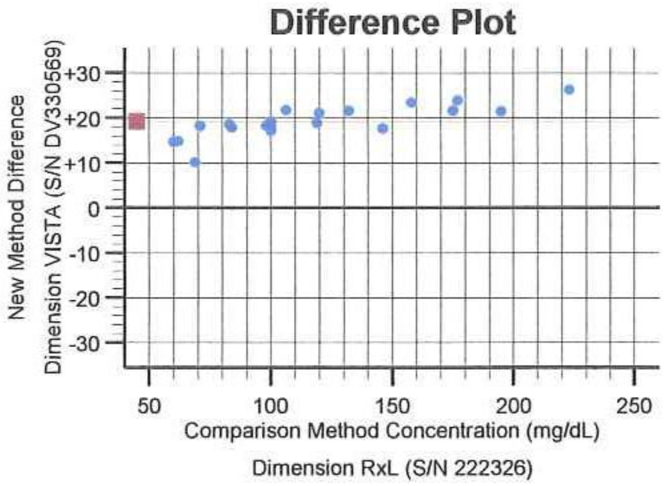
Transferring a reference interval



$Y = 1.063X + 9.1$

$r^2 = 0.9998$

Average difference = +19 mg/dL



Adjusted reference intervals

Notified physicians

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Case 2: Proficiency Testing workup

- PT challenges are **opportunities**
- PT results reported against "peer group"

Free T4		CHM-11		
Method	No of labs	mean	SD	CV
A	229	3.23	0.24	7.3
B	22	1.67	0.13	7.7
C	278	3.12	0.16	5.1
D	225	2.82	0.17	6.1
E	178	4.07	0.19	4.6
F	338	3.79	0.12	3.2
G	55	6.91	0.06	0.9

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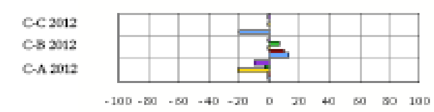
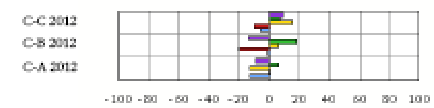
Case 2: Proficiency testing

ORIGINAL

Test / Unit of Measure / Peer Group	Specimen	Your Result	Mean	S.D.	No. of Labs	S.D.I	Lower	Upper	Your Grade	Plot of the Relative Distance of Your Results from Target as Percentages of allowed Deviation (Survey -100------------Mean-----------+100)
Potassium, serum	CHM-11	2.6	2.61	0.03	553	-0.4	2.1	3.2	Acceptable	
mmol/L	CHM-12	4.3	4.30	0.05	558	+0.1	3.7	4.8	Acceptable	
ION SELECT ELECT DIL	CHM-13	6.4	6.41	0.07	558	-0.1	5.9	7.0	Acceptable	
SIEMENS DIMENSION VIST	CHM-14	4.3	4.30	0.05	557	+0.1	3.7	4.8	Acceptable	
	CHM-15	5.8	5.90	0.06	549	-1.7	5.4	6.5	Acceptable	
Protein, total, serum	CHM-11	4.8	4.75	0.07	561	+0.7	4.2	5.3	Acceptable	
g/dL	CHM-12	4.7	4.66	0.08	562	+0.5	4.1	5.2	Acceptable	
BIURET	CHM-13	2.7	2.64	0.06	560	+1.0	2.3	3.0	Acceptable	
SIEMENS DIMENSION VIST	CHM-14	4.6	4.66	0.07	558	-0.7	4.1	5.2	Acceptable	
	CHM-15	3.4	3.43	0.07	564	-0.5	3.0	3.8	Acceptable	
Sodium, serum	CHM-11	136	136.4	1.6	554	-0.3	132	141	Acceptable	

Ideally: sample results dispersed on both sides of mean and not far from mean

Report gives "**SDI**" – Standard Deviation Index – measure of the difference of your result from the group mean compared to group SD

$$SDI = (\text{your result} - \text{group mean}) \div \text{group SD}$$

$$SDI = (4.8 - 4.75)/0.07 = 0.05/0.07 = +0.7$$

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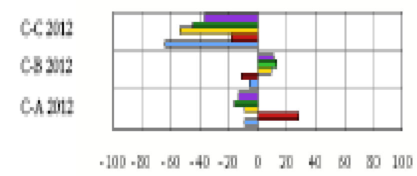
Case 2: PT work-up

Albumin	CHM-11	2.8	2.92	0.08	560	-1.4	2.6	3.3	Acceptable
g/dL	CHM-12	2.7	2.87	0.08	559	-2.2	2.5	3.2	Acceptable
DYE BINDING-BCP	CHM-13	1.6	1.72	0.06	557	-2.3	1.5	1.9	Acceptable
SIEMENS DIMENSION VIST	CHM-14	2.8	2.87	0.07	557	-0.9	2.5	3.2	Acceptable
	CHM-15	2.0	2.18	0.06	561	-2.7	1.9	2.4	Acceptable



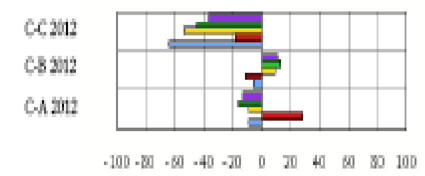
This should trigger an investigation.

- method was running along the mean previously
- SD1 approaching 2.5

SDI > ±2.5, only 0.6% probability that result will fall within the peer group

Case 2: PT work-up

Albumin	CHM-11	2.8	2.92	0.08	560	-1.4	2.6	3.3	Acceptable
g/dL	CHM-12	2.7	2.87	0.08	559	-2.2	2.5	3.2	Acceptable
DYE BINDING-BCP	CHM-13	1.6	1.72	0.06	557	-2.3	1.5	1.9	Acceptable
SIEMENS DIMENSION VIST	CHM-14	2.8	2.87	0.07	557	-0.9	2.5	3.2	Acceptable
	CHM-15	2.0	2.18	0.06	561	-2.7	1.9	2.4	Acceptable



Go back and investigate:

- QC – any shifts of changes in QC values
- Reagent lots – change in lot number of reagents?
- Calibrations – when was method last calibrated – how did the calibration look
- Instrument maintenance – was this done or does it need to be done
  if done, did it effect QC
- How the PT samples were handled

A single outlying result on PT could be operator;

All PT challenges – systemic issue, i.e. lot number

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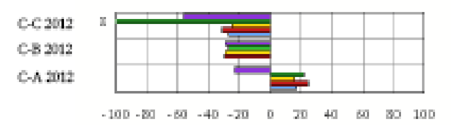
Case 2: PT failure

Test Unit of Measure Peer Group	Specimen	Your Result	Mean	S.D.	No. of Labs	S.D.I	Limits of Acceptability Lower	Limits of Acceptability Upper	Your Grade
Urea Nitrogen	CHM-11	36.0	37.97	1.26	561	-1.6	34.5	41.4	Acceptable
mg/dL	CHM-12	21.0	23.73	0.85	562	-3.2	21.5	25.9	Unacceptable
UREASE WITH GLDH	CHM-13	11.0	11.52	0.56	566	-0.9	9.5	13.6	Acceptable
SIEMENS DIMENSION VIST	CHM-14	23.0	23.70	0.84	563	-0.8	21.5	25.9	Acceptable
	CHM-15	13.0	13.57	0.59	565	-1.0	11.5	15.6	Acceptable

Plot of the Relative Distance of Your Results from Target as Percentages of allowed Deviation

Survey -100-----------Mean-----------+100



x: Result is outside the acceptable limits

Go back and investigate:

- QC – any shifts of changes in QC values
- Reagent lots – change in lot number of reagents?
- Calibrations – when was method last calibrated – how did the calibration look
- Instrument maintenance – was this done or does it need to be done
  if done, did it effect QC
- How the PT samples were handled

A single outlying result on PT could be:

operator error/mishandling of specimen
typo putting in results
something you never figure out (instrument short-sampled that test?)

Case 3: Clinical validity/utility sensitivity/specificity/predictive values

- **Specificity:** the frequency of a negative test when no disease is present

$$\text{Spec.} = \frac{TN}{TN + FP} \times 100 = \quad (\%)$$

- **Sensitivity:** the frequency of a positive test when disease is present, or ability of test to detect disease

$$\text{Sens.} = \frac{TP}{TP + FN} \times 100 = \quad (\%)$$

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Case 3: sensitivity/specificity

$$\text{Spec.} = \frac{TN}{TN + FP} \times 100 = \quad (\%)$$

$$\text{Sens.} = \frac{TP}{TP + FN} \times 100 = \quad (\%)$$

3-OHFAs data – good test for diagnosing LCHAD and SCHAD? Tested 197 patients

SCHAD			LCHAD		
	SCHAD	No SCHAD		LCHAD	No LCHAD
Postive	6 (TP)	15 (FP)	Positive	8 (TP)	0 (FP)
Negative	0 (FN)	182 (TN)	Negative	0 (FN)	197 (TN)

Spec for SCHAD = 182/197 X100 = 92.4%

Sens for SCHAD = 6/6 X100 = 100%

Spec for LCHAD = 197/197 X100 = 100%

Sens for LCHAD = 8/8 X100 = 100%

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Case 3: clinical/diagnostic utility

- **Positive predictive value (PPV)** – predictive value of a positive test

$$\mathbf{PPV} = \frac{\mathbf{TP}}{\mathbf{TP + FP}} \ \mathbf{X\ 100 = \qquad \%}$$

For SCHAD: 6/21 X 100 = 28.6%
For LCHAD: 8/8 X 100 = 100%

- **Negative predictive value (NPV) –** predictive value of a negative test

$$\mathbf{NPV} = \frac{\mathbf{TN}}{\mathbf{TN + FN}} \ \mathbf{X\ 100 = \qquad \%}$$

For SCHAD: 199/199 X100 = 100%
For LCHAD: 197/197 X100 = 100%
test good for ruling out both disorders

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Case 4: ROC curves

- Graphical way to present sensitivity and specificity data, also gives you:
  - PPV, NPV
  - +LR, -LR – likelihood a pos test will be seen in a patient with the disease compared to a patient without the disease
    - ↑ +LR – the better the test is for diagnosing disease
    - ↑ -LR – the better the test is at ruling out the disease
- Sensitivity and specificity can be considered reciprocals

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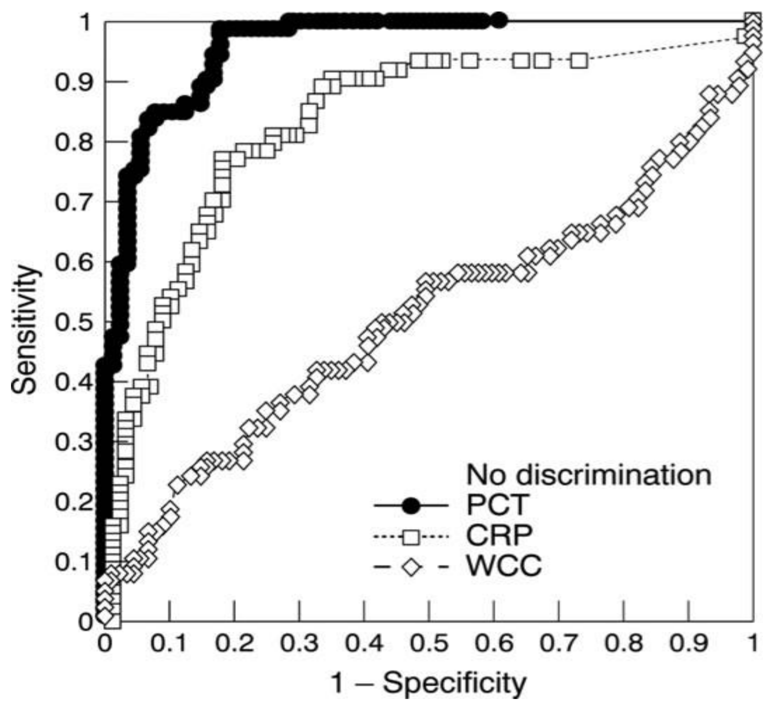
Case 4: ROC curves



True positive rate

False positive rate

AUC = 1.00
perfect test
100% sensitive and specific

AUC = 0.500
test is no better than
flipping a coin

To set up a ROC curve

– For each data point, assign a 1 (disorder present) or a 0, (disorder absent)

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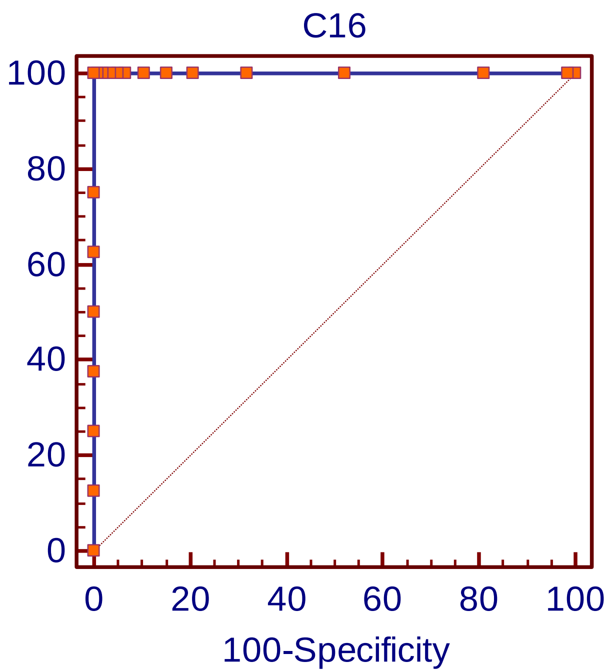
ROC curves - LCHAD



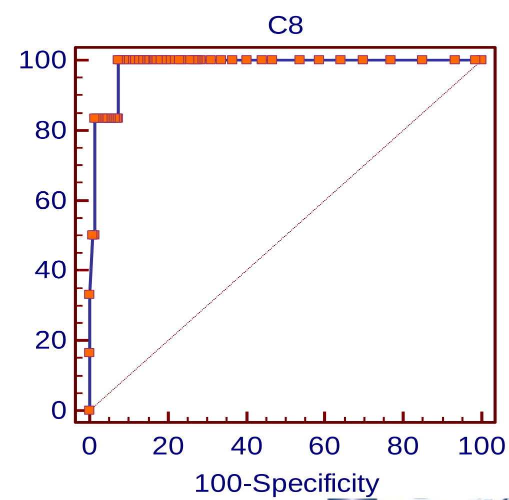
AUC = 1.000

Criterion	Sens	Spec	+PV	-PV	+LR	-LR
≥0.2	100.00	0.00	3.9		1.00	
>0.2	100.00	1.52	4.0	100.0	1.02	0.00
>0.3	100.00	18.78	4.8	100.0	1.23	0.00
>0.4	100.00	47.72	7.2	100.0	1.91	0.00
>0.5	100.00	68.02	11.3	100.0	3.13	0.00
>0.6	100.00	79.19	16.3	100.0	4.80	0.00
>0.7	100.00	84.77	21.1	100.0	6.57	0.00
>0.8	100.00	89.34	27.6	100.0	9.38	0.00
>0.9	100.00	93.40	38.1	100.0	15.15	0.00
>1	100.00	94.92	44.4	100.0	19.70	0.00
>1.1	100.00	96.45	53.3	100.0	28.14	0.00
>1.2	100.00	97.97	66.7	100.0	49.25	0.00
>1.4	100.00	98.98	80.0	100.0	98.50	0.00
>1.5	100.00	100.00	100.0	100.0		0.00
>2.7	75.00	100.00	100.0	99.0		0.25
>3.4	62.50	100.00	100.0	98.5		0.37
>6	50.00	100.00	100.0	98.0		0.50
>6.3	37.50	100.00	100.0	97.5		0.62
>7.2	25.00	100.00	100.0	97.0		0.75
>21.3	12.50	100.00	100.0	96.6		0.88
>25.9	0.00	100.00		96.1		1.00

ROC curve: SCHAD

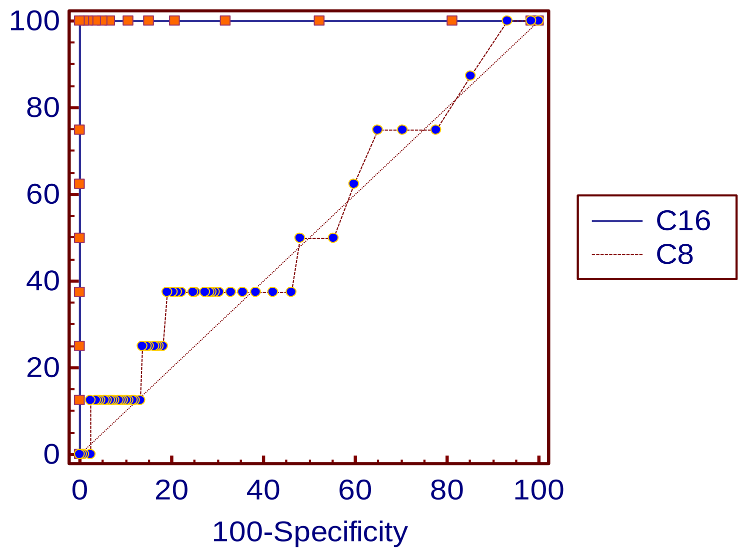
Criterion	Sens	Spec	+PV	-PV	+LR	-LR
≥0.2	100.00	0.00	2.9		1.00	
>0.2	100.00	1.51	3.0	100.0	1.02	0.00
>0.3	100.00	6.53	3.1	100.0	1.07	0.00
>0.4	100.00	15.08	3.4	100.0	1.18	0.00
>0.5	100.00	23.12	3.8	100.0	1.30	0.00
>0.6	100.00	30.15	4.1	100.0	1.43	0.00
>0.7	100.00	35.68	4.5	100.0	1.55	0.00
>0.8	100.00	41.21	4.9	100.0	1.70	0.00
>0.9	100.00	46.23	5.3	100.0	1.86	0.00
>1	100.00	53.27	6.1	100.0	2.14	0.00
>1.1	100.00	55.78	6.4	100.0	2.26	0.00
>1.2	100.00	59.80	7.0	100.0	2.49	0.00
>1.3	100.00	63.32	7.6	100.0	2.73	0.00
>1.4	100.00	66.33	8.2	100.0	2.97	0.00
>1.5	100.00	68.84	8.8	100.0	3.21	0.00
>1.6	100.00	71.36	9.5	100.0	3.49	0.00
>1.7	100.00	72.36	9.8	100.0	3.62	0.00
>1.8	100.00	72.86	10.0	100.0	3.69	0.00
>1.9	100.00	73.37	10.2	100.0	3.75	0.00
>2	100.00	74.37	10.5	100.0	3.90	0.00
>2.1	100.00	76.38	11.3	100.0	4.23	0.00
>2.2	100.00	76.88	11.5	100.0	4.33	0.00
>2.3	100.00	79.40	12.8	100.0	4.85	0.00
>2.4	100.00	80.40	13.3	100.0	5.10	0.00
>2.5	100.00	81.41	14.0	100.0	5.38	0.00

Criterion	Sens	Spec	+PV	-PV	+LR	-LR
>2.6	100.00	82.41	14.6	100.0	5.69	0.00
>2.9	100.00	83.92	15.8	100.0	6.22	0.00
>3	100.00	84.92	16.7	100.0	6.63	0.00
>3.2	100.00	85.43	17.1	100.0	6.86	0.00
>3.3	100.00	85.93	17.6	100.0	7.11	0.00
>3.4	100.00	86.93	18.8	100.0	7.65	0.00
>3.7	100.00	87.44	19.4	100.0	7.96	0.00
>3.8	100.00	88.44	20.7	100.0	8.65	0.00
>3.9	100.00	89.45	22.2	100.0	9.48	0.00
>4.1	100.00	90.45	24.0	100.0	10.47	0.00
>4.2	100.00	90.95	25.0	100.0	11.06	0.00
>4.3	100.00	91.96	27.3	100.0	12.44	0.00
>4.7	100.00	92.46	28.6	100.0	13.27	0.00
>4.8	83.33	92.46	25.0	99.5	11.06	0.18
>5.2	83.33	92.96	26.3	99.5	11.85	0.18
>5.3	83.33	93.47	27.8	99.5	12.76	0.18
>5.5	83.33	94.47	31.2	99.5	15.08	0.18
>5.8	83.33	94.97	33.3	99.5	16.58	0.18
>6.5	83.33	95.48	35.7	99.5	18.43	0.17
>6.6	83.33	95.98	38.5	99.5	20.73	0.17
>6.8	83.33	96.48	41.7	99.5	23.69	0.17
>7	83.33	97.49	50.0	99.5	33.17	0.17
>7.2	83.33	97.99	55.6	99.5	41.46	0.17
>8.2	83.33	98.49	62.5	99.5	55.28	0.17
>8.5	50.00	98.49	50.0	98.5	33.17	0.51
>8.8	50.00	98.99	60.0	98.5	49.75	0.51
>11.9	33.33	100.00	100.0	98.0		0.67
>29.4	16.67	100.00	100.0	97.5		0.83
>54.4	0.00	100.00		97.1		1.00

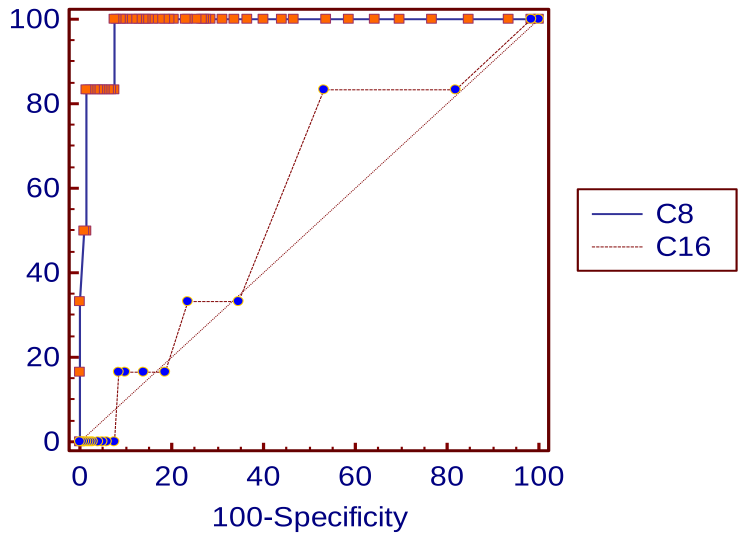


AUC = 0.982

Comparing ROC curves



For diagnosing LCHAD:
C16 AUC = 1.000
C8 AUC = 0.534



For diagnosing SCHAD:
C16 AUC = 0.581
C8 AUC = 0.982

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Case 4: Student t test

If comparing a sample with the population from which it was selected:

$$t = \frac{\bar{x} - \mu}{s/\sqrt{N}}$$

Or, if comparing two samples:

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}}}$$

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Case 4: Student t test

If comparing a sample with the population from which it was selected:

$$t = \frac{\bar{x} - \mu}{s / \sqrt{N}}$$

Average age of attendees at a conference is 32

The ages of the 10 attendees in the front row are 35, 37, 40, 30, 34, 35, 38, 32, 34 and 39. Are older attendees more likely to sit on the front row?

Mean = 35.4
S = 3.13
9 degrees of freedom

t = (35.4 – 32) ÷ (3.13/ √10)

= 3.4 ÷ (3.13/3.16)

= 3.4/0.99 = **3.4243**

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Case 4: Student t test

If comparing a sample with the population from which it was selected:

$$t = \frac{\bar{x} - \mu}{s/\sqrt{N}}$$

t = **3.4243**

9 degrees of freedom
(N – 1)

Older attendees are more likely to sit on the front row.

P = 0.0075

	1-tail: 0.25	0.1	0.05	0.025	0.01	0.005	0.001
d.f.	2-tail: 0.50	0.2	0.1	0.05	0.02	0.01	0.002
1	1.000	3.078	6.314	12.706	31.821	63.657	318.309
2	0.816	1.886	2.920	4.303	6.965	9.925	22.327
3	0.765	1.638	2.353	3.182	4.541	5.841	10.215
4	0.741	1.533	2.132	2.776	3.747	4.604	7.173
5	0.727	1.476	2.015	2.571	3.365	4.032	5.893
6	0.718	1.440	1.943	2.447	3.143	3.707	5.208
7	0.711	1.415	1.895	2.365	2.998	3.499	4.785
8	0.706	1.397	1.860	2.306	2.896	3.355	4.501
9	0.703	1.383	1.833	2.262	2.821	3.250	4.297
10	0.700	1.372	1.812	2.228	2.764	3.169	4.144
11	0.697	1.363	1.796	2.201	2.718	3.106	4.025
12	0.695	1.356	1.782	2.179	2.681	3.055	3.930
13	0.694	1.350	1.771	2.160	2.650	3.012	3.852
14	0.692	1.345	1.761	2.145	2.624	2.977	3.787
15	0.691	1.341	1.753	2.131	2.602	2.947	3.733
16	0.690	1.337	1.746	2.120	2.583	2.921	3.686
17	0.689	1.333	1.740	2.110	2.567	2.898	3.646
18	0.688	1.330	1.734	2.101	2.552	2.878	3.610
19	0.688	1.328	1.729	2.093	2.539	2.861	3.579
20	0.687	1.325	1.725	2.086	2.528	2.845	3.552
21	0.686	1.323	1.721	2.080	2.518	2.831	3.527
22	0.686	1.321	1.717	2.074	2.508	2.819	3.505
23	0.685	1.319	1.714	2.069	2.500	2.807	3.485
24	0.685	1.318	1.711	2.064	2.492	2.797	3.467
25	0.684	1.316	1.708	2.060	2.485	2.787	3.450
26	0.684	1.315	1.706	2.056	2.479	2.779	3.435
27	0.684	1.314	1.703	2.052	2.473	2.771	3.421
28	0.683	1.313	1.701	2.048	2.467	2.763	3.408
29	0.683	1.311	1.699	2.045	2.462	2.756	3.396
30	0.683	1.310	1.697	2.042	2.457	2.750	3.385

Case 4: Student t test

Or, if comparing two samples:

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}}}$$

Measured 8 controls yesterday:
Mean = 8.7
S = 1.42

Measured 10 controls today:
Mean = 7.9
S = 0.86

Is there a significant bias between the two days?

Case 4: Student t test

Or, if comparing two samples:

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}}}$$

$\sqrt{(1.42)^2/8 + (0.79)^2/10}$

$= \sqrt{0.252 + 0.062}$

$= 0.56$

Measured 8 controls yesterday:
Mean = 8.7
S = 1.42

Measured 10 controls today:
Mean = 7.9
S = 0.86

t = (8.7 – 8.0) ÷ 0.56

= 0.7/ 0.56

= **1.25**

Case 4: Student t test

t = **1.25**

16 degrees of freedom

($N_1 + N_2 - 2$)

no significant bias between the 2 days

P = 0.1952

	1-tail: 0.25	0.1	0.05	0.025	0.01	0.005	0.001
d.f.	2-tail: 0.50	0.2	0.1	0.05	0.02	0.01	0.002
1	1.000	3.078	6.314	12.706	31.821	63.657	318.309
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8	0.706	1.397	1.860	2.306	2.896	3.355	4.501
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27	0.684	1.314	1.703	2.052	2.473	2.771	3.421
28	0.683	1.313	1.701	2.048	2.467	2.763	3.408
29	0.683	1.311	1.699	2.045	2.462	2.756	3.396
30	0.683	1.310	1.697	2.042	2.457	2.750	3.385

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Volume of Distribution (V_d)

- The Volume of Distribution (V_d) is the amount of blood, per Kg body weight, necessary to contain all of the body burden of drug at equilibrium concentration.

$$Plasma\ Concentration = \frac{Total\ Body\ Stores}{Volume\ of\ Distribution}$$

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Interpreting V_d

- Drugs with low V_d are contained mostly in the plasma, because . . .
  - They are highly water soluble (plasma water content is higher than tissues), or
  - They are highly protein bound (which prevents them from freely diffusing into tissues
- Drugs with high V_d are mostly in tissues, and plasma levels may not reflect body burden

Example of V_d calculation

A 70 Kg man takes a 5 mg dose of phenobarbital (V_d = 1.0 L/Kg). What is the *maximum* plasma phenobarbital concentration you can expect?

Plasma concentration = total body stores ÷ volume of distribution

$$C = (5\text{mg}/70\text{ Kg}) \div 1.0\text{ L/Kg}$$

$$= 0.07\text{ mg/Kg} \div 1.0\text{ L/Kg}$$

$$= 0.07\text{mg/L} \quad = \quad \mathbf{70\ \mu g/L}$$

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Example of V_d calculation

A 55 Kg woman has a plasma theophylline (V_d = 0.5 L/Kg) concentration of 15 µg/L.   What is her total body burden of theophylline?

Plasma concentration = total body stores ÷ volume of distribution

15 µg/L = (concentration/55 Kg) ÷ 0.5 L/Kg

(15 µg/L)(0.5 Kg/L) = concentration/55 Kg

7.5 µg/Kg = concentration/55 Kg

(7.5 µg/Kg)(55 Kg) = concentration

412.5 µg

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