

LESS IS MORE

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Professor

Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC, Canada

MORE OR LESS

REPORTING 'lab' results - the cause of, AND
the solution to, the overdiagnosis problem

therapeuticseducation.org
medicationmythbusters.com

TO GET A HANDOUT GO HERE
<http://therapeuticseducation.org/handouts>



- ✓ Entire salary comes through the UBC Faculty of Pharmaceutical Sciences - also some legal/educational work

- ✓ I have received no honorarium or research money from the drug industry in the last 25 or so years



- ✓ iOS apps (iPad/iPhone) KidneyCalc and MyStudies - mystudies.org

- ✓ Premium podcast subscription Best Science (BS) Medicine podcast - therapeuticseducation.org



A Critical Reevaluation of the “Therapeutic Range” of Aminoglycosides

James P. McCormack and Peter J. Jewesson

From the Faculty of Pharmaceutical Sciences, University of British Columbia; the Department of Pharmacy, St. Paul's Hospital; and the Department of Pharmacy and Division of Infectious Diseases, Department of Medicine, Vancouver General Hospital, Vancouver, British Columbia, Canada

“After a critical review of the literature, it was concluded that the evidence was insufficient to support the presently accepted normal therapeutic range”

Clin Inf Dis 1992;14:320-39

An Emotional-Based Medicine Approach to Monitoring Once-Daily Aminoglycosides

James P. McCormack, Pharm.D.

“no clinical trials show or suggest that monitoring of serum aminoglycoside concentrations for ODA is of benefit”

Pharmacotherapy 2000;20:1524-7

Estimating Renal Function for Drug Dosing: Rewriting the Gospel?

CG vs MDRD

Deonne Dersch and James McCormack

“Proactively determining rational starting doses and monitoring a patient’s response to the dose chosen should be the new gospel for pharmacists who adjust drug dosages on the basis of renal function. If they do so, the debate about which formula to use could seem somewhat trivial.”

CJHP 2008;61:138-43

Essay

Measuring hsCRP—An Important Part of a Comprehensive Risk Profile or a Clinically Redundant Practice?

James P. McCormack^{1*}, G. Michael Allan²

1 Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada, **2** Faculty of Medicine, University of Alberta, Edmonton, Alberta, Canada

“The substantial intra-subject variation in hsCRP measurements makes it virtually impossible to assess the impact a therapy has on hsCRP in an individual patient.”

PLoS Med 2010;7:1-5

MY BELIEF



All Health Care Providers should
have their practice underpinned
by the best available evidence

EVIDENCE-BASED PRACTICE

WHAT IT ISN'T

IT'S NOT ABOUT GUIDELINES

140/90
 $< 6.5\%$
 < 2.0

GUIDELINES RARELY
 CONSIDER
**PATIENT
 PREFERENCES**

IT'S NOT ABOUT RCTs

ONLY ARE LIMITED
 BUT THEY ONLY
HELP
 INFORM DECISIONS

IT'S NOT CHECKBOX MEDICINE

PEOPLE
 DON'T
 FIT
 INTO BOXES



IT'S NOT NECESSARILY ABOUT INFLUENCING OUTCOMES



IT'S NOT SOMETHING "NEW"



DOING THE
 RIGHT THING
 IS NOT A
 NEW IDEA

IT'S NOT ABOUT IGNORING BASIC SCIENCE

WE NEED TO
 UNDERSTAND
 HOW IT
 WORKS

IT'S NOT ABOUT ZERO COMPETING INTERESTS

RESEARCH
 COSTS MONEY
 SOMEBODY HAS TO
 PAY FOR IT

WHAT IT IS

IT'S A WAY OF THINKING

BEST AVAILABLE EVIDENCE
 USED IN A HIERARCHICAL WAY TO
 ANSWER CLINICAL QUESTIONS

Patient
 Intervention
 Comparator
 Outcome



USING CLINICAL EXPERTISE

Diagnostician
 Knowledge Broker
 Communicator
 Being Kind & Careful



INFORMING PATIENTS



ELICITING



INTEGRATING PREFERENCES

Evidence-based
 practice IS

**SIMPLY
 DOING
 THE
 RIGHT
 THING**



IT'S NOT ABOUT GUIDELINES

140/90
 $< 6.5\%$
 < 2.0

GUIDELINES RARELY
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IT'S NOT CHECKBOX MEDICINE

PEOPLE
 DON'T
 FIT
 INTO BOXES



IT'S NOT SOMETHING "NEW"



DOING THE
 RIGHT THING
 IS NOT A
 NEW IDEA

IT'S NOT ABOUT SAVING MONEY



RATIONING
 IS NOT THE
 MOTIVE

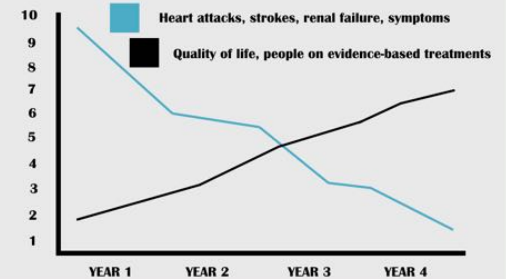
IT'S NOT ABOUT RCTs



RCTs ARE USEFUL
 BUT THEY ONLY
HELP
 INFORM DECISIONS

$p < 0.05 \neq \text{GOOD}$ $p > 0.05 \neq \text{BAD}$

IT'S NOT NECESSARILY ABOUT INFLUENCING OUTCOMES



IT'S NOT ABOUT IGNORING BASIC SCIENCE



WE NEED TO
 UNDERSTAND
**HOW IT
 WORKS**

IT'S NOT ABOUT ZERO COMPETING INTERESTS

RESEARCH
 COSTS MONEY
 SOMEBODY HAS TO
 PAY FOR IT



WE NEED TO
 UNDERSTAND
 BIAS IS
 EVERYWHERE

WHAT IT IS



IT'S A WAY OF THINKING



EVIDENCE-BASED PRACTICE

BEST AVAILABLE EVIDENCE
USED IN A **HIERARCHICAL** WAY TO
ANSWER **CLINICAL QUESTIONS**

Patient
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USING **CLINICAL EXPERTISE**

Diagnostician

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Being Kind & Careful



INFORMING PATIENTS

&
ELICITING
&

INTEGRATING PREFERENCES



Just a few of the diagnoses that are solely or partially lab-based dependent

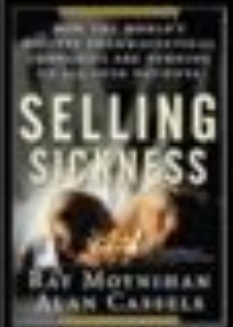
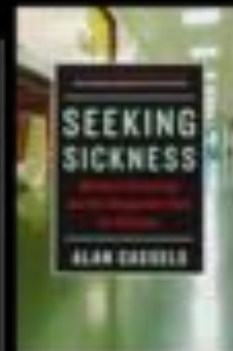
Acid-Base Disorders	Celiac Sprue	Folic Acid or B9 Deficiency	Inhalation anthrax	Nephrotic Syndrome	SLE
Acidosis and Alkalosis	Cervical Cancer	Food and Waterborne Illness	Inherited Copper Toxicity	Neural Tube Defects	Small Cell Lung Cancer
Acidosis/Alkalosis	CF	Food Poisoning	Insulin Resistance	Neuropathy	Spina bifida
aCL Syndrome	CFIDS	Fungal Infections	Insulin Resistance Syndrome	NHL	Spinal dysraphism
ACS	CFS	Gastroenteritis	Iron Overload Disease	Non-Hodgkin lymphoma	Spinal Meningitis
Acute DIC	CHF	Gluten-Sensitive Enteropathy	Iron Storage Disease	Non-Small Cell Lung Cancer	SSc
Acute Idiopathic Polyneuritis	Chlamydia	Gonorrhea	Jaundice	Nontuberculous Mycobacteria	Stable angina
Acute Inflammatory Demyelinating	Chronic Fatigue and	Gout	JIA	Nontuberculous Mycobacteria Infections	Staph
Polyneuropathy	Immune Dysfunction Syndrome	Gouty Arthritis	JRA	NTD	Staph aureus
Acute Kidney Injury	Chronic Fatigue Syndrome	Graves Disease	Juvenile Idiopathic Arthritis	NTM	Staph Infections
Acute Myocardial Infarct	Chronic Kidney Disease	GSE	Juvenile Rheumatoid Arthritis	OA	Staph Infections and Methicillin-Resistant
Acute Renal Failure	Chronic Thyroiditis	Guillain-Barré Syndrome	Keratoconjunctivitis Sicca	Obesity Syndrome	Staphylococcus aureus
AD	Circumscribed Scleroderma	H1N1	Kidney Disease	Osteoarthritis	Staphylococcus aureus
Addison Disease	Cirrhosis	H3N2	Lactase Deficiency	Osteoarthritis	STDs
Adrenal Insufficiency	CKD	H5N1	Lactose Intolerance	Osteoporosis	Stein-Leventhal Syndrome
Adrenal Insufficiency and Addison Disease	Coagulopathy	H7N9	Landry's Ascending Paralysis	Ovarian Cancer	Sticky Blood Syndrome
AKI	Cobalamin Deficiency	Hashimoto Thyroiditis	LE	PA	STIs
Albuminuria	Colon Cancer	HBP	Lead Poisoning	Pancreatic Cancer	Stomach Flu
Alcohol dependence	Colorectal Cancer	HD	Leukemia	Pancreatic Diseases	Stroke
Alcoholism	Community-Acquired Pneumonia	Healthcare-Associated Pneumonia	Limited Cutaneous Scleroderma	Pancreatic Insufficiency	Subacute Cutaneous Lupus
Allergies	Congenital Adrenal Hyperplasia	Heart Attack	Linear Scleroderma	Pancreatitis	Swine Flu
Alzheimer Dementia	Congenital Alactasia	Heart Attack and Acute Coronary Syndrome	Liver Disease	Parathyroid Cancer	Syndrome X
Alzheimer Disease	Congestive Heart Failure	Heart Disease	Lobar Pneumonia	Parathyroid Diseases	Syphilis
AMI	Conn Syndrome	Heart Failure	Localized Scleroderma	PCOS	Systemic Exertion Intolerance Disease
Anemia	Consumption Coagulopathy	Hematuria	Lower Respiratory Tract Infection	Pelvic Inflammatory Disease	Systemic Lupus Erythematosus
Anencephaly	Copper Storage Disease	Hemochromatosis	Lung Cancer	Peptic Ulcer	Systemic Scleroderma
Angitis	CREST	Hemoglobin Abnormalities	Lung Diseases	PID	Systemic Sclerosis
Angina	Crohn Disease	Hemoglobin Barts	Lupus	Pituitary Disorders	TB
Angina pectoris	Cushing Syndrome	Hemoglobin C Disease	Lupus Anticoagulant Syndrome	Plasma Cell Dyscrasia	Testicular Cancer
Ankylosing Spondylitis	Cutaneous anthrax	Hemoglobin E Disease	Lupus Erythematosus	Plasma Cell Myeloma	Thalassemia
Anthrax	CVD	Hemoglobin S	Lyme Disease	Plasma Cell Neoplasm	Thrombophilia
Anticardiolipin Antibody Syndrome	Cystic Fibrosis	Hemoglobin Variants	Lymphocytic Thyroiditis	Plasmacytoma	Thyroid Cancer
Antiphospholipid Antibody Syndrome	Degenerative Joint Disease	Hemoglobinopathy	Lymphoma	Plasmacytoma of Bone	Thyroid Diseases
Antiphospholipid Syndrome	Dehydration	Hepatic Disease	Malabsorption	Pneumonia	Toxemia
aPL Syndrome	Dermatosclerosis	Hepatitis	Malaria	Polycystic Ovary Syndrome	Toxic Diffuse Goiter
APLS	Diabetes	Hepatolenticular Degeneration	Malignancy	Porphyria	Travelers' Diseases
APS	Diabetes mellitus	Hereditary Persistence of Fetal Hemoglobin	Malignant tumor	Post-infectious Arthritis	Trich
ARF	Diarrhea	Herpes	Malnutrition	Pre-eclampsia	Trichomonas
Arteritis	DIC	Herpes Zoster	MDS	Pregnancy	Trichomoniasis
Arthritis	Diffuse Cutaneous Scleroderma	High Blood Pressure	ME	Pregnancy-induced Hypertension	Trisomy 21
AS	Diffuse Thyrotoxic Goiter	HIV	Melanoma	Presenile Dementia	Tuberculosis
Asthma	Disaccharidase Deficiency	HIV Infection and AIDS	Meningitis and Encephalitis	Primary Aldosteronism	Types of Liver Disease
Atypical Mycobacteria	Discoïd Lupus	HL	Meningococcal Meningitis	Primary Hyperaldosteronism	Ulcerative Colitis
Atypical Pneumonia	Disseminated Intravascular Coagulation	Hodgkin Disease	Menopause	Prinzmetal's angina	Unstable angina
Autoimmune Diseases	Disseminated Intravascular Coagulopathy	Hodgkin Lymphoma	Metabolic Syndrome	Prostate Cancer	Urinary Tract Infection
Autoimmune Thyroiditis	Disseminated Lupus Erythematosus	Hospital-Acquired Pneumonia	MG	Protein in urine	UTI
Avian Flu	DJD	HPFH	MI	Proteinuria	Vaginal Infection
Bacillus anthracis infection	Double Pneumonia	HPV	Morphea	RA	Vaginitis and Vaginosis
Bacterial Arthritis	Down Syndrome	Hughes Syndrome	MOTT	Reactive Arthritis	Vaginitis/Vaginosis
Bacterial Vaginosis	Drug-induced Lupus	Huntington Disease	MPDs	Reaven Syndrome	Variant angina
Benign Prostatic Hyperplasia	DS	Huntington's Chorea Disease	MPNs	Renal Disease, Kidney Failure	Vasculitis
Benign Prostatic Hypertrophy	Dysmetabolic Syndrome	Hypercoagulable Disorders or States	MRSA	Rheumatoid Arthritis	VD
Biological Warfare	Ebola Hemorrhagic Fever	Hyperparathyroidism	MS	Rheumatoid Spondylitis	Venereal Diseases
Bioterrorism Agents	Ebola Virus Disease	Hypersensitivity	Multiple Myeloma	Sarcoidosis	Vitamin B12 and Folate Deficiencies
Bleeding Disorders	Ebola Virus Infection	Hypertension	Multiple Sclerosis	SCD	Vitamin B12 Deficiency
Blood in the urine	Encephalitis	Hyperthyroidism	Myalgic Encephalomyelitis	Scleroderma	Vitamin K Deficiency
Bone Marrow Disorders	End Stage Renal Disease	Hypoparathyroidism	Myasthenia Gravis	SEID	Vulvovaginitis
Borrelia burgdorferi Infection	Endocrine Syndromes	Hypothyroidism	Mycobacteria other than tuberculosis	Seizure Disorder	Walking Pneumonia
Borrelia mayonii Infection	Endocrine System and Syndromes	IBD	Mycoses	Sepsis	West Nile Virus
BPH	Epilepsy	Icterus	Myelocoele	Septic Arthritis	Wilson Disease
Breast Cancer	ESRD	Infectious Arthritis	Myelodysplasia	Sexually Transmitted Diseases	WNV
CAH	EVD	Infectious Polyneuritis	Myelodysplastic Syndrome	Sexually Transmitted Infections	Wound and Skin Infections
Cancer	Excessive Clotting Disorders	Infertility	Myelomenigocele	Shingles	
Candidiasis	Extraosseous Plasmacytoma	Inflammatory Bowel Disease	Myeloproliferative Disorders	Sicca Syndrome	
Carbohydrate Intolerance	Fibromyalgia	Influenza	Myeloproliferative Neoplasms	Sickle Cell Anemia	
Cardiovascular Disease	Flu	Influenza A	Myocardial Infarct	Sickle Cell Disease	
Celiac Disease	Folate Deficiency	Influenza B	Neonatal Lupus	Sjögren Syndrome	

“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

250
200
150
100
50
0

PubMed Overdiagnosis Citations 1970-2014



Preventing overdiagnosis: how to stop harming the healthy
A strategy for reducing the number of unnecessary health-care services that cause more harm than good. The authors discuss the importance of the health-care system in preventing overdiagnosis and the role of the health-care system in preventing overdiagnosis.

GPs—Do you want to join the debate on overdiagnosis?
John S. Treweek's general practitioners and the overdiagnosis debate.

Overdiagnosis: too much of a good thing?
David Williams

Overdiagnosis: too much of a good thing?
David Williams

Science of overdiagnosis to be served up with a good dose of humility
The Preventing Overdiagnosis international scientific conference gets under way next month. Ray Moynihan, author, journalist, and senior research fellow, Royal College, Australia.

Overdiagnosis of Disease: A Modern Epidemic
A Modern Epidemic



Commentary: The overdiagnosis nightmare: a time for caution
Sofiane Clavier

Overdiagnosis: when good intentions meet vested interests—an essay by John Moynihan
Overdiagnosis: when good intentions meet vested interests—an essay by John Moynihan.

LESS IS MORE: Overdiagnosis and Overtreatment: Evaluation of What Physicians Tell Their Patients About Screening Harms
Evaluation of What Physicians Tell Their Patients About Screening Harms.

Overdiagnosis – overtreatment
"Medical science has made such tremendous progress that there is hardly a healthy human left" – Andrew Feinstein



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 Cartabellotta⁵**

“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.”

Wrong guidelines: why and how often they occur

**Primiano Iannone,¹ Nicola Montano,² Monica Minardi,³
James Doyle,³ Paolo Cavagnaro,⁴ Antonino Cartabellotta⁵**

“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”



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



Golden Pill Award

	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”

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

MY THESIS

“For much in medicine, we knowingly sell preeminent precision even though we all know in our heart of hearts we can only deliver educated imprecision.

I believe most patients would be very understanding about this imprecision if we were just more open about it.”

-James McCormack, Pharm D (1959 - hopefully not soon)

“We also CAN’T be precise about the imprecision”

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.	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%

Two Problems with Faking Precision



FALSE BELIEFS

BELIEF #1 - when the numbers change these changes are real

BELIEF #2 - the good/bad thresholds are relatively black and white

These beliefs can potentially lead to inappropriate feelings
of fear, happiness, frustration, confusion...

Both in patients AND clinicians

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)



I am speaking in general, and do realise there are always some exceptions

I am presenting concepts

I will be providing ball-park estimates

I may be speaking to the converted or at least the very knowledgable

When we do tests, typically
we are wondering

what are the results NOW, and/or

have they changed from PREVIOUS
measurements



A
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Every “measurement”
will be different

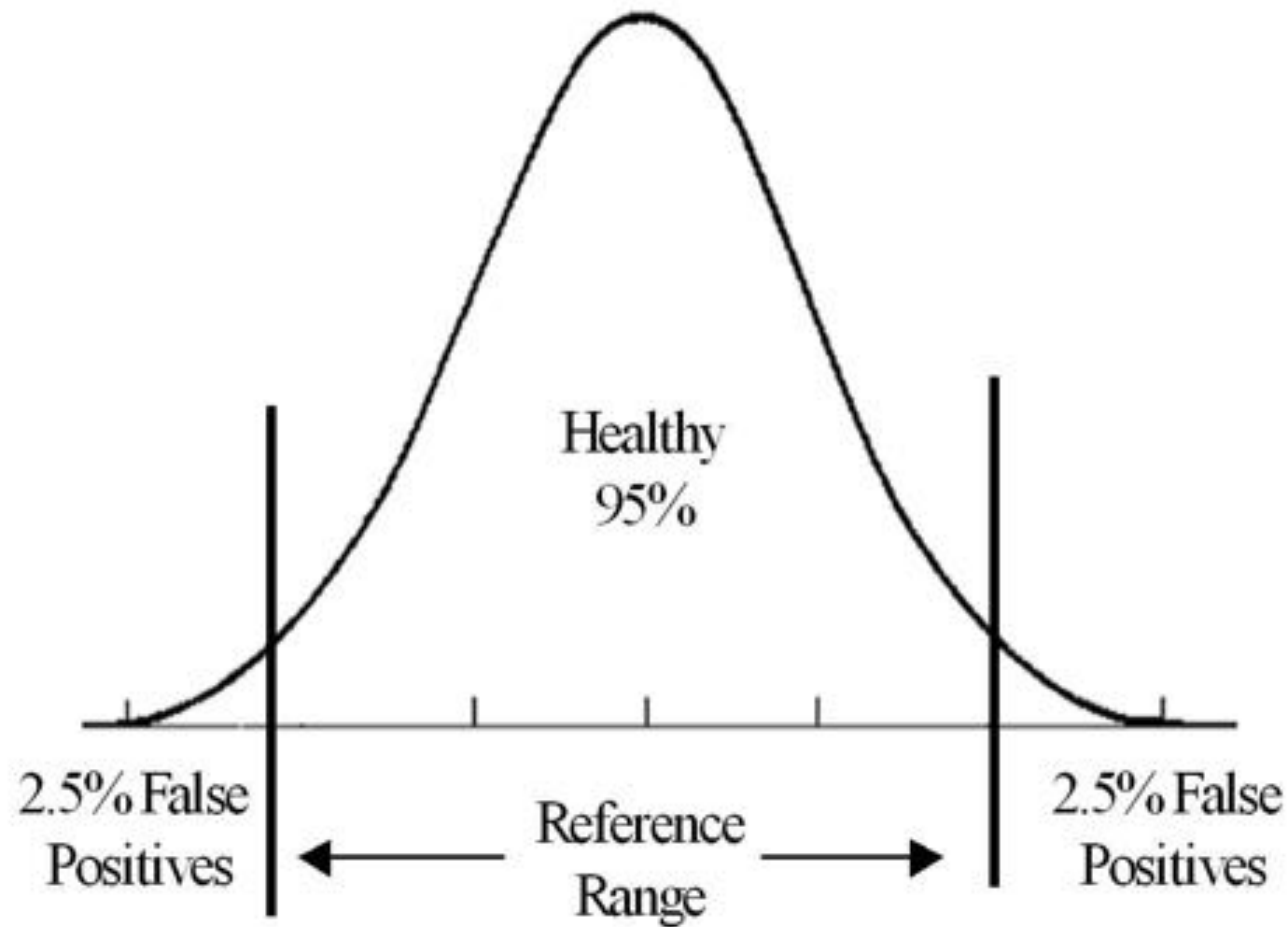
Analytic variability

Biologic variability

Population-based
reference intervals

Population-based reference intervals

The interval/range where 95% of healthy people fall



Chances of at least one abnormal test

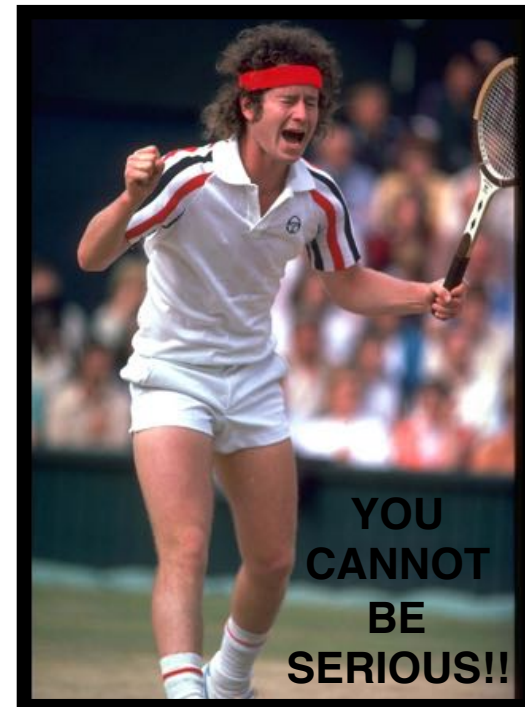
5% of test results from patients WITHOUT disease will be outside the reference range

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

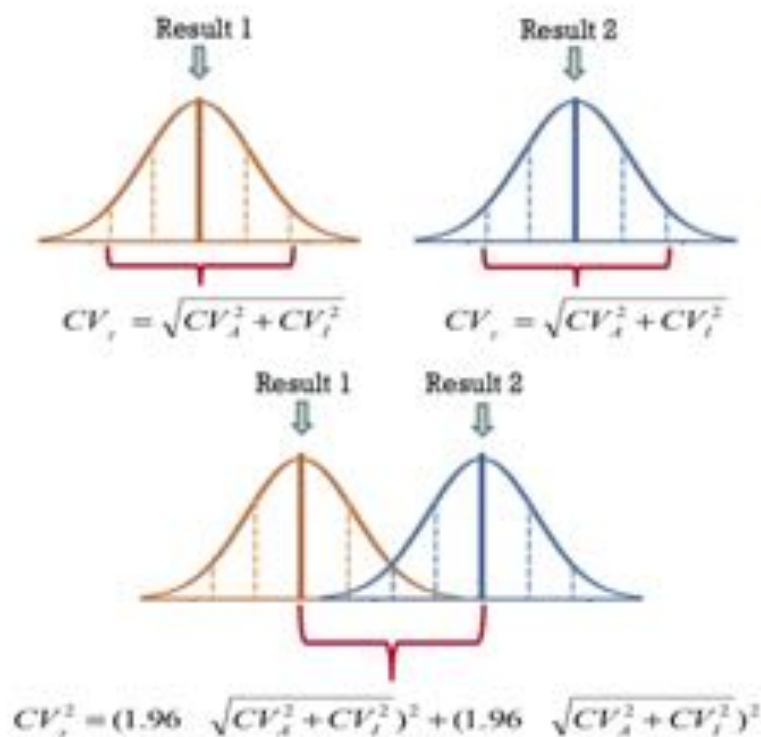
Reference Change Values (RCV)

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

$$RCV = \sqrt{2} * 1.96 * \sqrt{(CV_{Analytical}^2 + CV_{Intraindividual}^2)}$$



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>



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 (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

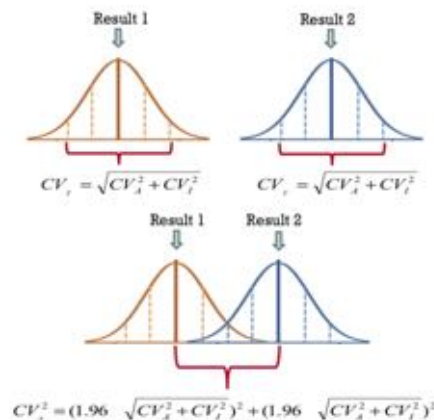
Misunderstandings about common statistical test damage science and society
BY TOM SIEGFRIED 10:30AM, MARCH 11, 2016

Reference Change Values

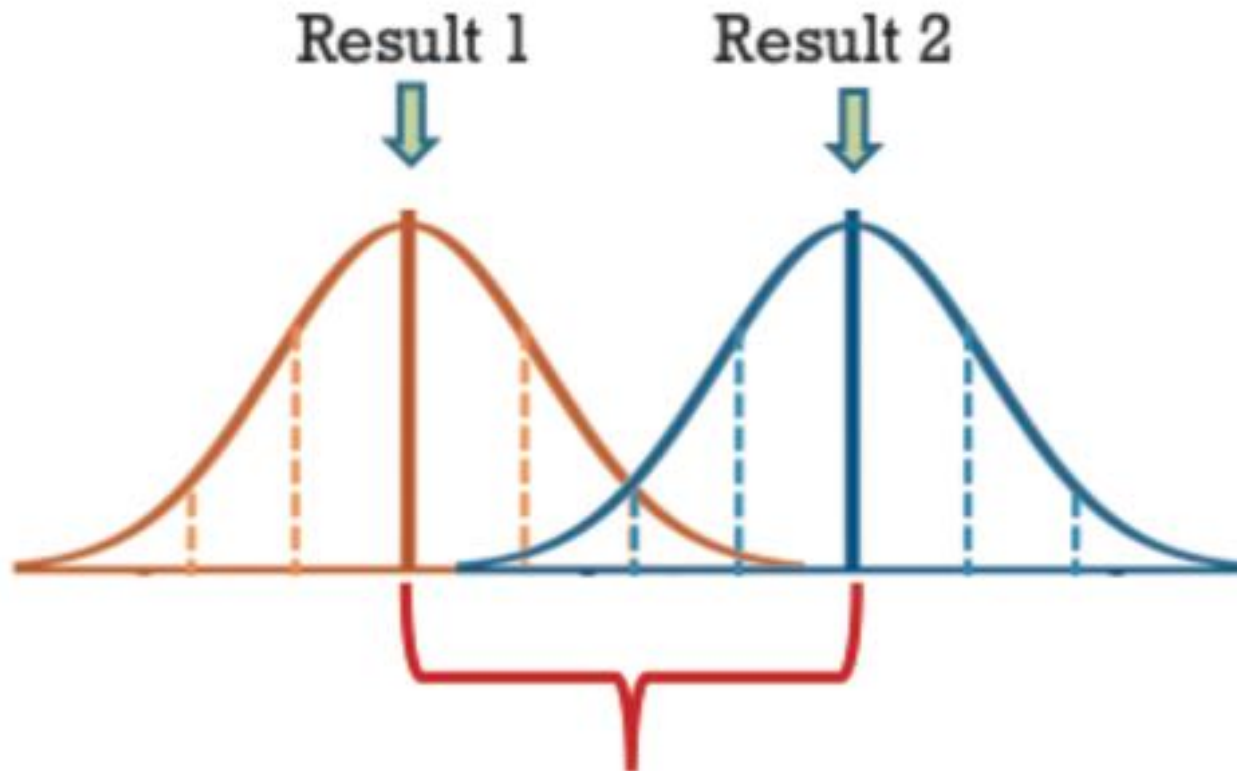
findings of a “significant difference” JUST means we are ruling out that the difference seen is due to chance

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%

DEBATE

Open Access

How confidence intervals become confusion intervals

James McCormack¹, Ben Vandermeer² and G Michael Allan^{3*}

The Word
SIGNIFICANT

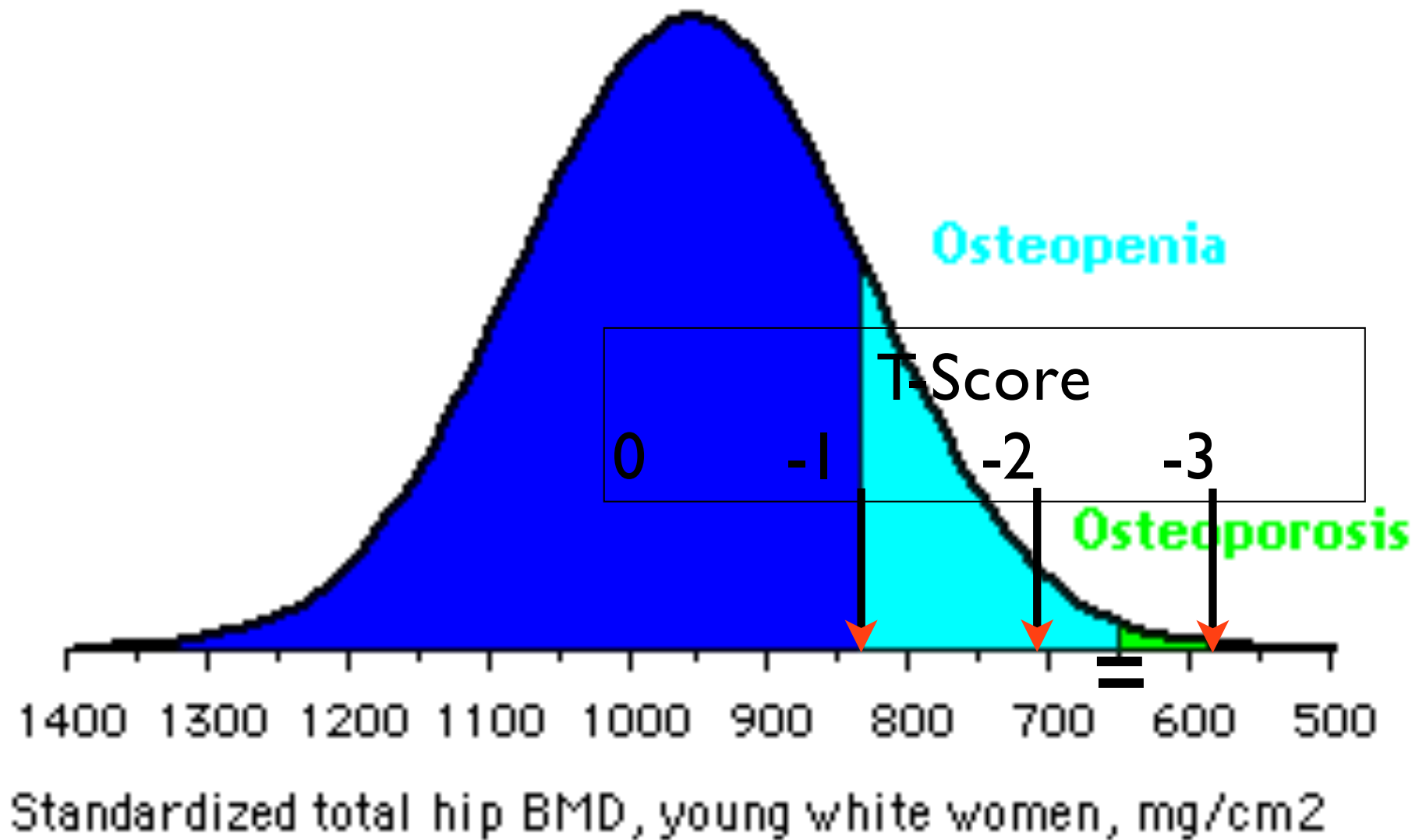
Bone Density
Cholesterol
Blood pressure
Glucose
Vitamin D

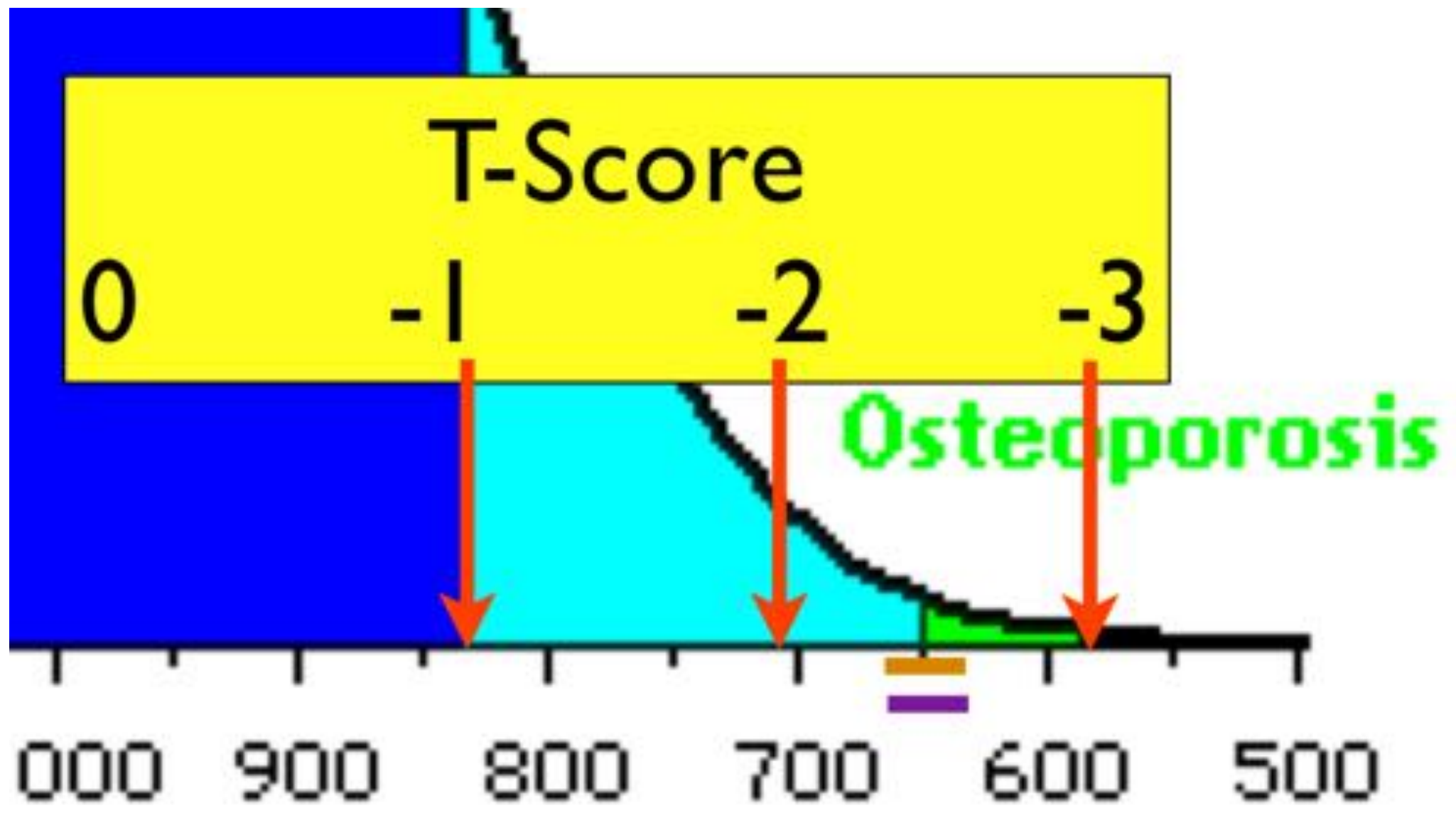


**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR
THE DIAGNOSIS AND TREATMENT OF
POSTMENOPAUSAL OSTEOPOROSIS 2010**

“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 $\sim 0.6\%$
- 2) Difference in BMD between drug and placebo - 3 years $\sim 5\%$
- 3) BMD measurement precision $\pm 2-3\%$





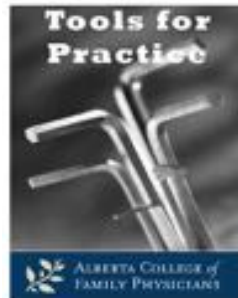
Other Smarter People

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”

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

“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”

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

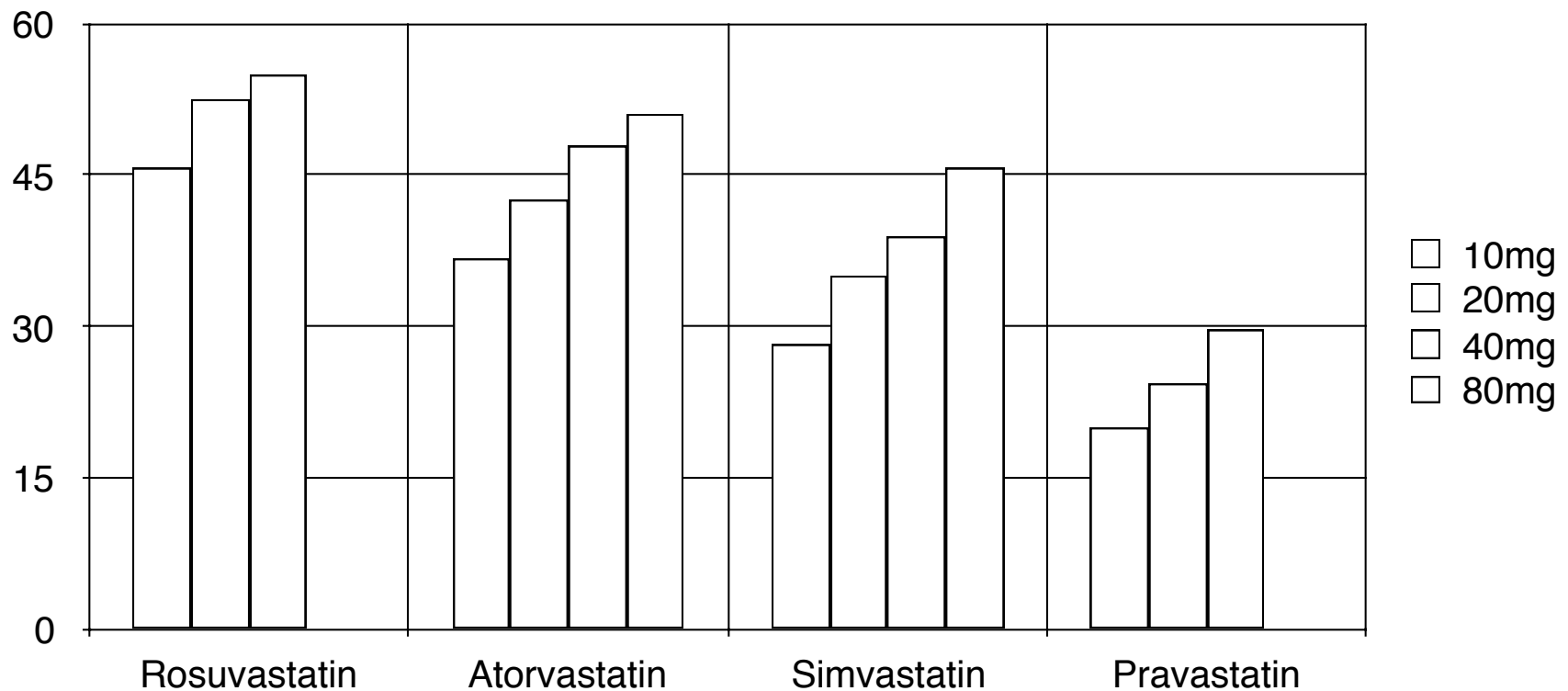
Total chol ~ - 0.80 to 0.80 mmol/L (~30 mg/dL)

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

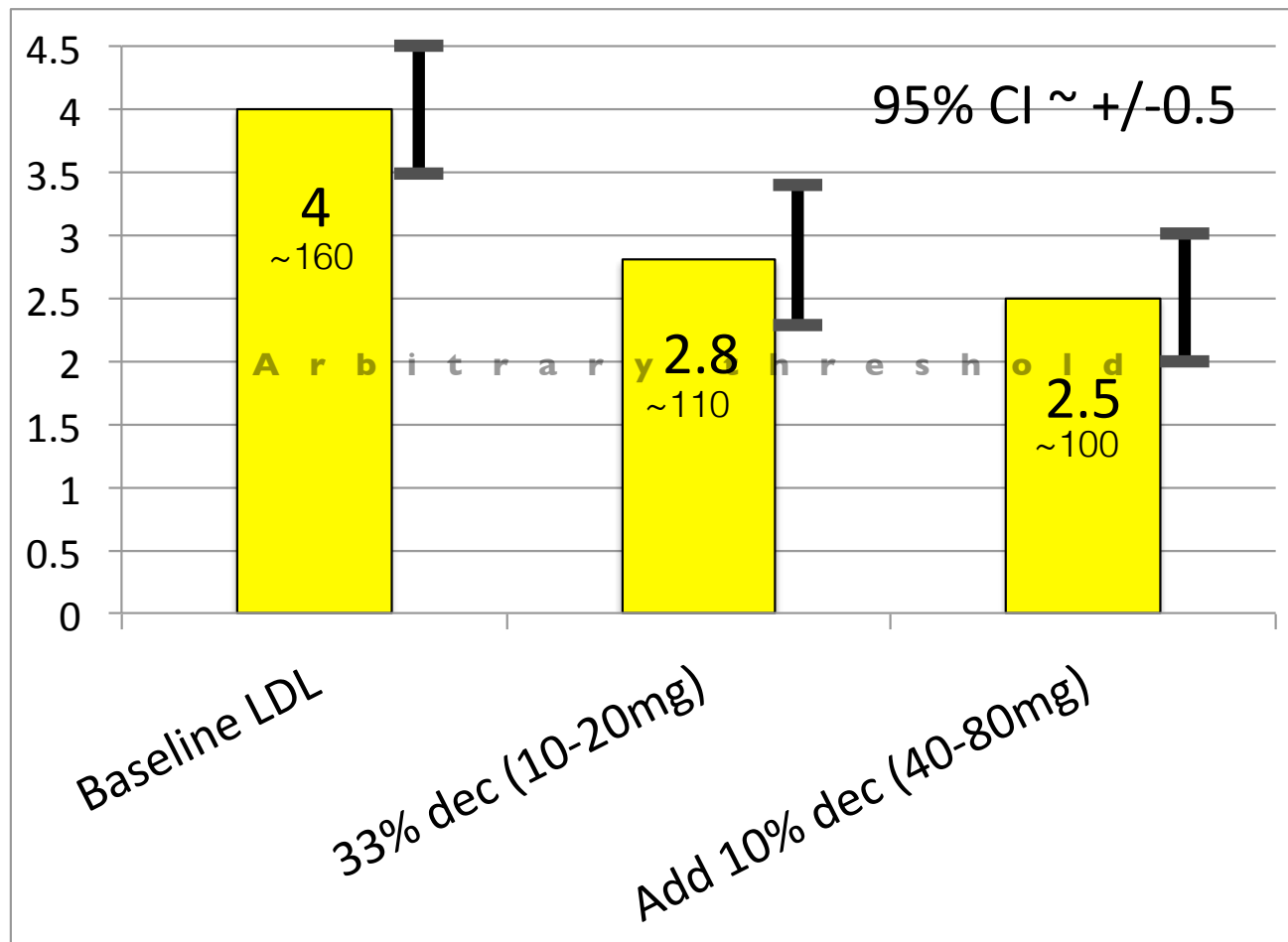
Average increase in cholesterol is 0.5-1%/year

“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



Editorial

American Journal of Hypertension (2008) 21:3–4; doi:10.1038/ajh.2007.20

Blood Pressure Variability: The Challenge of Variation

Tom P Marshall [T.P.Marshall](mailto:T.P.Marshall@bham.ac.uk)

¹Department of Public Health and Epidemiology, University of Birmingham, Edgbaston, Birmingham, UK

Correspondence: Tom P. Marshall, (T.P.Marshall@bham.ac.uk) (mailto:T.P.Marshall@bham.ac.uk)

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”

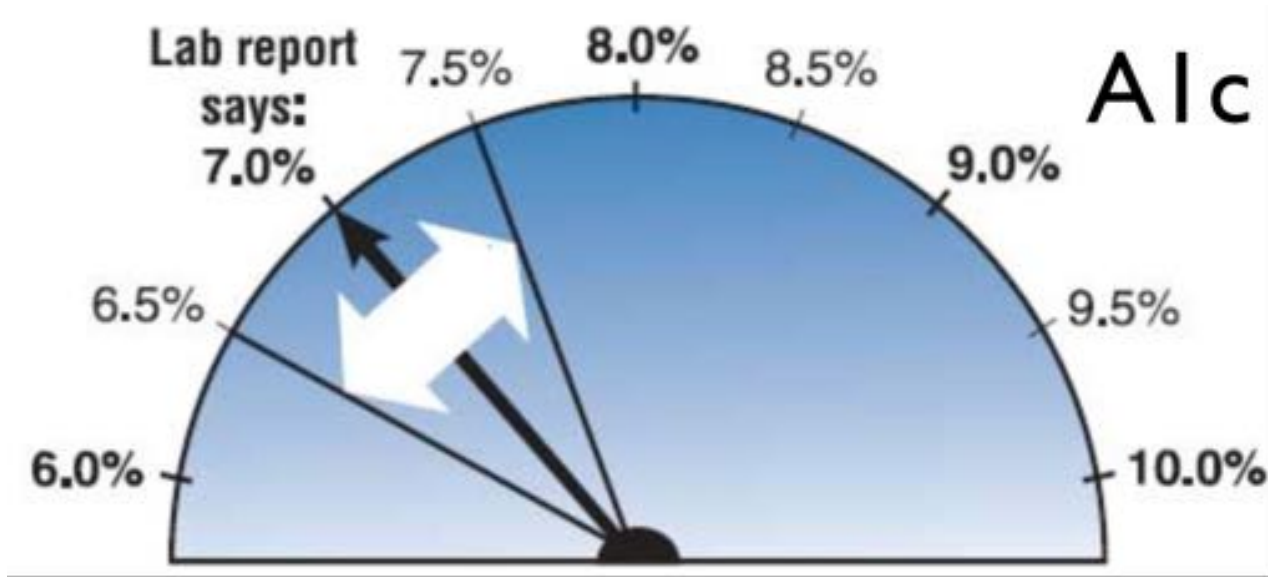
“coefficients of variation for systolic office, ambulatory, and self-monitored blood pressure, compared at baseline and 6 weeks, were 8.6%, 5.5%, and 4.2% respectively”

Br J Gen Pract 2010; 60: 675–80

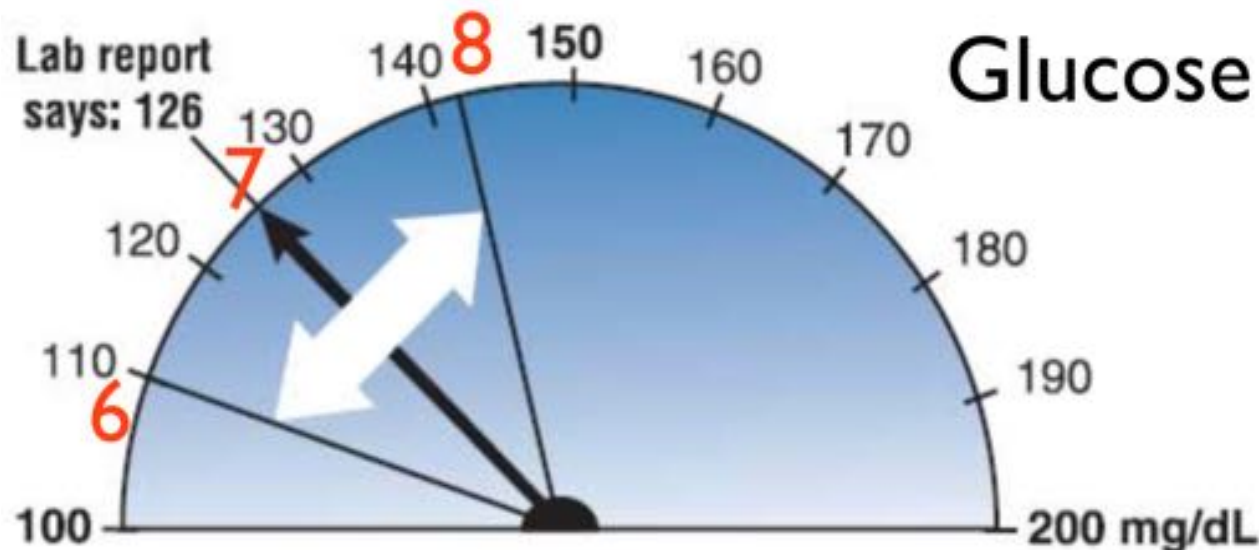
“a single careful blood pressure measurement taken a few months after the start of treatment is not useful for monitoring”

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

Yet another IMPORTANT issue for measurements of glucose, cholesterol, blood pressure and bone density

These are RARELY measures of any disease

They are simply RISK FACTORS

They should be presented in the context of the risk of developing important clinical outcomes - heart attacks, strokes, ESRD etc

The Absolute CVD Risk/Benefit Calculator

Framingham
Heart attacks + angina/coronary insufficiency + heart failure + strokes + intermittent claudication

QRISK[®]2-2014
Heart attacks + strokes

ACC/AHA ASCVD
CHD death + nonfatal heart attacks + fatal/nonfatal strokes

Age
 years

Gender
☒ Male ☐ Female

Smoker
☐ Yes ☒ No
CVD risk is reversed after 5-10 years of no smoking

Diabetes
☐ Yes ☒ No

Systolic Blood Pressure
 mmHg
Blood pressure should be prior to drug treatment
120 mmHg is used for baseline risk

On treatment for BP
☐ Yes ☒ No

Total Cholesterol
 mmol/L
Cholesterol should be prior to drug treatment
3 mmol/L is used for baseline risk.
[Click to change to mg/dL.](#)

HDL Cholesterol
 mmol/L
HDL should be prior to drug treatment
1.3 mmol/L is used for baseline risk.

Family History of Early CHD
 %

Relative Benefit: 30%
Benefit often has nothing to do with the effect on the surrogate marker. At present, you can only select one intervention at a time.

☐ Physical Activity
☐ Mediterranean Diet vs Low fat
☐ Vitamin/Omega-3 supplements
☒ BP meds (not atenolol/doxazosin)

Harm Of Intervention

- Types of side effects vary between drugs
- Having to stop drug due to intolerability NNH 10
- Inconvenience of surrogate remeasurements
- Drug Cost

☐ Low-mod intensity statins
☐ High intensity statins ☐ Fibrates
☐ Niacin ☐ Ezetimibe ☐ Metformin
☐ Sulfonylureas ☐ Insulins ☐ Glitazones
☐ GLPs ☐ DPP-4s ☐ Meglitinides
☐ SGLT2 ☐ Smoking Cessation
☐ ASA
[Benefit Estimate Details](#)

Risk Time Period
10 years

	74.0%	No event
	18.2%	Total with an event
	7.8%	Number who benefit from treatment
NNT	13	Number needed to treat
	15.8%	Baseline events using baseline factors alone
	2.4%	Additional events "caused" by risk factors

As with all risk calculators, calculated risk numbers are +/- 5% at best. [More information](#)

Print Report

Calculate ballpark 10-yr risk of CVD - BP, chol, diabetes

Make estimate of benefit based on the best available evidence

Gives a list of adverse effects to discuss

cvdcalculator.com

Cost? \$50-60 - 2-3 x the yearly treatment cost



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Provinces struggle with demand for Vitamin D tests

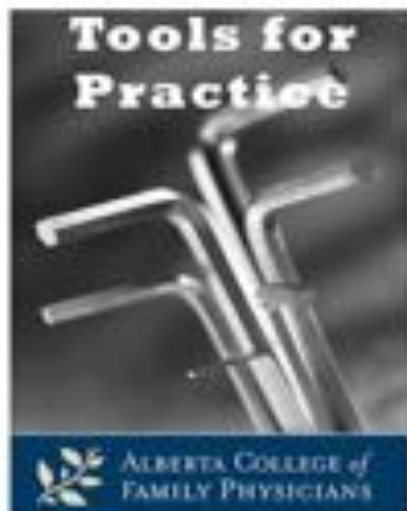
Martin Mittelstaedt

Published on Wednesday, Jan. 06, 2010 6:56PM EST

“the most-ordered
hormone assay in the
United States”

J Clin Endocrinol Metab
2009;94:1092–3

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

Now What?!!



“The obscure we see eventually.
The completely obvious, it seems,
takes longer.”

Edward R Murrow 1908-1965



Important caveats not discussed

Biological variances are typically from populations - can vary with age etc

Evidence behind the population-based reference intervals

Arbitrary thresholds in “guidelines”

One-sided vs two-sided testing

Not all lab tests are Gaussian/normally distributed

Bayesian approaches - pre-test and post-test probabilities

Point of Care Testing (POCT) is a whole other story

NIGHTMARE

of fear of change/IT/Legal - blah blah blah

Just the facts, Ma'am

Should we...

Openly explain and present lab variability - YES

Openly discuss the potentially black and white things about lab variability - ABSOLUTELY

Continue to use words like low, medium, high, significant - NO, NO, NO, NO

Use a 95% or a 90% or an 85% significance threshold - UNKNOWABLE

Get hung-up on the fact the evidence-base isn't perfect - NO - USE THE BEST AVAILABLE EVIDENCE

Care who is the driver of change - WHOEVER CAN DO IT RIGHT

Report SDs, levels of significance, error bars - IN GENERAL, NO

Discuss the variability or the exceptions to the rule - OF COURSE

Be OK with “ball parking” - WELCOME TO HEALTH CARE

Care if improved lab reporting improves patient outcomes - IT'S REALLY ABOUT DECISIONS AND THE “TRUTH”

Believe it is just the “other” lab's problem not ours - THAT'S ADORABLE

If I was the boss of “LAB” result reporting

All of this could be done today

Shift from a laboratory perspective to a patient-centered viewpoint

Using **BALLPARK** estimates

ALWAYS provide the imprecision

Provide MUCH more definitive guidance

Stop using terms like low, medium, high or significant

If they are “risk factor” measurements then they should only be provided with “risk” estimates

Do not do a test without discussion of a pre-test probability and then provide a post-test probability

Make many tests more “inconvenient”?



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

As much as
humanely possible

DO NOT use “flags”, adjectives, or mention SDs, Gaussian distributions, two-sided tests, Z-scores, T-scores, confidence intervals, or p-values.

Not sure if we even need point estimates



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
pCO₂
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



~WHAT CHANGE
IN HEIGHT CAN
YOU PICK UP?

RCV 2% - 5'11" - 6'1"

RCV 5% - 5'10" - 6'2"

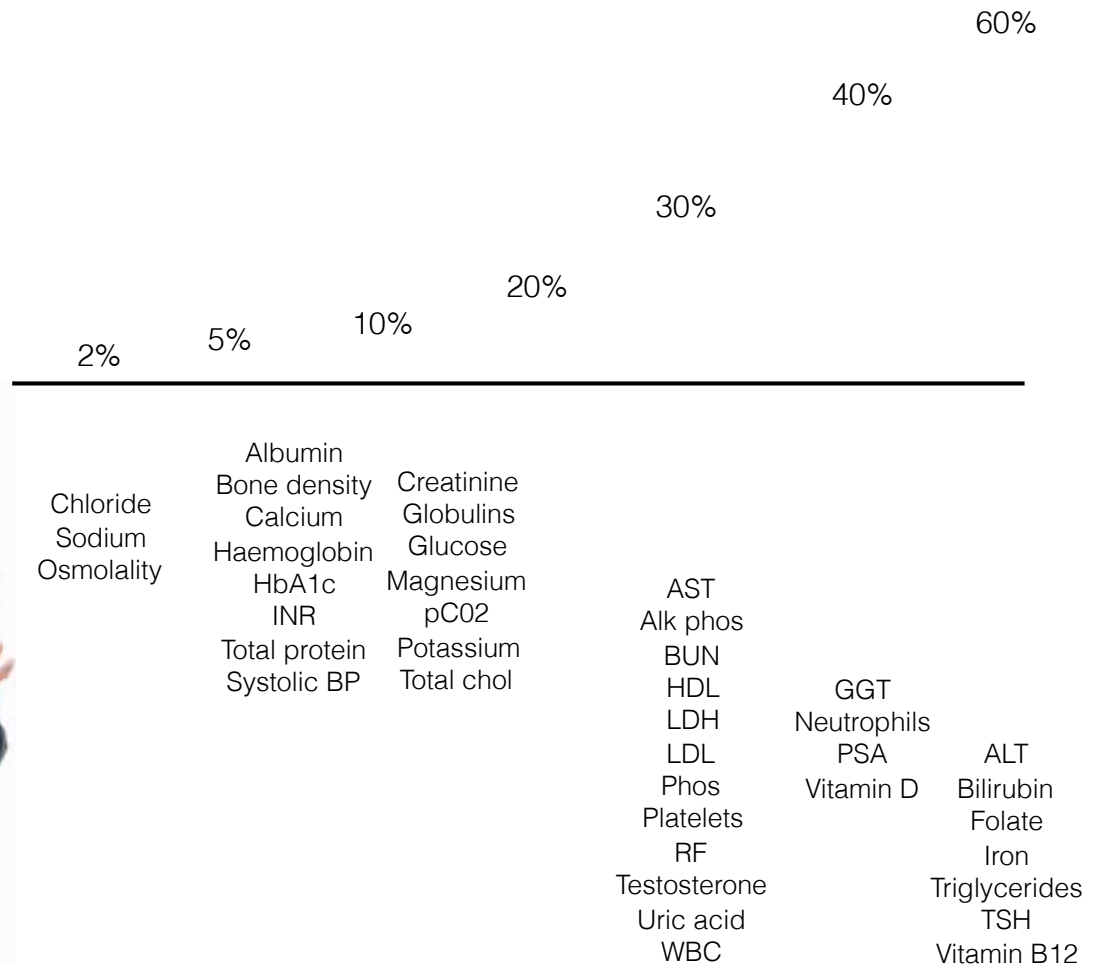
RCV 10% - 5'9" - 6'3"

RCV 20% - 5'6" - 6'6"

RCV 30% - 5'0" - 7'0"

RCV 40% - 4'6" - 7'6"

RCV 60% - 4'0" - 8'0"



BALLPARK RCV ranges VS typical changes

Cholesterol

Total cholesterol RCV

LDL RCV

HDL RCV

Triglycerides RCV

Avg. cholesterol inc. per year

Avg. LDL initial dec. with statin

Avg. LDL dec. with inc. dose of statin

Avg. HDL inc. with statin

Avg. LDL dec. with exercise

Glucose

A1c RCV

Avg A1c inc. per year

Avg. A1c dec. with glucose med

Blood pressure

Systolic blood pressure RCV

Avg SBP inc. per year

Avg. SBP dec. with BP med

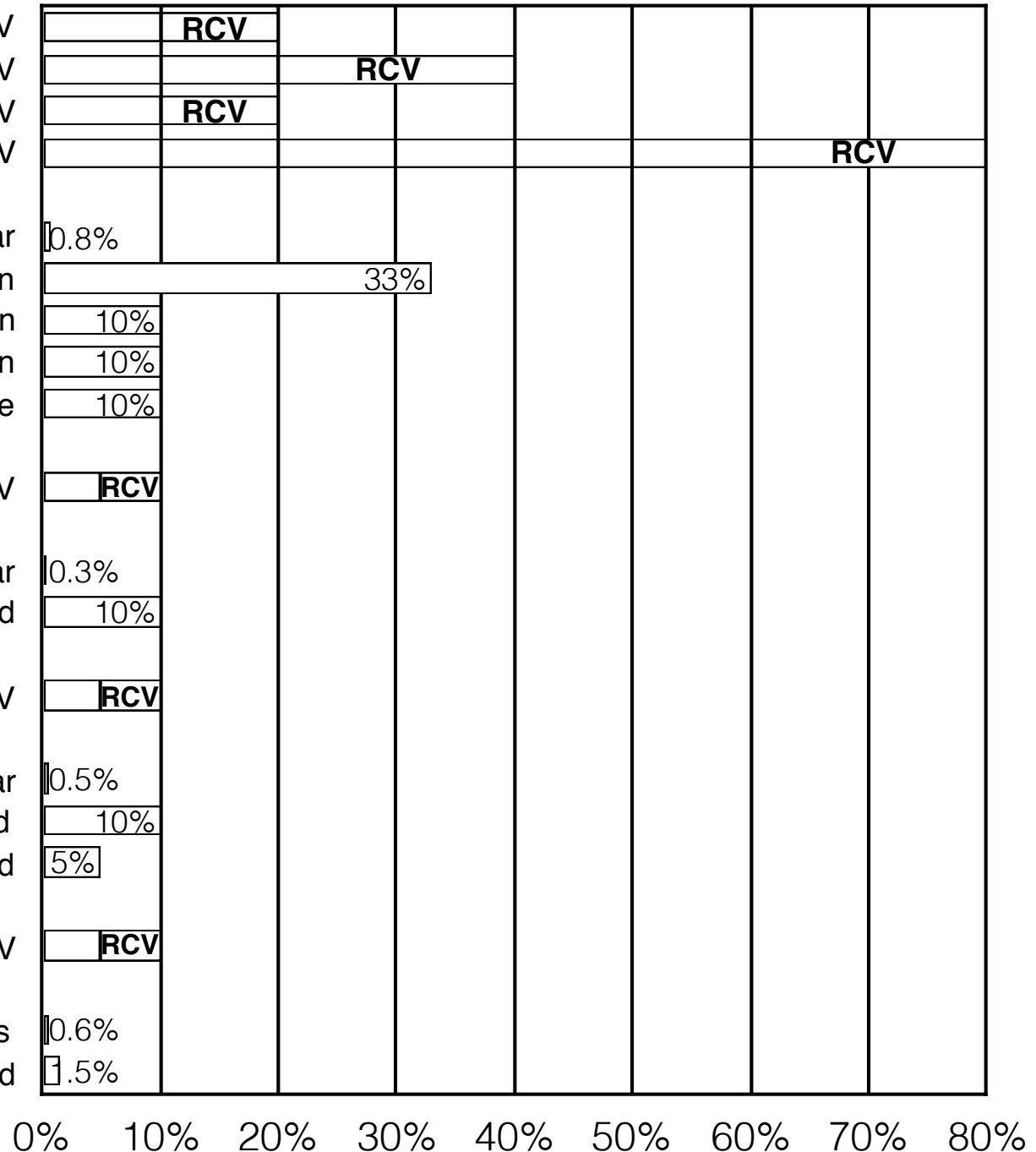
Avg. SBP dec. with inc. dose of BP med

Bone density

Bone density RCV

Avg. yearly bone density loss

Avg. yearly bone density inc. with med



Patient Information ☐ Show More Patient Details

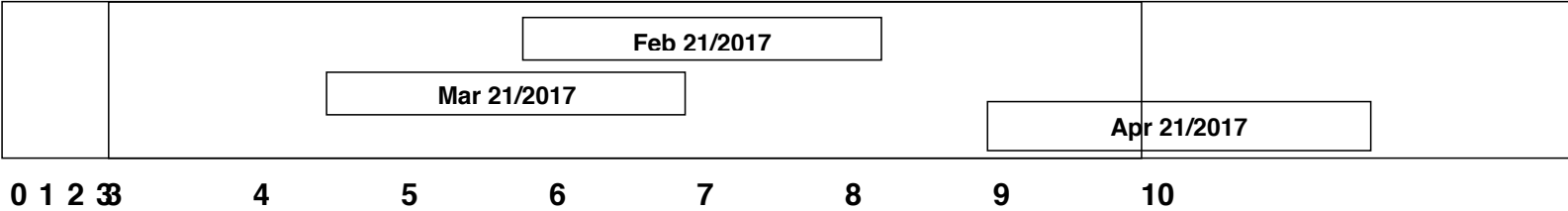
Patient: LLOYD, TESSA JANE ELSWITHA
PHN: 9083126918 Phone: (604)538-7132 Lab No: 17-141460231

Flags Results Reference Range Units

General Comments Because of lab test and human variation, lab tests results can only be provided within a range

THE TRUE RESULTS ARE LIKELY SOMEWHERE IN THE RANGE INDICATED BY THE YELLOW STRIP

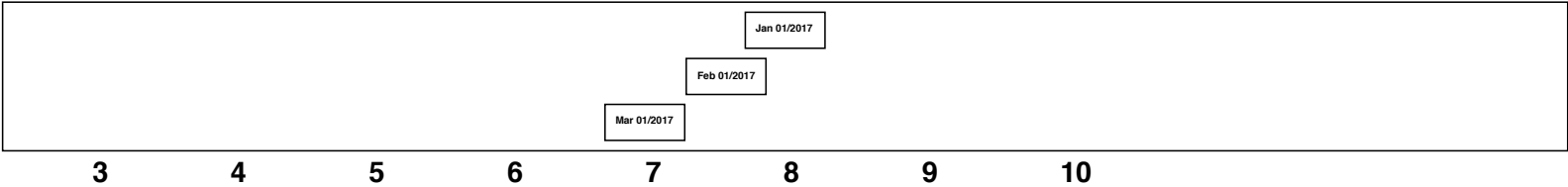
White blood cells



Potassium (mEq/L)



HbA1c (%)



95% of HEALTHY people have results somewhere in this range

Typically, results in this range are considered in the “normal” range

5% of HEALTHY people have results somewhere in this range

Typically, results in this range are considered outside of the “normal” range

There is no “normal/abnormal ”range - the higher the value the higher your CVD risk - discuss your risk with your HCP

DATE 1 DATE 2 Typically, if 2 test results from different times overlap we consider the results to not be different
If they don't overlap then we likely think they have changed

Deals with the reference interval

Deals with the analytical and human variability

Deals with risk lab tests

DATE 1

DATE 2

OVERLAP Deals with reference change values