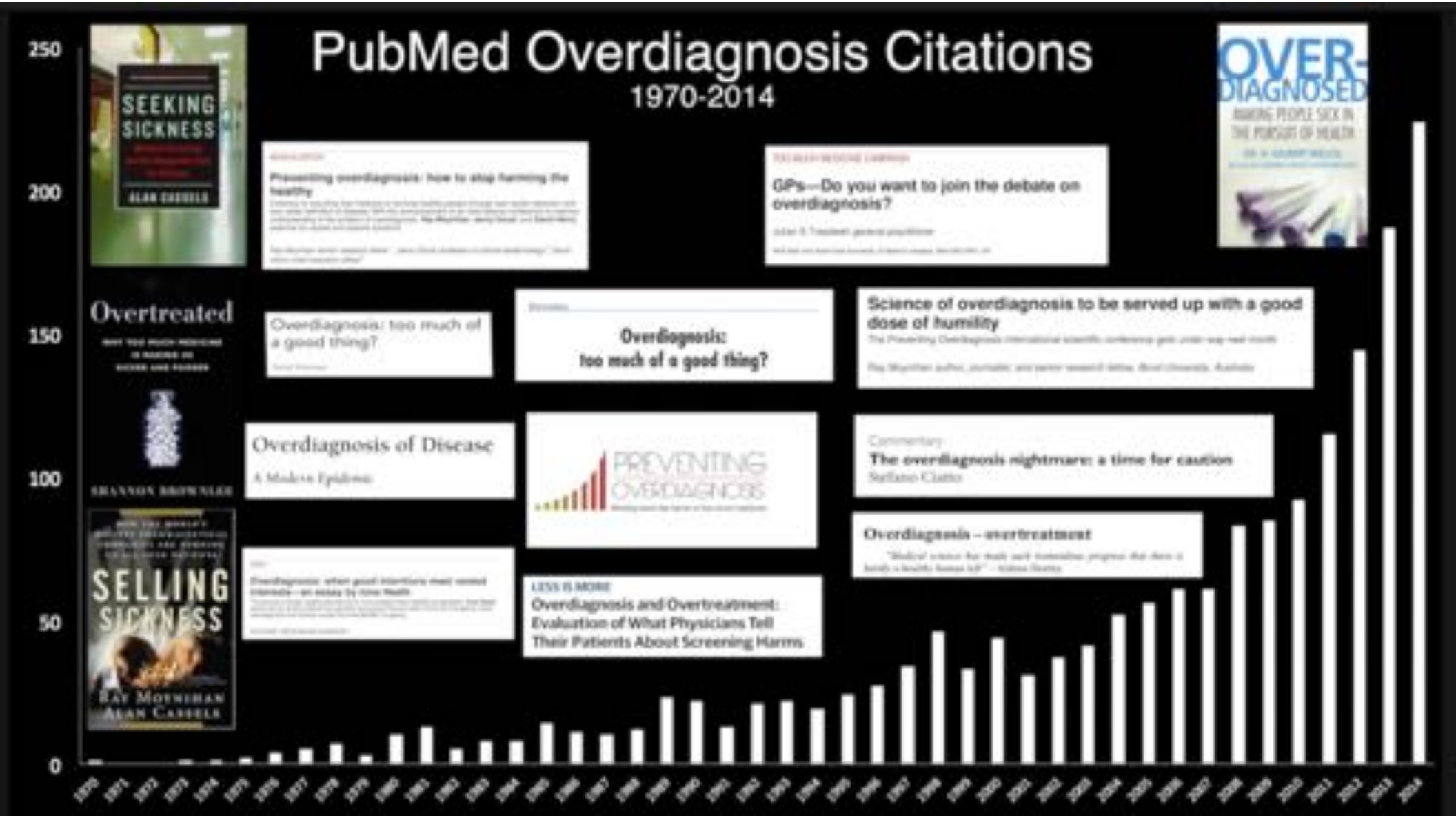
“It is commonly thought that laboratory tests provide two-thirds to three-fourths of the information used for making medical decisions. If so, test results had better tell the truth about what is happening with our patients.”

Clinica Chimica Acta 2004;346:3-11


PubMed Overdiagnosis Citations
1970-2014
250
200
150
100
50
0
SEEKING SICKNESS
ALAN CASSELS
Preventing overdiagnosis: how to stop harming the healthy
GPs—Do you want to join the debate on overdiagnosis?
OVER-DIAGNOSED
Overtreated
Overdiagnosis: too much of a good thing?
Overdiagnosis: too much of a good thing?
Science of overdiagnosis to be served up with a good dose of humility
SHANNON BROWNLEE
Overdiagnosis of Disease
A Modern Epidemic
PREVENTING OVERDIAGNOSIS
Commentary
The overdiagnosis nightmare: a time for caution
Stefano Canto
SELLING SICKNESS
RAY MOYNIHAN
ALAN CASSELS
Overdiagnosis – overtreatment
LESS IS MORE
Overdiagnosis and Overtreatment: Evaluation of What Physicians Tell Their Patients About Screening Harms

The Overdiagnosis Problem

It's multifactorial - everyone involved in health care (clinicians, technicians and patients) plays a role

Or in other words - EVERY HUMAN

Overdiagnosis is not just the "lab's" fault - but it is a MAJOR player

Clinical Practice Guidelines - also MAJOR culprits

The Media!

Wrong guidelines: why and how often they occur

Primiano Iannone,[1] Nicola Montano,[2] Monica Minardi,[3] James Doyle,[3] Paolo Cavagnaro,[4] Antonino Cartabellotta[5]

"Unfortunately, depending on how their reliability is measured, up to 50% of guidelines can be considered untrustworthy. This carries serious consequences for patients' safety, resource use and health economics burden."

EBM 2017;22:1-3

Wrong guidelines: why and how often they occur

Primiano Iannone,[1] Nicola Montano,[2] Monica Minardi,[3] James Doyle,[3] Paolo Cavagnaro,[4] Antonino Cartabellotta[5]

"guideline reliability is largely over-stated, and guidelines still suffer methodological flaws, limited panel composition and conflicts of interests, making their conclusions often untrustworthy. Even when evidence-based methodology is claimed, it is often not fully adopted and the 'evidence-based quality mark' gets misappropriated by vested interests"

EBM 2017;22:1-3

Most targets in guidelines are arbitrary and rarely if ever based on a discussion of the balance of benefits and harms

Golden Pill Award

PRESCRIRE AWARDS

	Major therapeutic advance	Clear advantage	Modest improvement
2011	0	0	0
2012	0	0	2 abiraterone (prostate CA) boceprevir (Hep C)
2013	0	0	1 meningococcal conjugate vaccine (infant immunization)
2014	1 cholic acid (hereditary bile acid deficiency)	3 imatinib (ALL) artesunate (malaria) sofosbuvir (HepC) conjugate vaccine (infant immunization)	1 sodium phenylbutyrate coated granules (urea cycle disorders)
2015	0	1 propranolol (severe infantile hemangioma)	2 permethrin (scabies) ketoconazole HRA (endogenous Cushing's syndrome)
2016	0	0	2 nivolumab (inoperable melanoma) trametinib (inoperable melanoma)

Many courts (UK, US, CA)

"The reasonable-patient standard … requires physicians and other health care practitioners to disclose all relevant information about the risks, benefits, and alternatives of a proposed treatment that an **OBJECTIVE PATIENT** would find material in making an intelligent decision as to whether to agree to the proposed procedure"

JAMA 2016;315:2063-4

New Rule Grants Patients Direct Access to Lab Results

By Melinda Beck

Feb. 3, 2014 1:05 p.m. ET

Clinical laboratories must give patients access to their own lab-test results upon request, without going through the physician who ordered them, according to a new federal rule announced Monday by the Department of Health and Human Services.

PROBLEM #1

It's typically the same report that goes to health care providers

PROBLEM #2

Many health care providers don't appreciate the key nuances of "lab" tests

Actual LAB errors

0.3%

~60% pre-analytical
~15% analytical
~ 25% post analytical

Table 1. Laboratory errors in stat testing.

Defects: detection steps	Defects found: No.	Defects found: Frequency, %
Preanalytical		
Specimen collected from infusion route	3	1.9
Sample contaminated	1	0.6
Tube filling error	21	13.1
Empty tube	11	6.9
Inappropriate container	13	8.1
Nonrefrigerated sample	3	1.9
Missing tube	5	3.1
Digoxin test timing error	1	0.6
Patient identification error	14	8.8
Request procedure error	12	7.5
Data communication conflict	6	3.8
Physician's request order missed	3	1.9
Order misinterpreted	2	1.3
Check-in not performed (in the Laboratory Information Systems)	4	2.5
Subtotal	99	61.9
Analytical		
Instrument-caused random error	3	1.9
Analytical inaccuracy not recognized	21	13.1
Subtotal	24	15
Postanalytical		
Results communication breakdown	32	20
Lack of communication within laboratory	3	1.9
TAT excessive	2	1.3
Subtotal	37	23.1

Clinical Chemistry 2007;53:1338-42

Dispensing errors ~1-2%

Measurement Landscape

Assuming no pre-analytic issues - timing/labelling etc

Population-based reference intervals

Analytical Variation

- CVA - analytical variation

Biological Variation

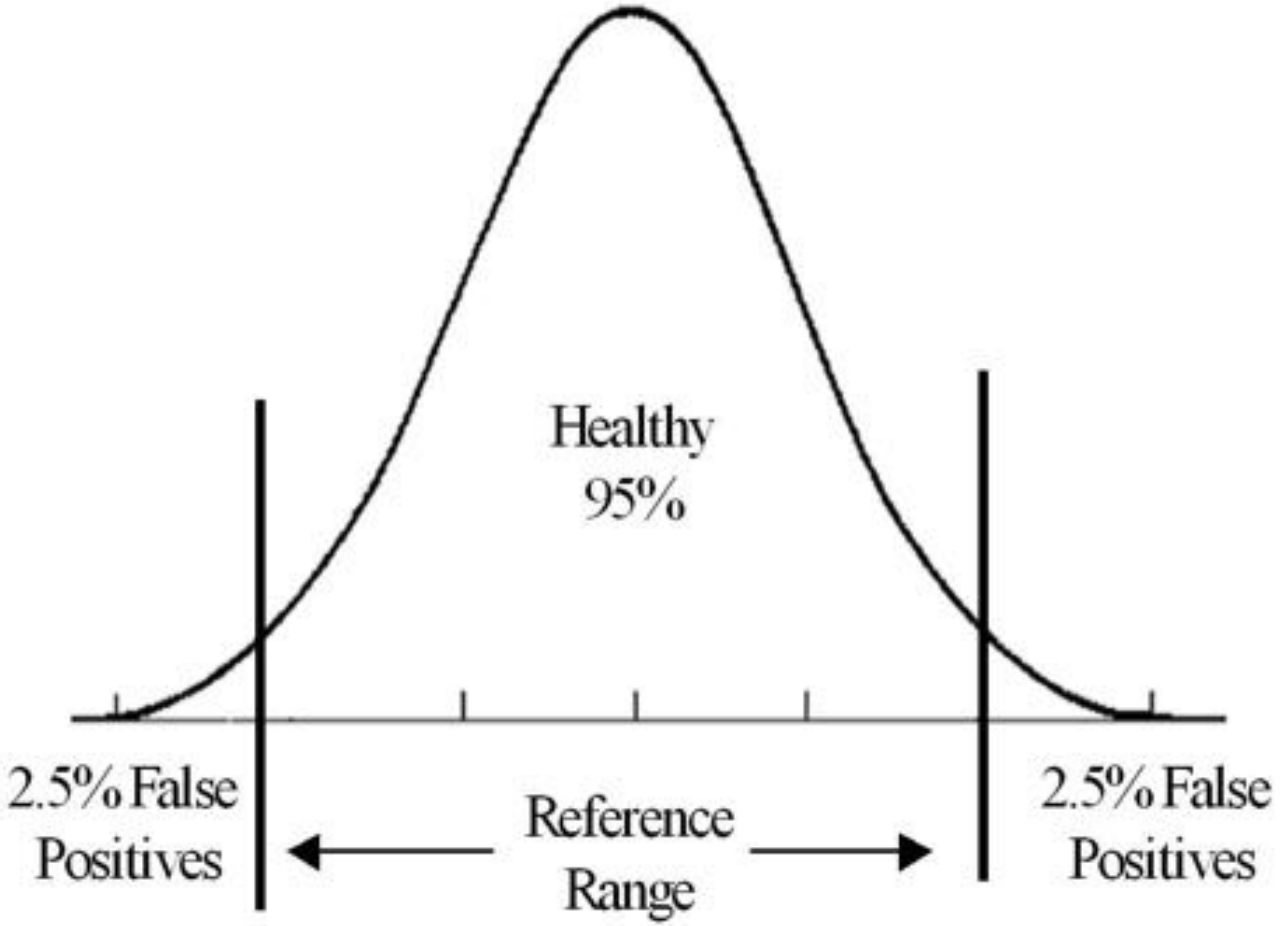
- CVI - within subject
- CVG - between subject

Reference change values (RCV)

Population-based reference intervals

Population-based reference intervals

The interval/range where 95% of healthy people fall

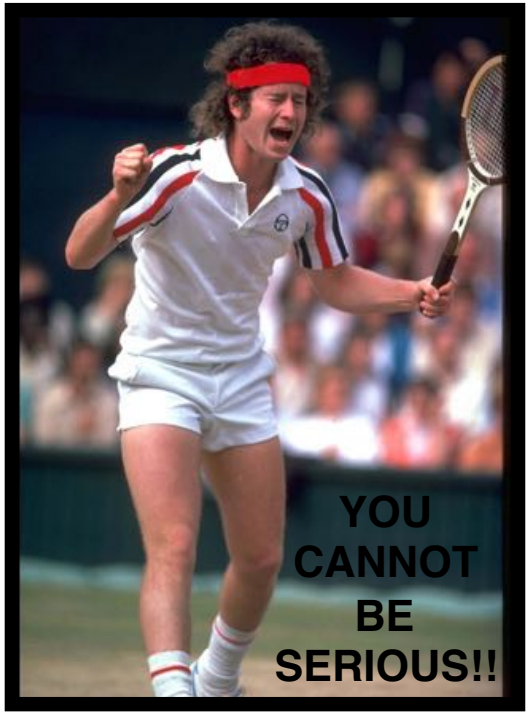


Chances of at least one abnormal test

5% of test results from patients WITHOUT disease will be outside the reference range

Number of Tests Ordered	Probability of at Least One Abnormal Test
1	5%
2	10%
5	23%
10	40%
15	54%
20	64%

Lab results report exact numbers
BUT
Every test result is really only a range that hopefully includes the true result
+/- 1-2% up to +/-20-30% or more



“population-based reference intervals are of very limited use in evaluating serial results obtained on an individual”

Clin Chem Lab Med 2012;50(5):807–812

Cumulative Report — Swap Axis — Sort Dates

	WBC	RBC	Hemoglobin	Hematocrit	MCV	MCH
2017-04-04						
2017-04-04						
2017-04-04	8.1	3.32	121	0.36	107	36.4
2017-02-27	8.6	3.05	112	0.34	113	36.7
2017-01-06	8.6	3.06	115	0.34	111	37.6
2016-12-10	7.1	3.29	119	0.37	111	36.2
2016-10-20						
2016-10-20	7.3	3.30	121	0.36	110	36.7
2016-09-10	7.5	3.38	124	0.37	109	36.7
2016-07-26	7.3	3.37	118	0.36	107	35.0

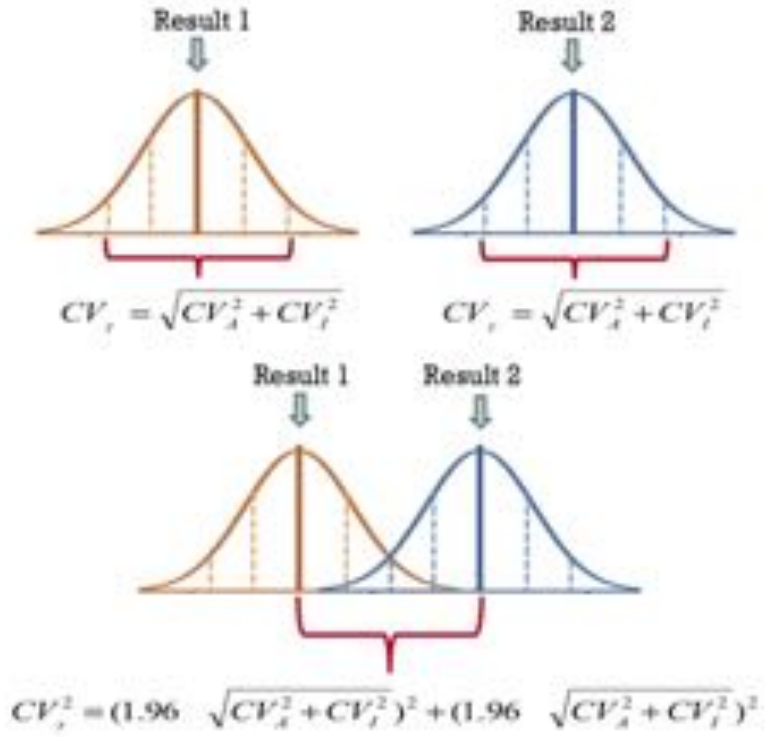
Reference Change Values (RCV)

a tool for assessment of the significance of differences in serial results from an individual

Reference Change Values

Used with SERIAL results to help deal with the analytic imprecision and biologic variation

Coefficients of Variation (total) = analytic PLUS biologic variation



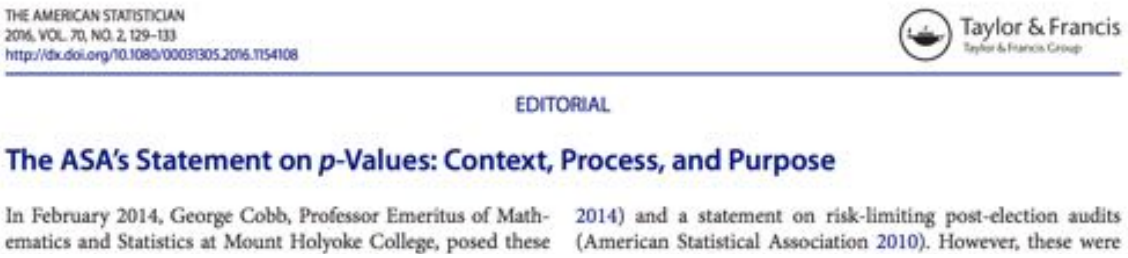
MINIMUM DIFFERENCE between two consecutive results which needs to be EXCEEDED in order for one to state a STATISTICALLY SIGNIFICANT change has taken place

How good, analytically speaking, does a “test” need to be

“The analytical CV (CVA) should be less than one-half the average within-subject biological variation (CVI)”

When it is, the CVA has almost no impact on the RCV - the RCV is pretty much determined by the CVI

Reference change values provide a “p-value” for the differences between two measurements



THE AMERICAN STATISTICIAN
2016, VOL. 70, NO. 2, 129–133
http://dx.doi.org/10.1080/00031305.2016.1154108

Taylor & Francis
Taylor & Francis Group

EDITORIAL

The ASA's Statement on *p*-Values: Context, Process, and Purpose

In February 2014, George Cobb, Professor Emeritus of Mathematics and Statistics at Mount Holyoke College, posed these

2014) and a statement on risk-limiting post-election audits (American Statistical Association 2010). However, these were

“It’s science’s dirtiest secret: The ‘scientific method’ of testing hypotheses by statistical analysis stands on a flimsy foundation.”

“Numerous deep flaws in null hypothesis significance testing.”

“Statistical techniques for testing hypotheses …have more flaws than Facebook’s privacy policies.”

Experts issue warning on problems with P values

Misunderstandings about common statistical test damage science and society

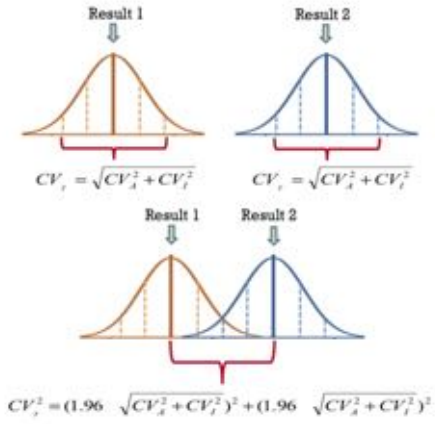
BY TOM SIEGFRIED 10:30AM, MARCH 11, 2016

Reference Change Values

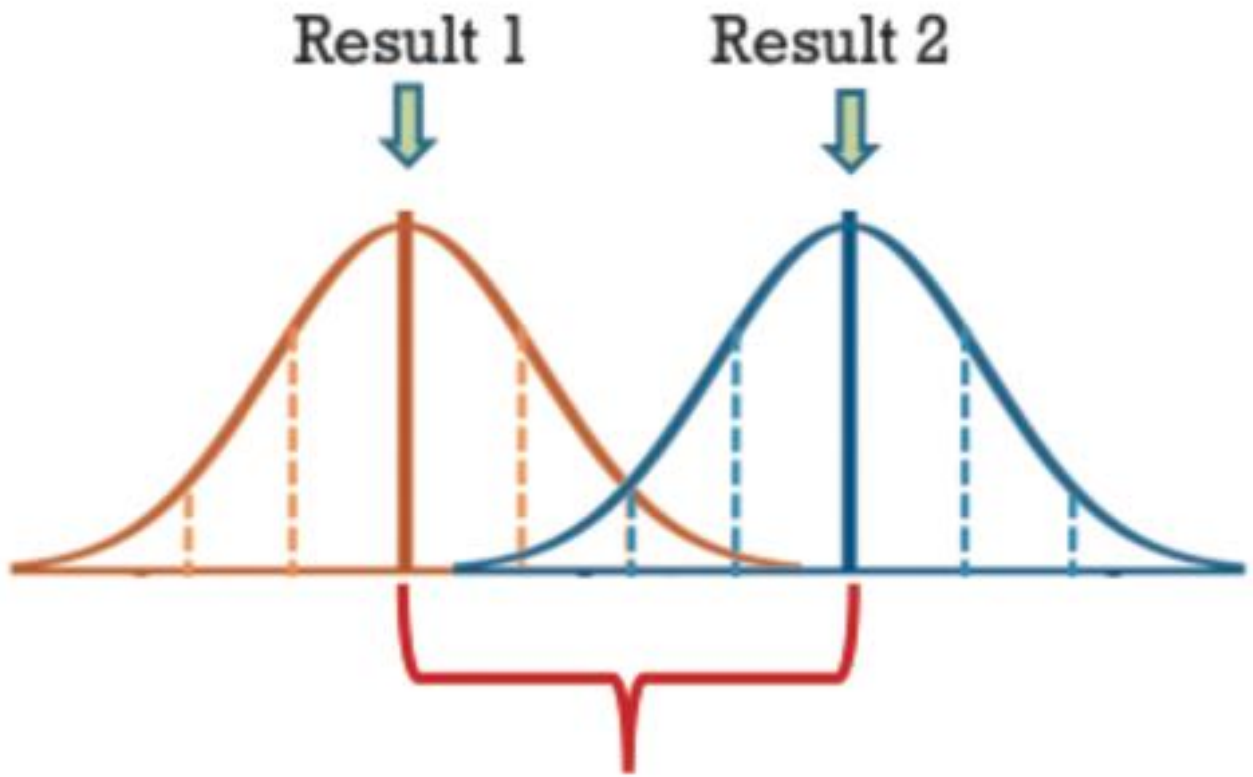
findings of a “significant difference" JUST means we are ruling out that the difference seen is due to chance

NOT

THAT THE MAGNITUDE OF THE DIFFERENCE SEEN IS THE ACTUAL MAGNITUDE OF THE DIFFERENCE



We believe these two results are different



can’t necessarily quantify this difference with any precision

What about multiple measurements?

Table 1. RCV using multiple estimates of the initial and new set points, expressed as a fraction of traditional RCV from two singleton measurements.

		Number of results estimating initial set point				
		1	2	3	4	5
Number of results estimating new set point	1	1.00	0.87	0.82	0.79	0.77
	2	0.87	0.71	0.65	0.61	0.59
	3	0.82	0.65	0.58	0.54	0.52
	4	0.79	0.61	0.54	0.50	0.47
	5	0.77	0.59	0.52	0.47	0.45

with 4 measurements before and 4 afterwards
(vs 1 before and 1 after)
you can lower the RCV by 50%

Annals of Clinical Biochemistry 2016;53:413-4

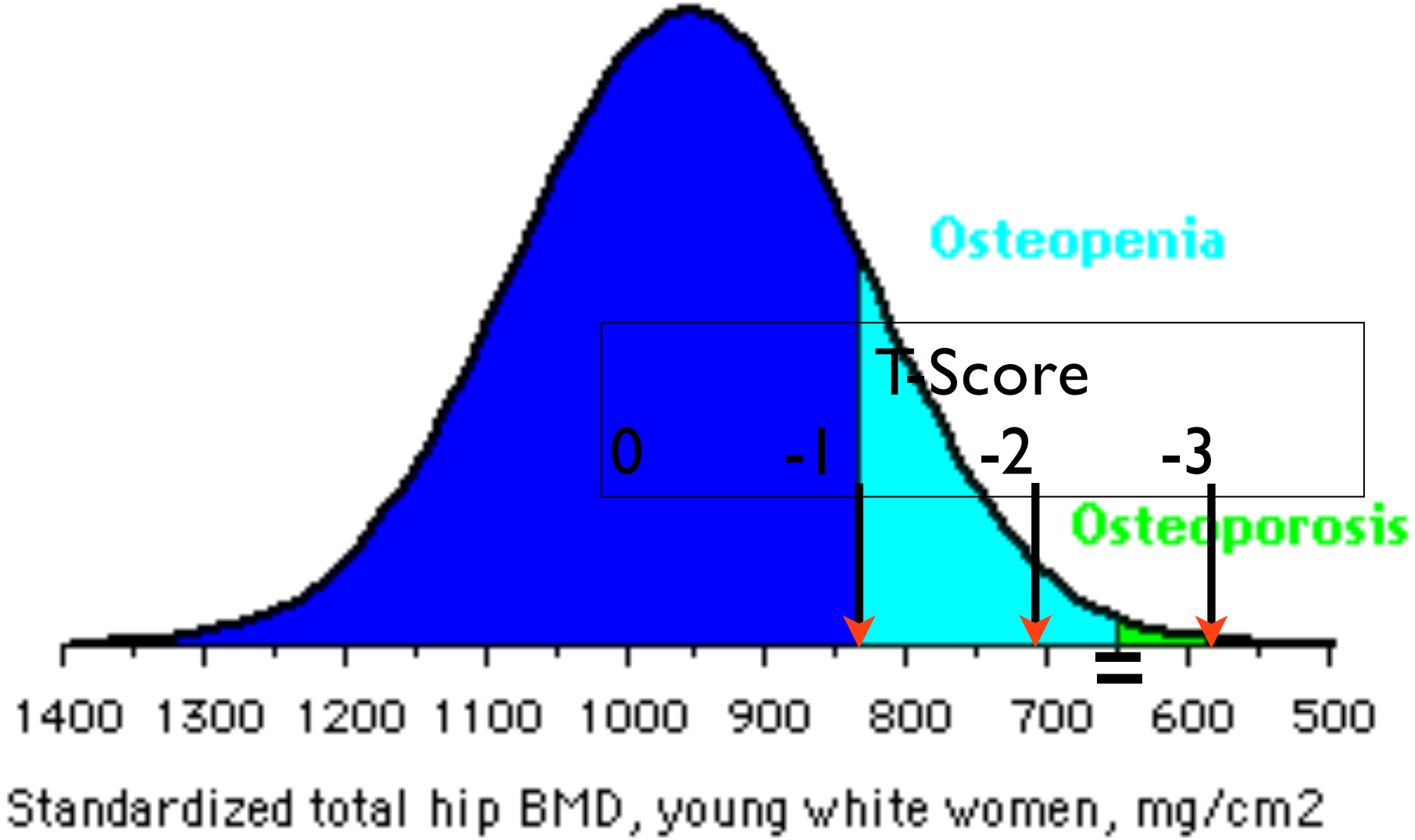
AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS **2010**

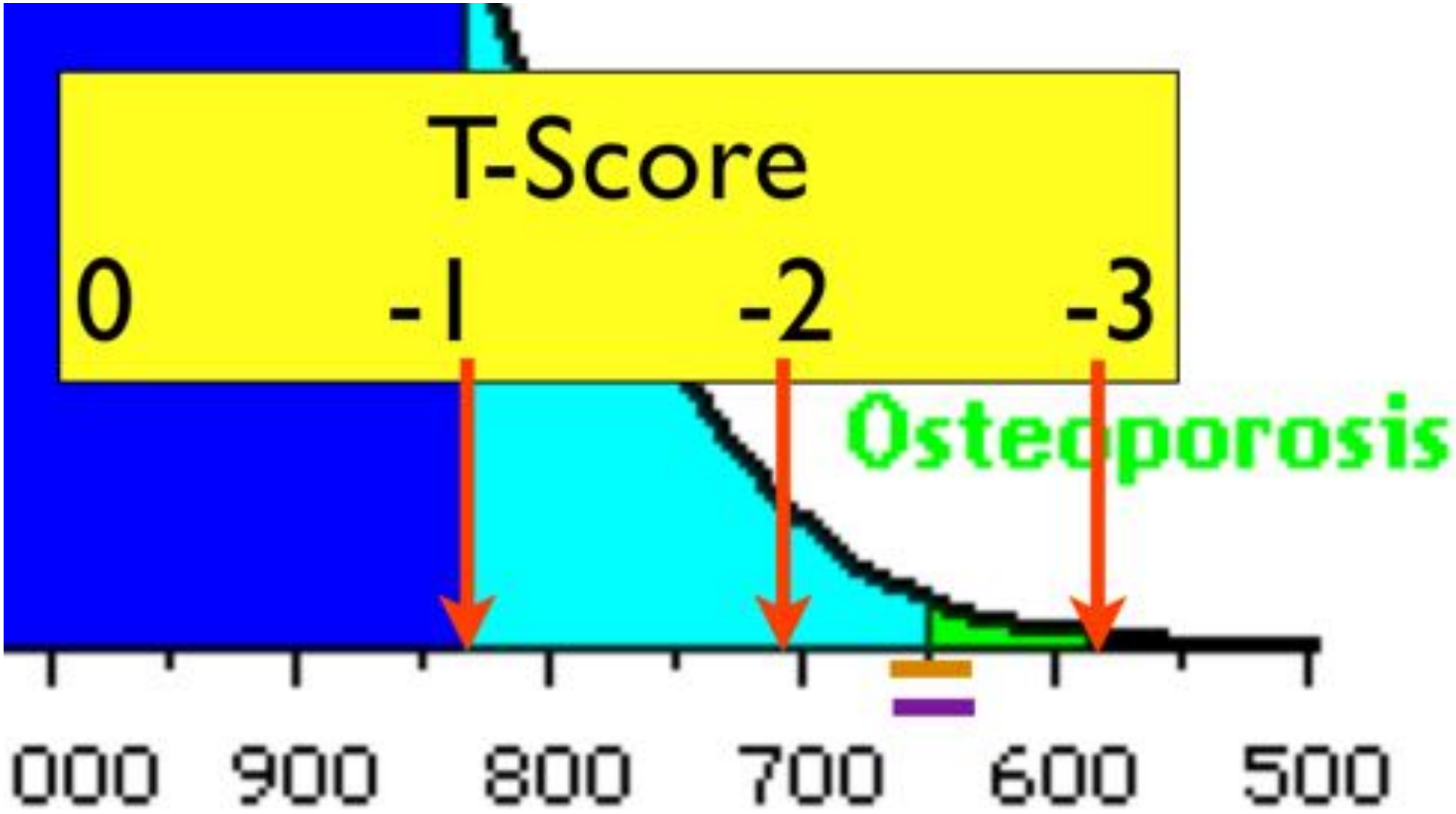
"Obtain a baseline DXA, and repeat DXA every 1 to 2 years until findings are stable. Continue with follow-up DXA every 2 years or at a less frequent interval"

1) Average bone loss per year ~ 0.6%

2) Difference in BMD between drug and placebo - 3 years ~5%

3) BMD measurement precision +/- 2-3%




T-Score
0
-1
-2
-3
Osteoporosis
000
900
800
700
600
500

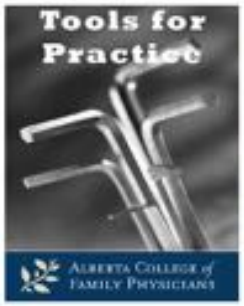
Other Smarter People

Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data

Katy J L Bell, Andrew Hayen, Petra Macaskill, Les Irwig, Jonathan C Craig, Kristine Ensrud and Douglas C Bauer

BMJ 2009;338;b2266;

"Monitoring BMD in the first 3 years after starting treatment with a bisphosphonate is unnecessary and may be misleading"



Bone Mineral Density – Too much of a good thing?

Clinical Question: Once we have initiated bisphosphonate therapy, how frequently should we check bone mineral density (BMD)?

#32 Christina Korownyk & Michael R. Kolber

"Repeating BMD in the first three years after starting treatment with a bisphosphonate is unnecessary and potentially confusing. The vast majority of patients taking a bisphosphonate will get an adequate increase in BMD after three years and have a reduced fracture risk regardless of BMD changes"

ACP American College of Physicians
Leading Internal Medicine, Improving Lives

2017 CLINICAL GUIDELINE

Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians

2017

"The data do not support monitoring BMD during the initial 5 years of treatment in patients receiving pharmacologic agents to treat osteoporosis."

Other Smarter People

Average bone loss per year ~ 0.6%

Evaluating the Value of Repeat Bone Mineral Density Measurement and Prediction of Fractures in Older Women

The Study of Osteoporotic Fractures

Teresa A. Hillier, MD, MS; Katie L. Stone, PhD; Doug C. Bauer, MD; Joanne H. Rizzo, MS; Kathryn L. Pedula, MS; Jane A. Cauley, DrPH; Kristine E. Ensrud, MD, MPH; Marc C. Hochberg, MD; Steve R. Cummings, MD

Arch Intern Med. 2007;167(2):155-160.

"repeat BMD [8 years] measurement provides little additional benefit as a screening tool"

Arch Intern Med 2007;167:155-60

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

"In individuals with a modified FRS of 5%-9%, yearly monitoring could be used to evaluate change in risk"

AACE 2017 Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

"Lipid status should be re-assessed 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved."

"While on stable lipid therapy, individuals should be tested at 6-to 12-month intervals"

ARTICLE | Annals of Internal Medicine

Monitoring Cholesterol Levels: Measurement Error or True Change?

Paul P. Glasziou, MBBS, PhD; Les Irwig, MBBS, PhD; Stephane Heritier, PhD; R. John Simes, MBBS, MD; and Andrew Tonkin, MBBS, MD, for the LIPID Study Investigators

Background: Cholesterol level monitoring is a common clinical activity, but the optimal monitoring interval is unknown and practice varies.

Objective: To estimate, in patients receiving cholesterol-lowering medication, the variation in initial response to treatment, the long-term drift from initial response, and the detectability of long-term changes in on-treatment cholesterol level ("signal") given short-term, within-person variation ("noise").

Design: Analysis of cholesterol measurement data in the LIPID

of variation, 7%) to 0.60 mmol/L (23 mg/dL) (coefficient of variation, 11%), but it took almost 4 years for the long-term variation to exceed the short-term variation. This slow increase in variation and the modest increase in mean cholesterol level, about 2% per year, suggest that most of the variation in the study is due to short-term biological and analytic variability. Our calculations suggest that, for patients with levels that are 0.5 mmol/L or more (≥19 mg/dL) under target, monitoring is likely to detect many more false-positive results than true-positive results for at least the first 3 years after treatment has commenced.

Ann Intern Med 2008;148:656-61

Within-person coefficient of variation is ~7%

Single measurement - 95% CI

Total chol ~ - 0.80 to 0.80 mmol/L (~30 mg/dL)

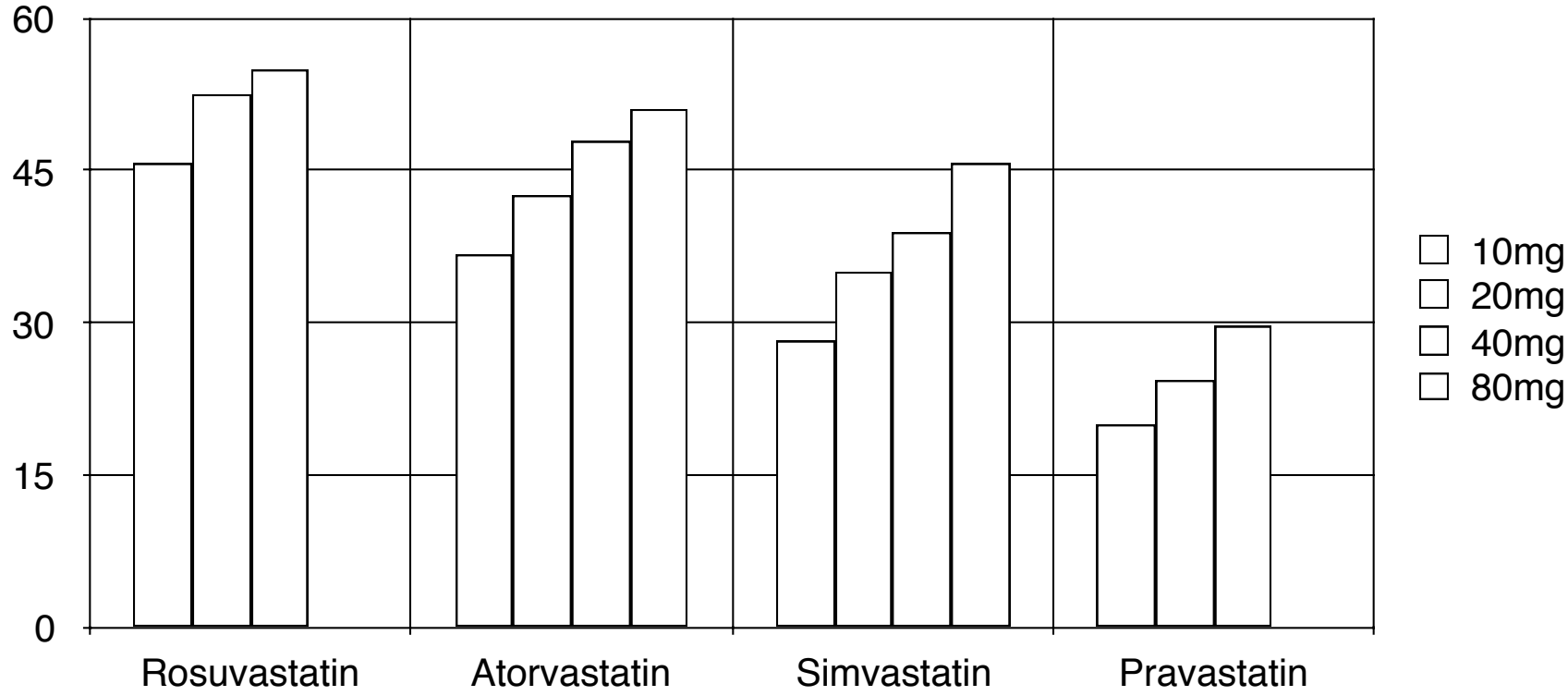
LDL chol ~ - 0.5 to 0.5 mmol/L (~20 mg/dL)

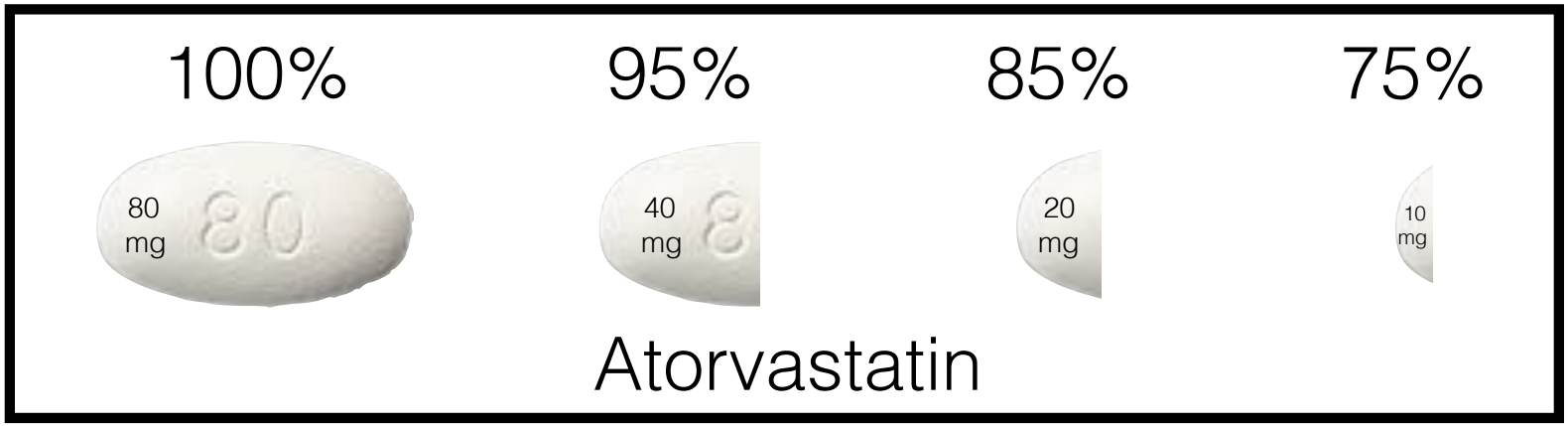
Average increase in cholesterol is 0.5-1%/year

"After initial change only measure every 3-5 years"

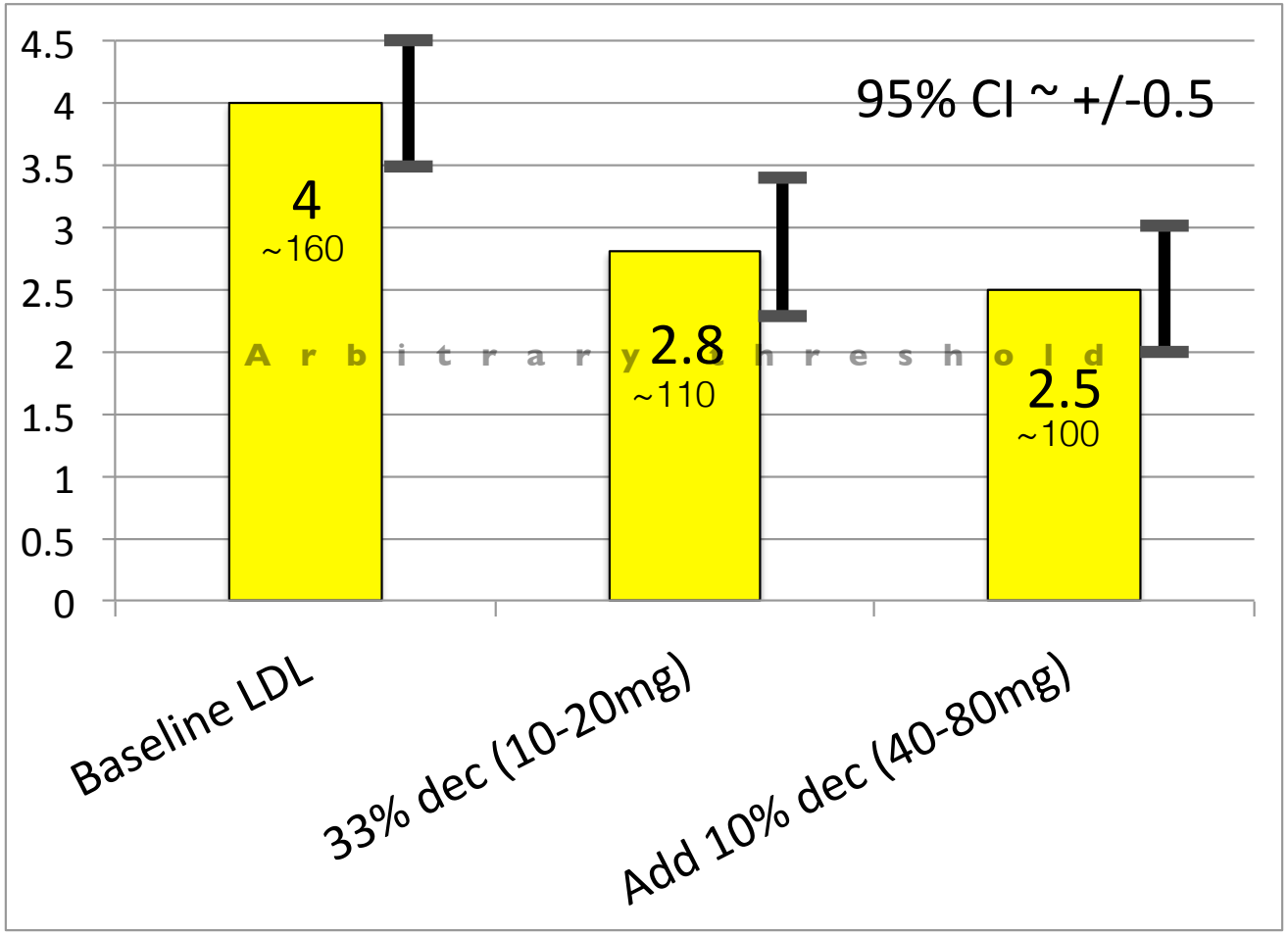
DOSE increases do not lead to proportional EFFECT increases

% reduction in LDL cholesterol





LDL cholesterol - 2 mmol/L ~80mg/dL



RESEARCH

When to remeasure cardiovascular risk in untreated people at low and intermediate risk: observational study

BMJ 2013; 346 doi: http://dx.doi.org/10.1136/bmj.f1895 (Published 3 April 2013)
Cite this as: *BMJ* 2013;346:f1895

"Repeat risk estimation before 8-10 years is not warranted for most people initially not requiring treatment"

Systolic blood pressure

TYPICAL CHANGES SEEN

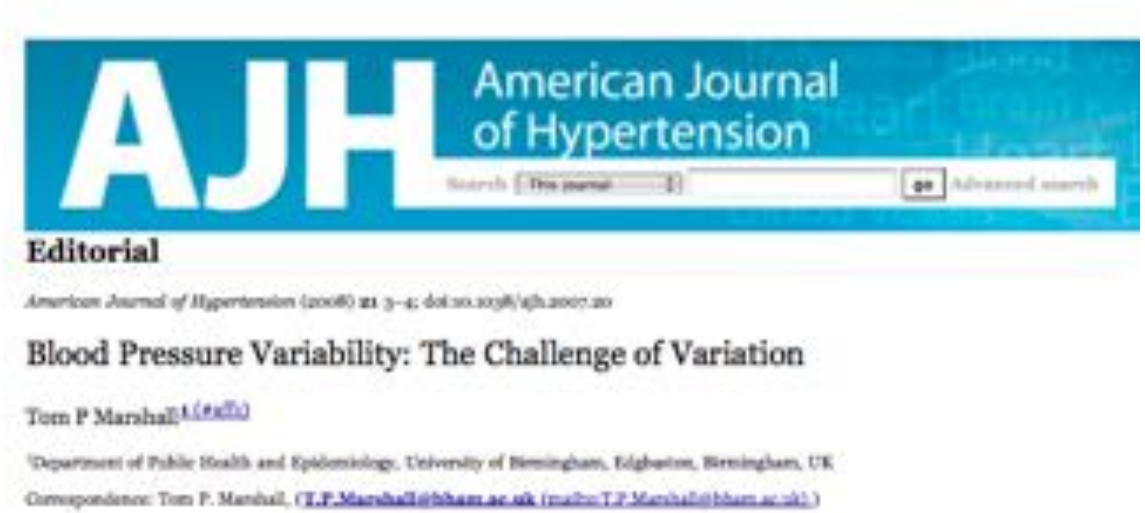
Start medication - avg 9 mmHg ⬇

Increase dose - avg 2-5 mmHg ⬇

Seasonal differences - avg 8 mmHg ⬇ when warm

Age related (per year) - avg 0.5-0.8 mmHg ⬆

Sample size calculation - 40 office measurements before and after treatment to be REASONABLY confident that a 5 mmHg change has occurred



Need changes of at least 10/5 mmHg before you can say there has been a change

Am J Hyper 2008;21:3–4

"clinicians cannot identify individuals who have good or poor responses to drugs"

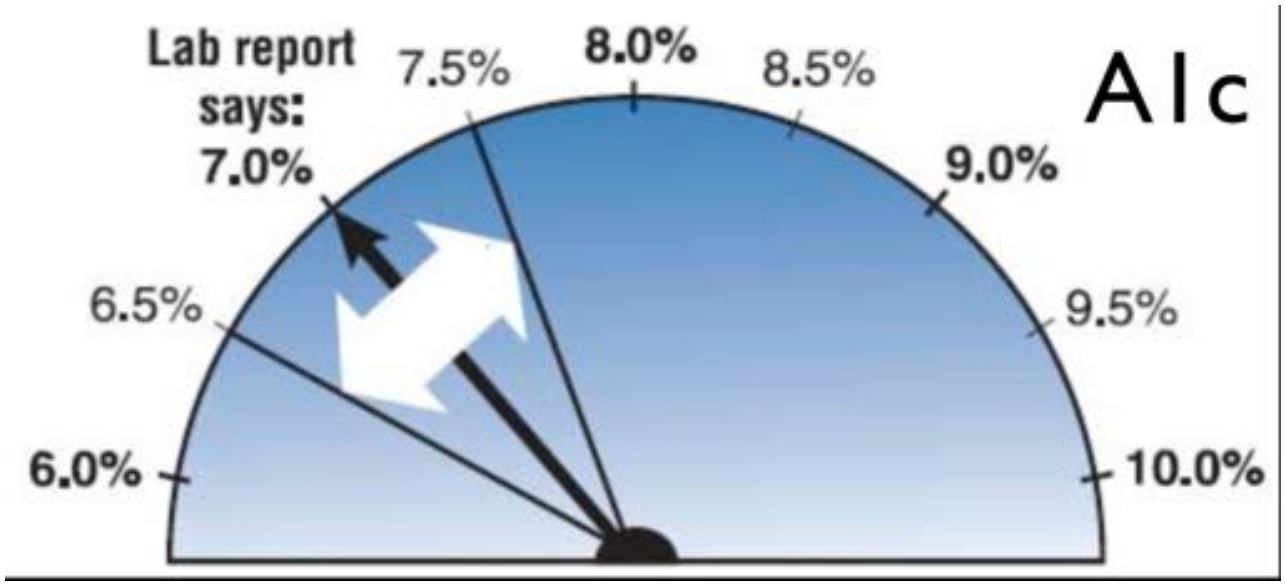
"coefficients of variation for systolic office, ambulatory, and self-monitored blood pressure, compared at baseline and 6 weeks, were 8.6%, 5.5%, and 4.2% respectively"

Br J Gen Pract 2010; 60: 675–80

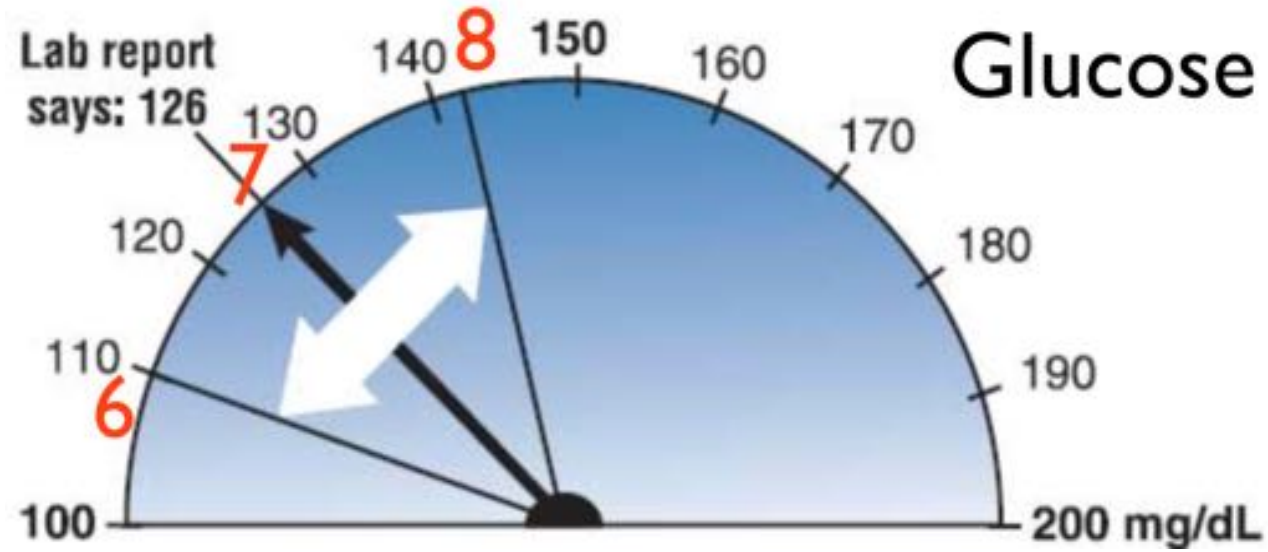
"a single careful blood pressure measurement taken a few months after the start of treatment is not useful for monitoring"

BMJ 2009;338:b1492

Glucose measurements



Typical A1c change seen with a medication = 0.7%⬇

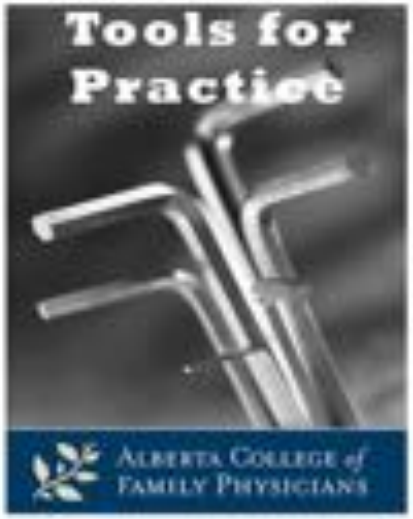


Seasonal variation
0.2-0.5%
Higher in winter
Am J Epi 2004;161:565-74

The A1C Test and Diabetes
National Diabetes Information Clearinghouse

Adrienne J Lindblad BSP ACPR PharmD, Scott Garrison MD PhD, James McCormack BScPharm PharmD

February 3, 2014



Vitamin D Levels: Vitamin Do or Vitamin Don't

Clinical Question: In adults, what is the evidence to test serum vitamin D levels?

Bottom Line: Routine testing of vitamin D levels is unnecessary. Laboratories often report serum levels between 50 and 75–80 nmol/L as insufficient but this is not supported by consistent or reliable evidence. Additionally, large variability in the test limits interpretation of repeat measurements.

Variability in Measurement

Between lab/Assay variability
"The differences between the mean values for serum 25(OH)D between the laboratories with the highest and lowest values was 38%"
Ost Int 1999;9:394-7

"the mean relative uncertainties...were 19.4%, 16.0%, and 11.3%"
Ost Int 2009 - 9 September 2009 -Online

Within patient variability - 15-20%
"The results of our analyses do not support the view that vitamin D supplements should be given on the basis of measurements of individual 25-OH-vitamin D levels. Conversely, our results indicate that subjects classified as having a sufficient vitamin D status may be diagnosed with vitamin D insufficiency in a subsequent measurement"
Ost Int 1998 8:222–30

Variability VS Change from Treatment

800 IU raises vitamin D levels by ~ 20 nmol/L

Scand J Clin Lab Invest 2006;66:227–38

This increase is only slightly more than the within-in patient variability (15-20%) in the measurement but we also have analytic variability

Black and White

LDL Cholesterol (statin)	Glucose/A1c (any meds)	Blood pressure (any meds)	Bone density (bisphosphonates)
These risk factors can all be used to estimate ballpark risks			
No point in measuring if increasing statin doses	No point in measuring?	No point in measuring? unless many measurements before and after No point in measuring if increasing doses	No point in measuring

All the above does not even take into account seasonal changes, timing of sample, different labs, sampling errors, etc

Ballpark RCVs

(means you have to see a change of this much to, by definition, to rule out chance)

<5%
Chloride
Sodium
Osmolality

5-10%
Albumin
Bone density
Calcium
Haemoglobin
HbA1c
INR
Total protein
Systolic BP

10-20%
Creatinine
Globulins
Glucose
Magnesium
pC02
Potassium
Total cholesterol

20-40%
AST
Alkaline phosphatase
BUN
HDL
LDH
LDL
Phosphorous
Platelets
Rheumatoid factor
Testosterone
Uric acid
WBC

40%-60%
GGT
Neutrophils
PSA
Vitamin D

60% +
ALT
Bilirubin
Folate
Iron
Triglycerides
TSH
Vitamin B12