James McCormack
BSc (Pharm), PharmD
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC, Canada

therapeuticseducation.org

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

“To alcohol! The cause of... and solution to... all of life's problems”

PLUGS® Summit 2017:

Can Hospitals, Labs, IT experts and the Insurance Industry Work Together to Improve Lab Test Utilization?

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

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

"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

If you're not sick you just haven't had enough tests

Robert Rangno, MSc, MD

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

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my Account

Change your email address, password or security questions. Register another person to your account or merge accounts.

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Report Details

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Patient Information — Show More Patient Details

Patient: LLOYD, TESSA JANE ELSWITHA
PHN: [redacted] **Phone:** [redacted] **Lab No:** [redacted]

	Flags	Results	Reference Range	Units

General Comments

General Information

This Standing Order will expire on 25-JUN-2017. If this Standing Order is still required, please provide your patient with a new laboratory requisition prior to this date.

Hematology

Differenti

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 estimates.
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"

1. I am speaking in general, and do realise there are always some exceptions
2. I am presenting concepts
3. I will be providing ball-park estimates

Two Problems with Faking Precision

FALSE BELIEFS

BELIEF #1 - the good/bad thresholds are relatively black and white

BELIEF #2 -when the numbers change these changes are real

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

Both in patients AND clinicians

Sources of Imprecision

Actual LAB errors

Lab Error

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%

Measurement Landscape

Assuming no pre-analytic issues - timing/labelling etc

Population-based reference intervals

Analytic variation

Analytical Variation

CVA - analytical variation

Biologic variation

Biological Variation

CVI - within subject

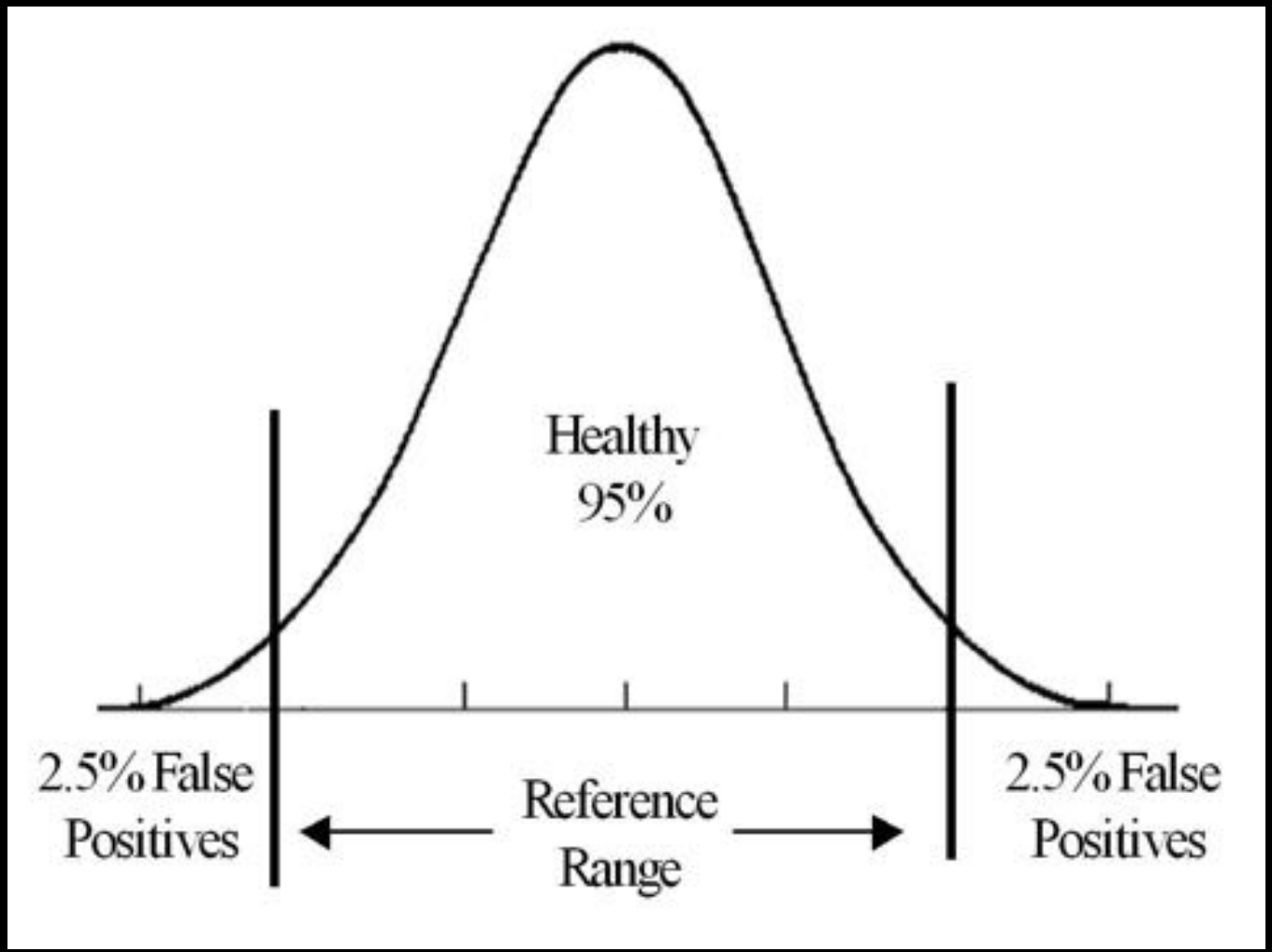
CVG - between subject

Reference change values (RCV)

Population-based reference intervals

Population-based reference intervals

The interval/range where 95% of healthy people fall



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

When we do tests, typically we are wondering

1. what are the results NOW, and/or
2. have they changed from PREVIOUS measurements

Analytic variation

Biologic variation

Every "measurement" will be "different"

1. Analytic variability
2. Biologic variability

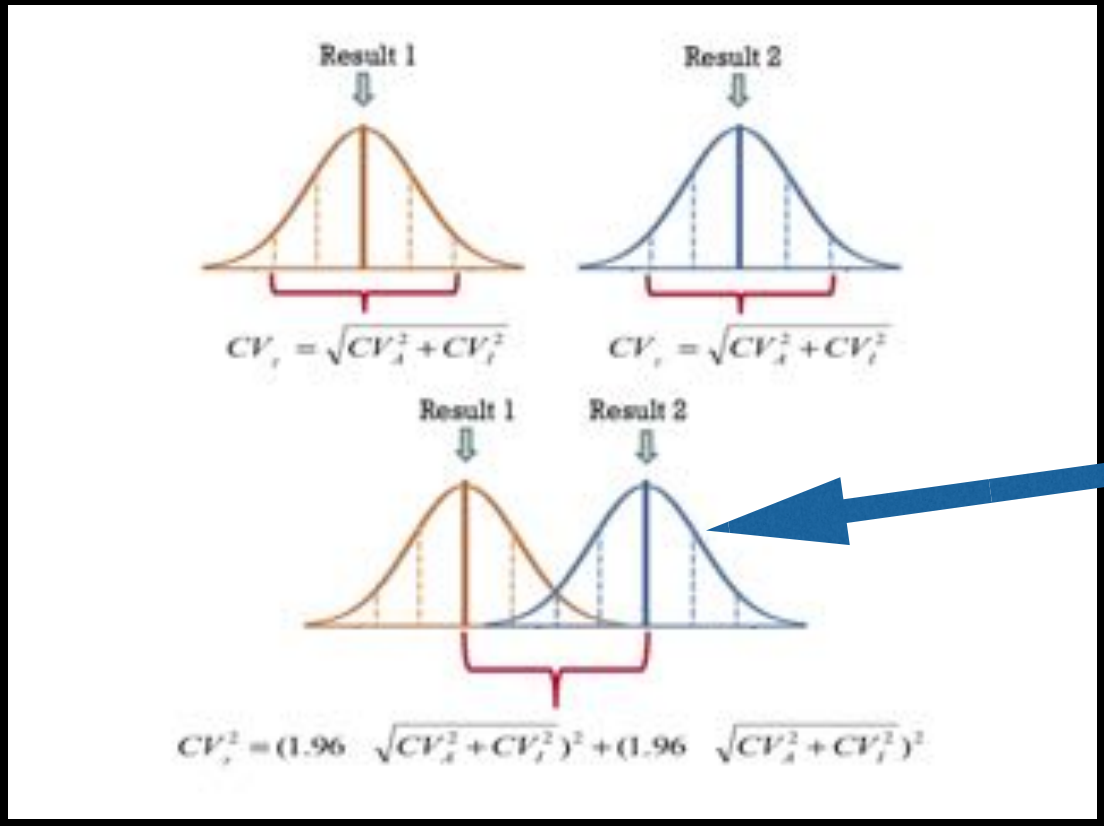
Reference Change Values (RCV)

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

Reference Change Values

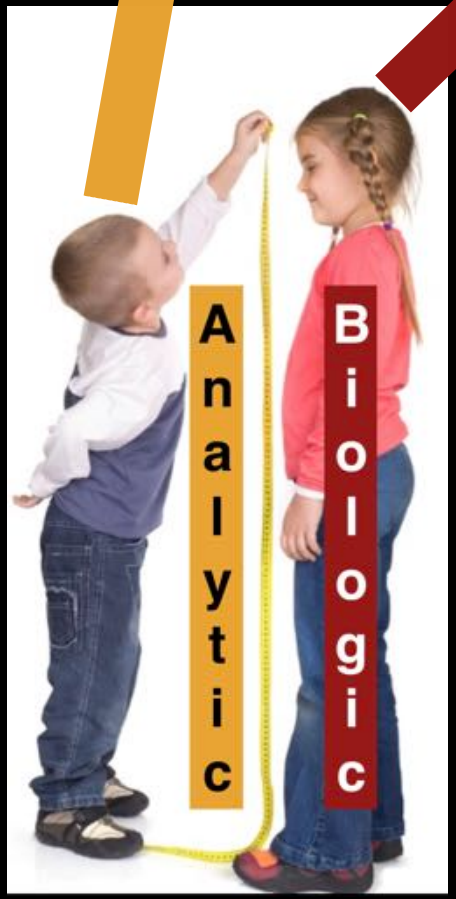
Used with SERIAL results to help deal with the analytic imprecision and biologic variation

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

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



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)”

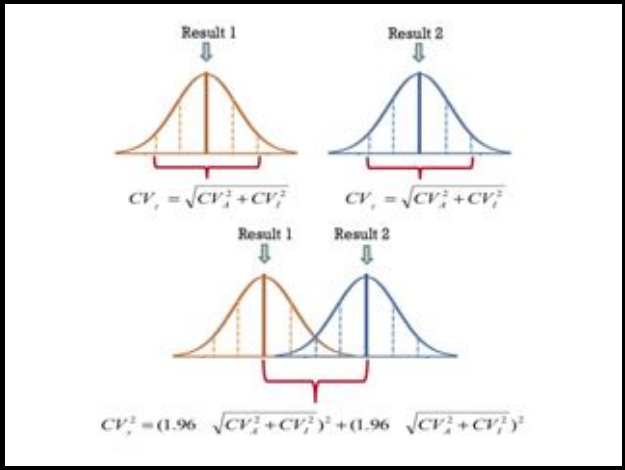
When it is, the CVA has almost no impact on the RCV - the RCV is pretty much determined by the CVI

Reference Change Values

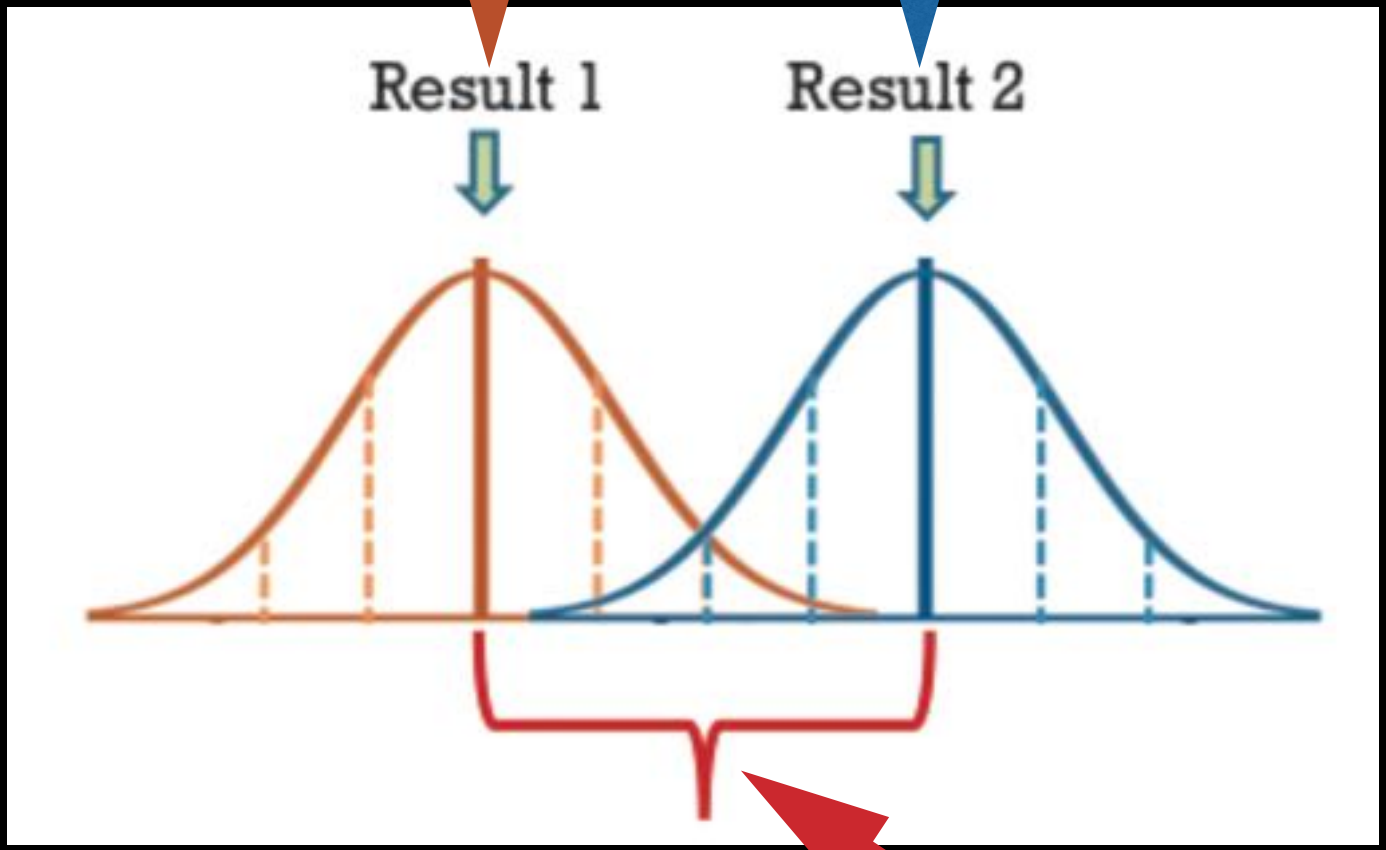
findings of a “significant difference" JUST means we are ruling out that the difference seen is due to chance

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

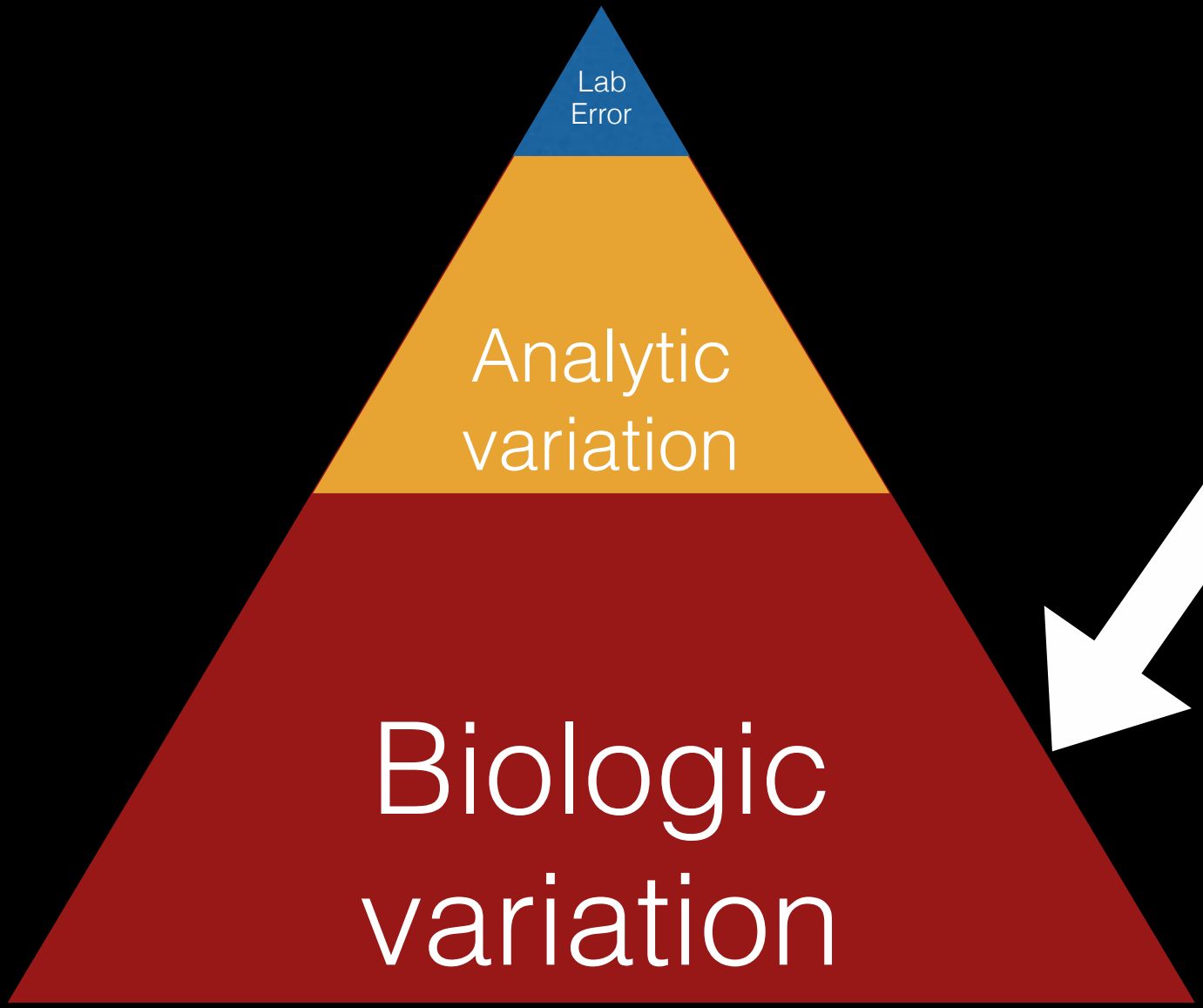
What about multiple measurements?

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



This is the problem and it is NOT fixable, it is only KNOWABLE

“Houston, we’ve had a problem here”

Jack Swigert and James Lovell

Cholesterol
Glucose

Cholesterol

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

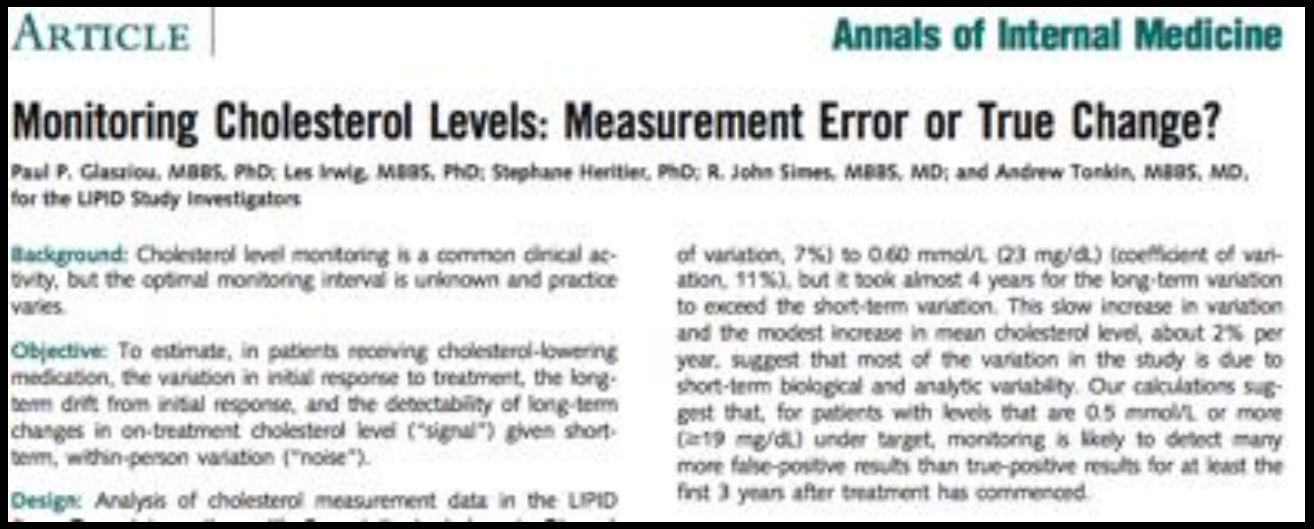
"In individuals with a modified FRS of 5%-9%, yearly monitoring could be used to evaluate change in risk"

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

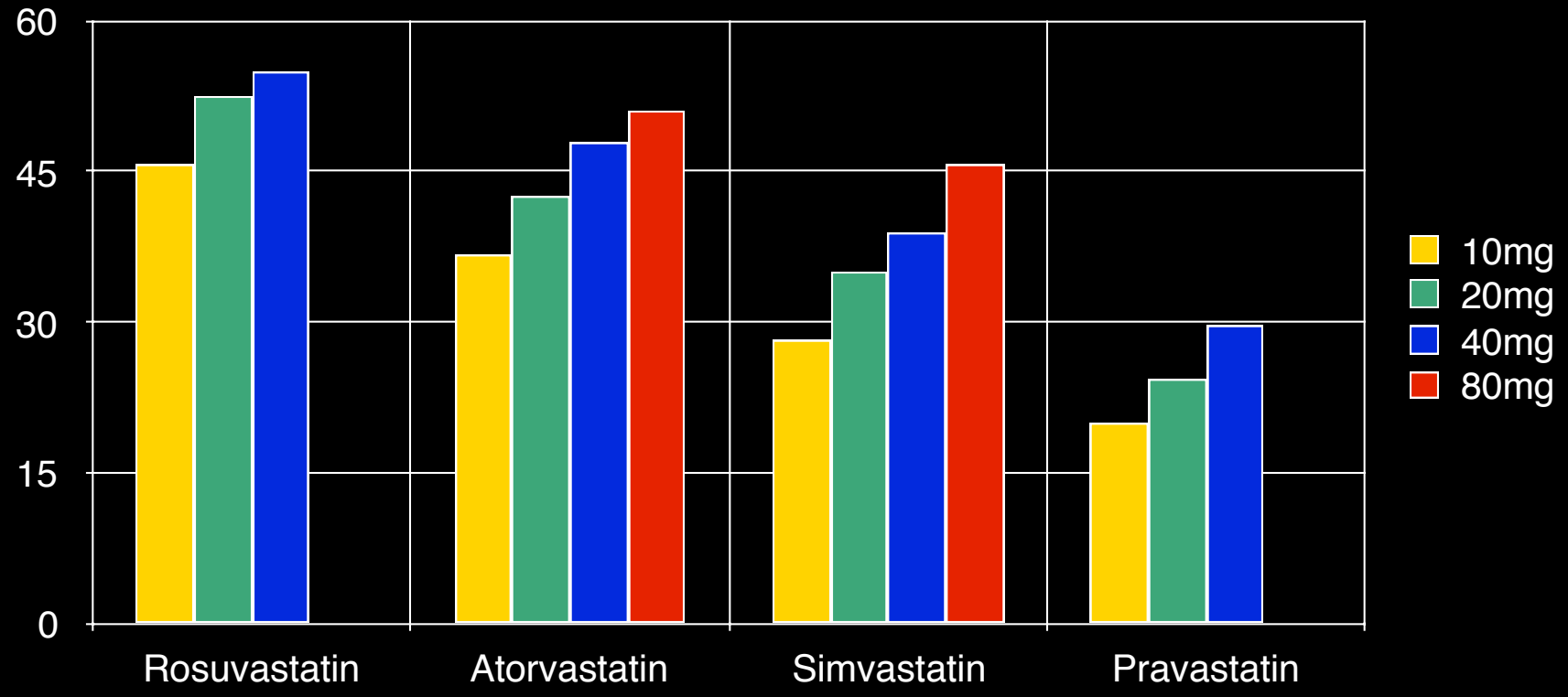
VARIATION
Total chol ~ - 0.80 to 0.80 mmol/L (~30 mg/dL)
LDL chol ~ - 0.5 to 0.5 mmol/L (~20 mg/dL)

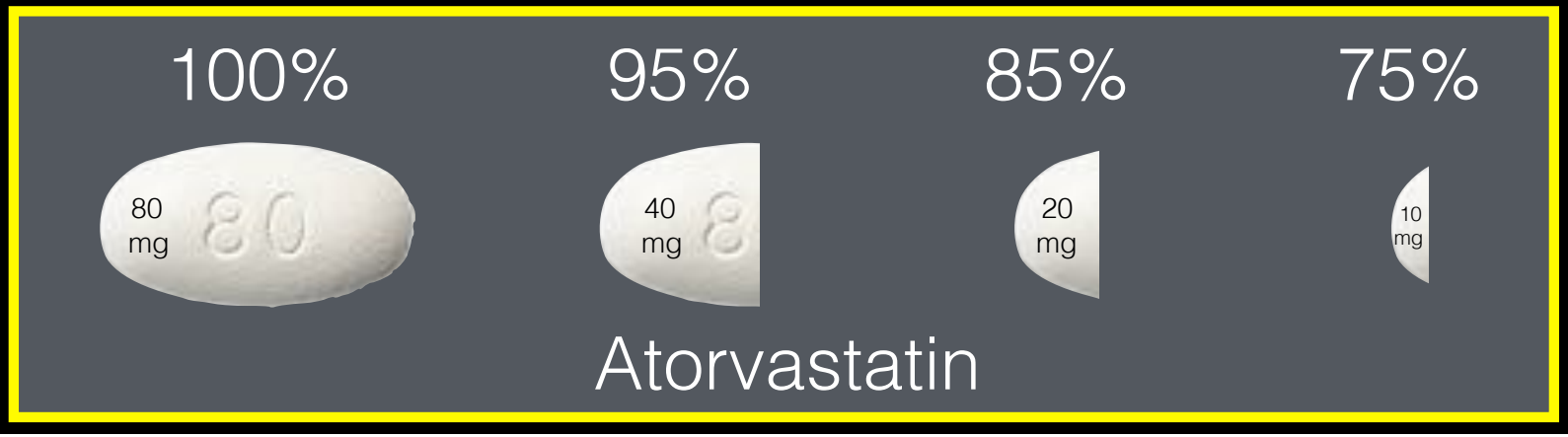
Average increase in cholesterol is 0.5-1%/year

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

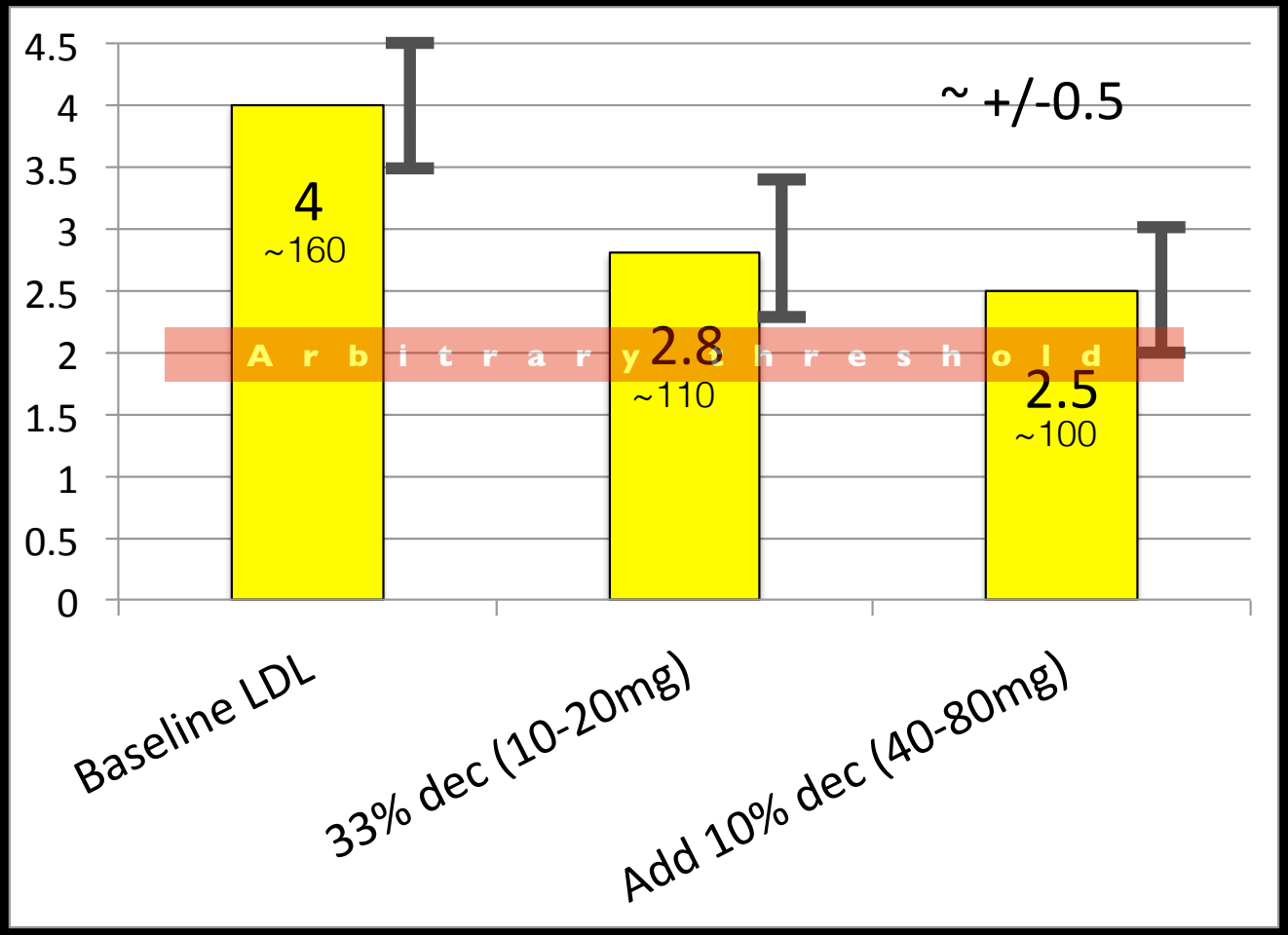
DOSE increases do not lead to proportional EFFECT increases

% 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

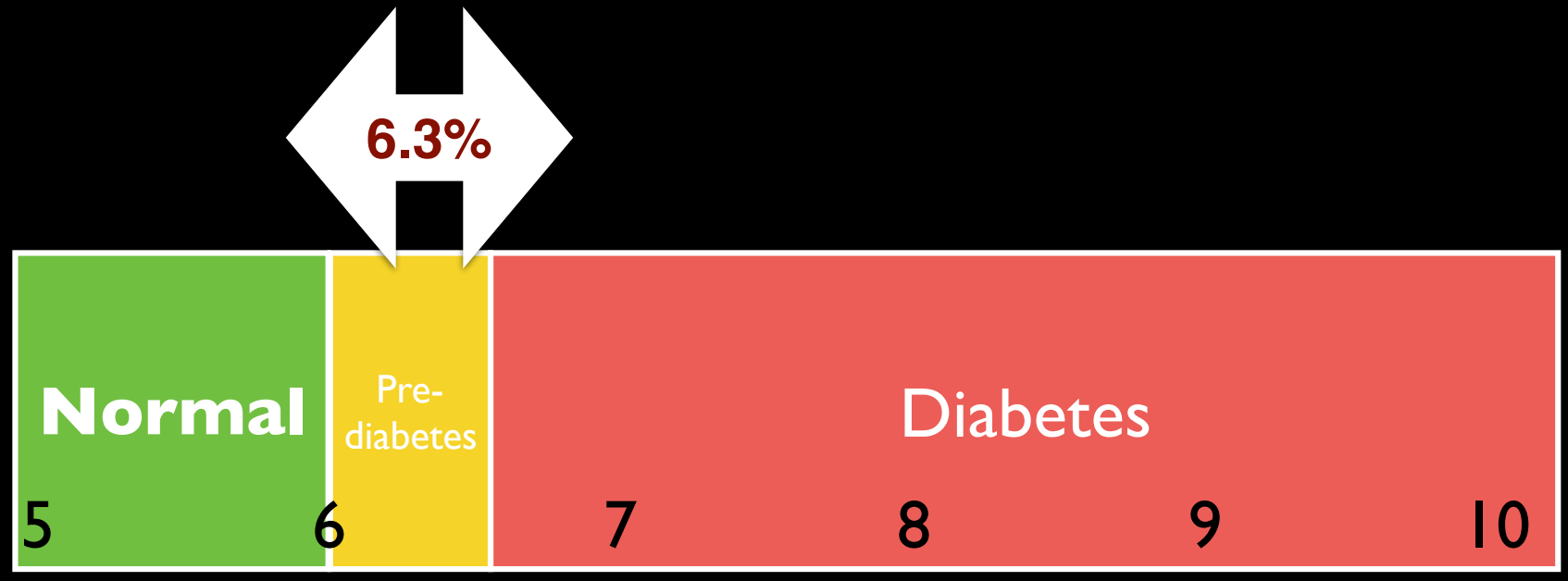
BMJ 2013; 346 doi: http://dx.doi.org/10.1136/bmj.f1895 (Published 3 April 2013)
Cite this as: *BMJ* 2013;346:f1895

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

Glucose

Precisely Imprecise

What an A1c result really means



Typical A1c change seen with a medication = 0.7% ⬇

Seasonal variation 0.2-0.5%
Higher in the winter

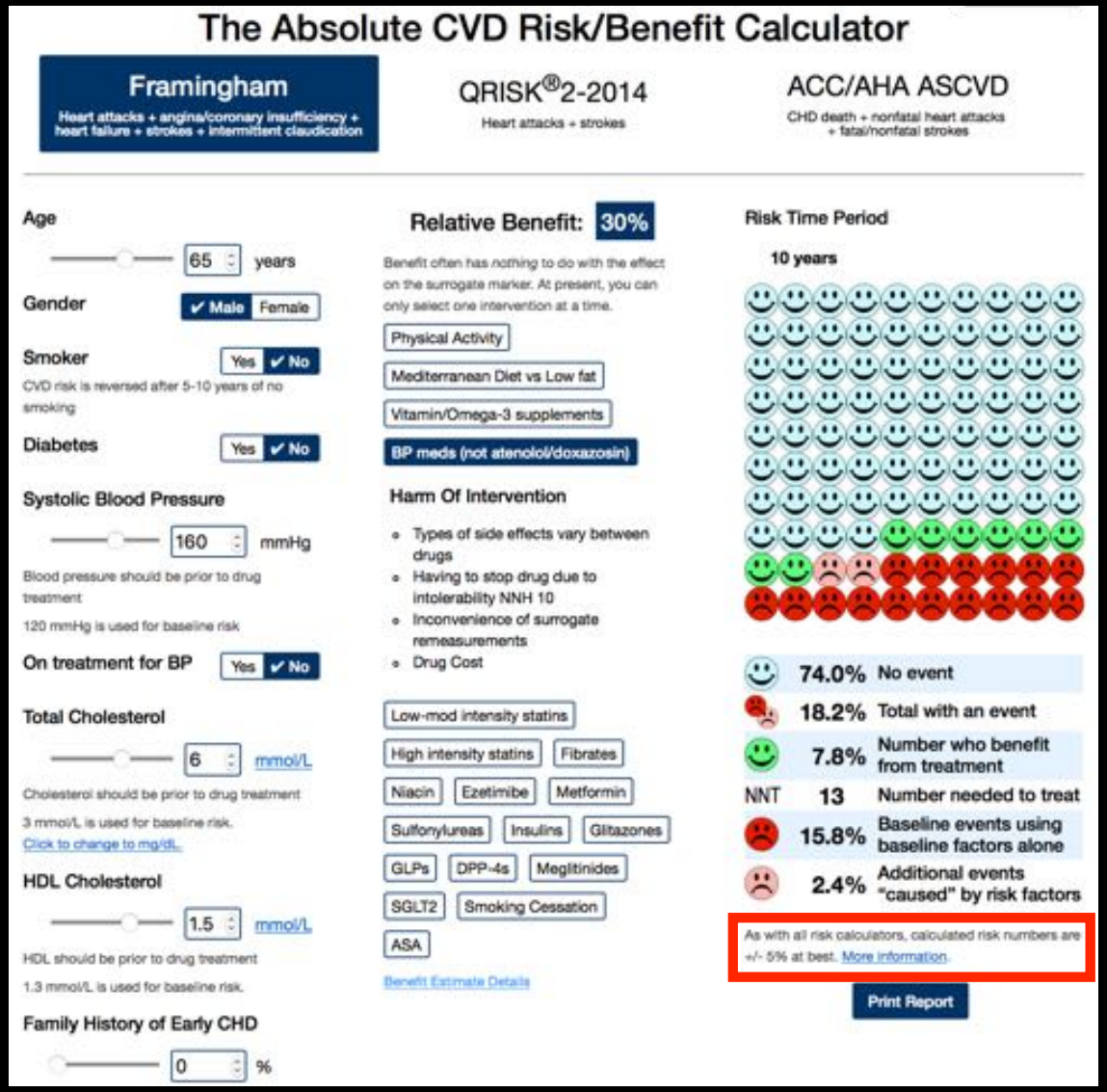
Am J Epi 2004;161:565-74

Yet another IMPORTANT issue for measurements pf 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



1. Calculate ballpark 10-yr risk of CVD - BP, chol, diabetes
2. Make estimate of benefit based on the best available evidence
3. Gives a list of adverse effects to discuss

cvdcalculator.com

Now What?!!

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

Edward R Murrow 1908-1965

The Problem
is
NOT Fixable,
it is
Only
KNOWABLE

Bottom Line

Embrace our “nudity”

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”?

The magnitude of the imprecision around routinely ordered medical measurements*						
MEASUREMENT	Chloride Sodium Osmolality	Albumin Bone density Calcium Hematocrit Hemoglobin HbA1c INR MCH MCV Total protein Systolic BP	Creatinine Globulins Glucose Magnesium pC02 Potassium PTT Total cholesterol T4	AST Alkaline phosphatase BUN HDL LDH LDL Phosphorous Platelets Rheumatoid factor Testosterone Uric acid WBC	GGT Neutrophils PSA Vitamin D	Aldosterone ALT Bilirubin Folate Iron Lactate Triglycerides TSH Vitamin B12
Approximate +/- range for a single measurement	~1-3%	~3-7%	~7-15%	~15-30%	~30-50%	~>50%
The magnitude of the change required between two serial measurements so one can be reasonably confident there has been a change**	~2-5%	~5-10%	~10-20%	~20-40%	~40-60%	~>60%

* based on the analytic and biologic variation

** also known as the reference change value

Data collated primarily from here - https://www.westgard.com/biodatabase1.htm
but some also taken and confirmed from a few other sources - numbers rounded off for ease of use
James McCormack BSc (Pharm), Pharm D - therapeuticseducation.org

~WHAT CHANGE IN HEIGHT CAN YOU PICK UP IF THE "HOM" RCV WAS…

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

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

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

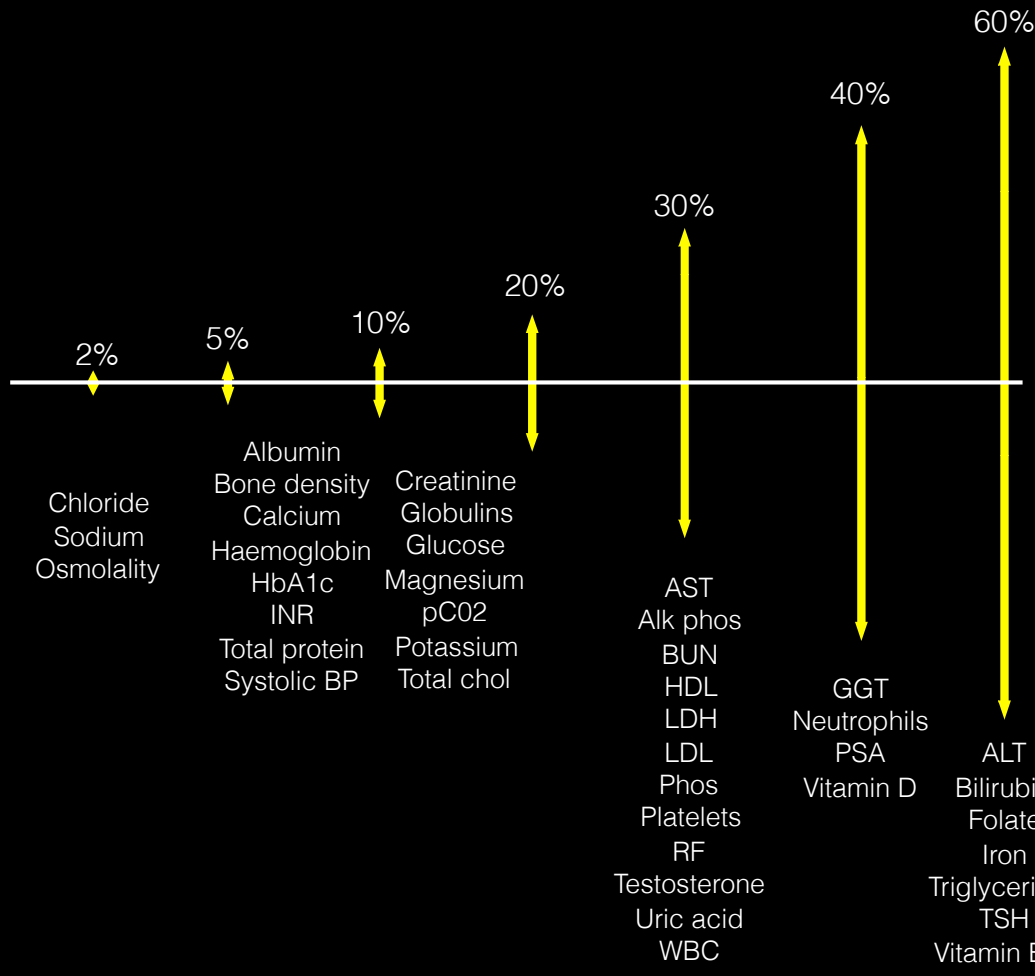
RCV 20% - 5'6"- 6'6"

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

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

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

6' TALL



It’s all about the presentation

Report Details

Close

Patient Information Show More Patient Details

Patient: LLOYD, TESSA JANE ELSWITHA
PHN: [redacted] **Phone:** [redacted] **Lab No:** [redacted]

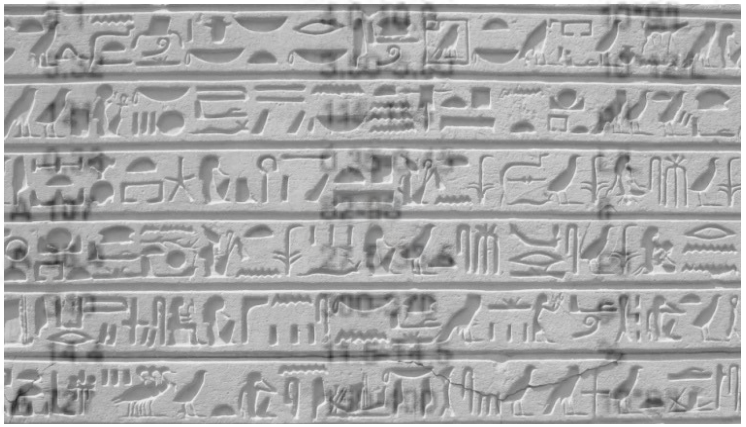
	Flags	Results	Reference Range	Units

General Comments

General Information

This Standing Order will expire on 25-JUN-2017. If this Standing Order is still required, please provide your patient with a new laboratory requisition prior to this date.

Hematology



Differential

Report Details

Close

Patient Information

Show More Patient Details

Patient: LLOYD, TESSA JANE ELSWITHA

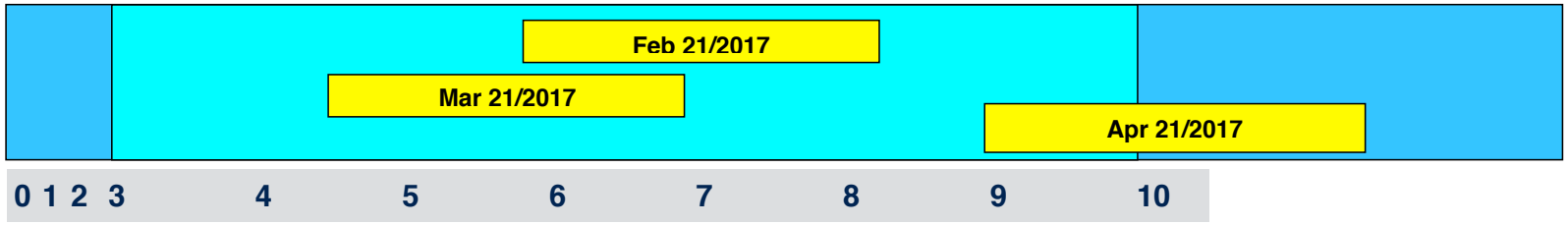
PHN: [redacted] Phone: [redacted] Lab No: [redacted]

	Flags	Results	Reference Range	Units

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

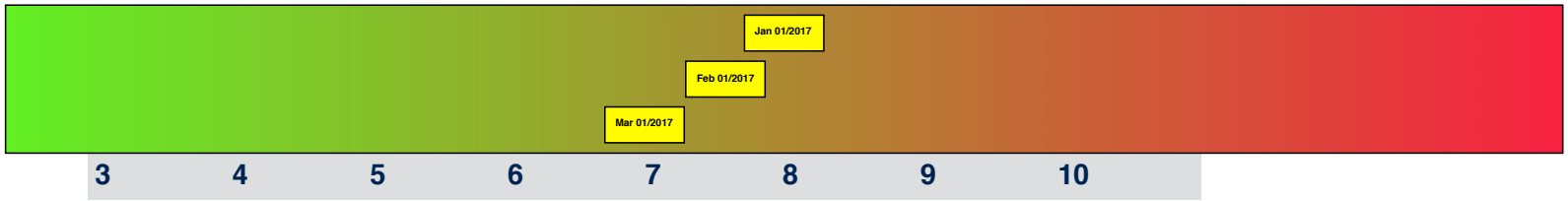
YOUR TRUE RESULTS ARE LIKELY SOMEWHERE IN THE RANGE INDICATED BY THE YELLOW STRIP

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

When someone does something wrong, don't forget all the things they did right.