



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

REPORTING
'lab' results

The Cause of, and
the Solution to

the Overdiagnosis
Problem

You can find a pdf of the handouts at
<http://therapeuticseducation.org/handouts>

Objectives

- 1) outline the problem of lab test measurement and reporting and some of the ways it contributes to the overdiagnosis problem
- 2) demonstrate with some examples (BP, LDL, glucose, bone density)
- 3) hopefully offer some useful tips, and suggestions and simple charts for how to deal with this extremely important and relevant healthcare conundrum
- 4) INTERACTIVE
Poll questions - internet access
Play with dice - work through a few scenarios



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

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

“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

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 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

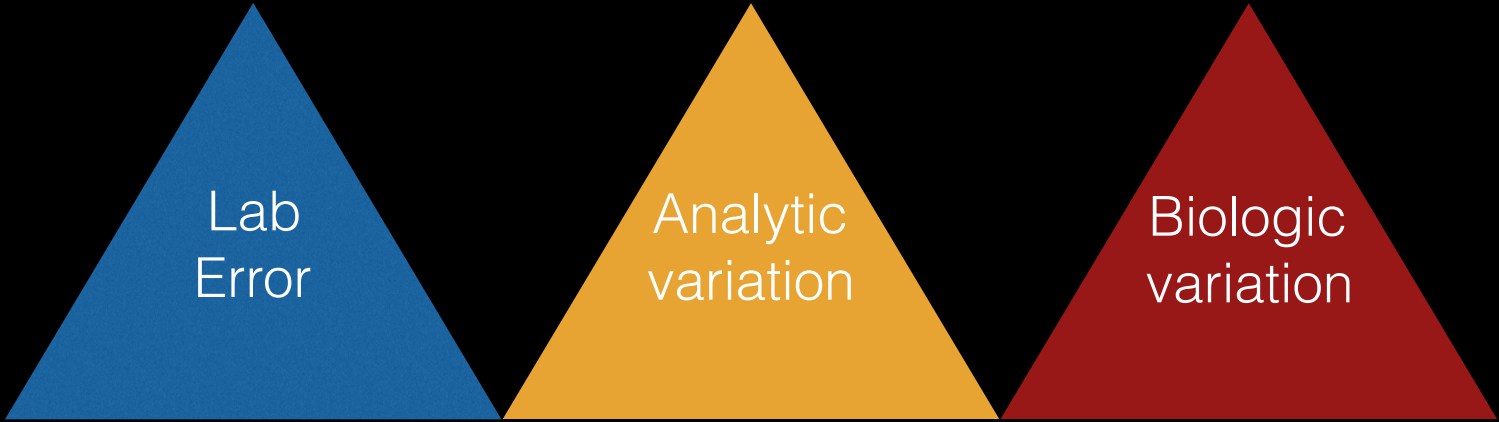
BELIEF #1 - the good/bad thresholds are relatively black and white

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



Lab
Error

Analytic
variation

Biologic
variation

Actual LAB errors

0.3%

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



Lab
Error

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

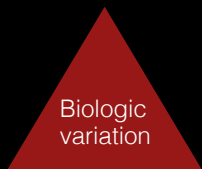
Assuming no pre-analytic issues - timing/labelling etc

Population-based reference intervals



Analytical Variation

CVA - analytical variation



Biological Variation

CVI - within subject

CVG - between subject

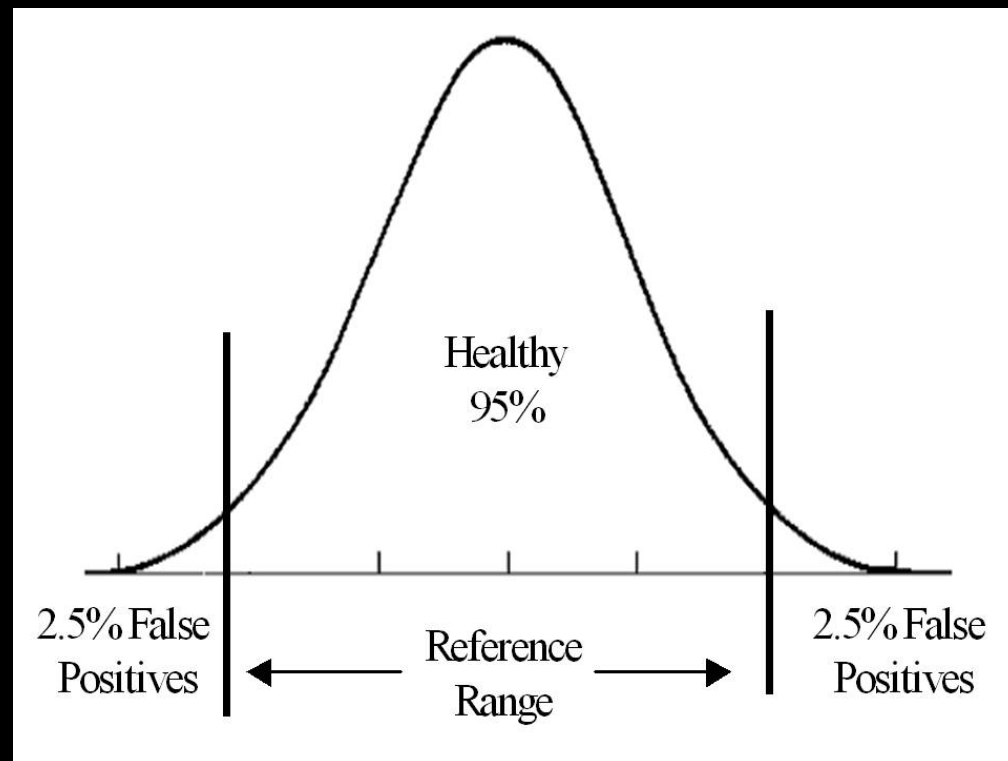


Reference change values (RCV)

Population-based reference intervals

Population-based reference intervals

The interval/range where 95% of healthy people fall

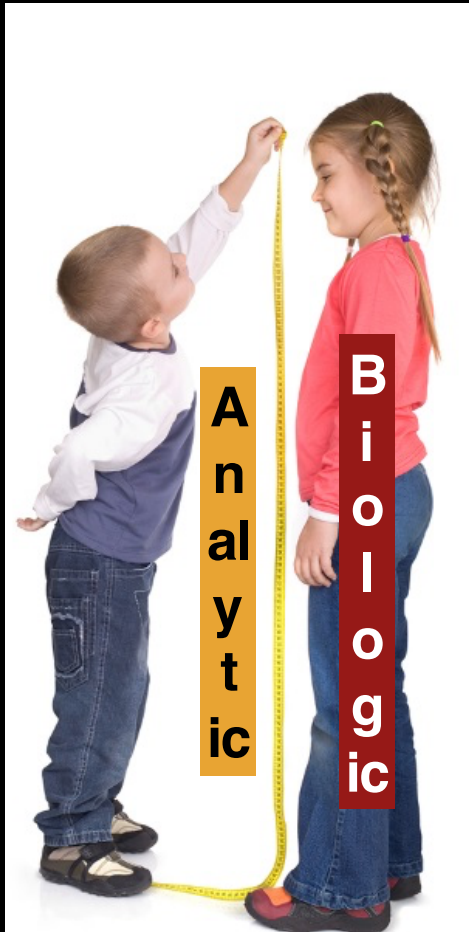


Lab results report
exact numbers
BUT
Every test result is
really only a range
that hopefully includes
the true result
*+/- 1-2% up to
+/-20-30% or more*

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

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

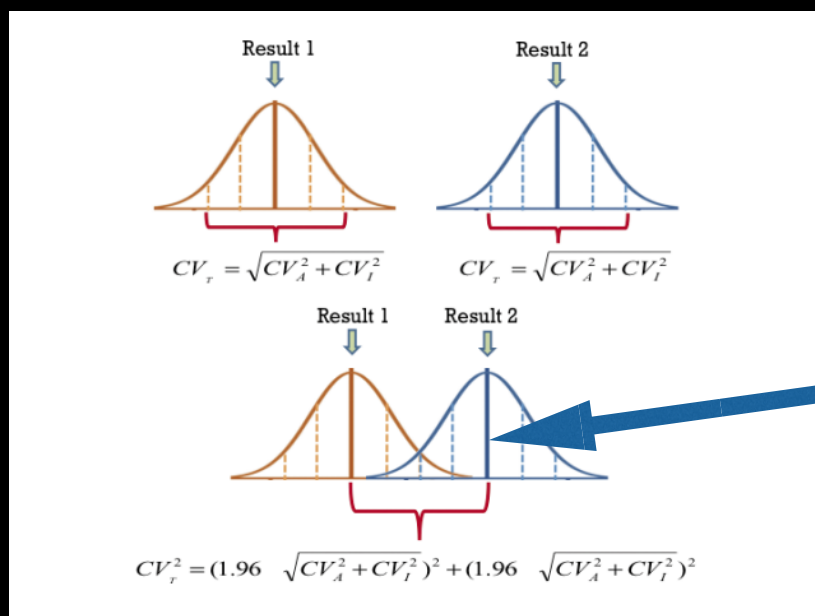
Reference Change Values (RCV)

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

Reference Change Values

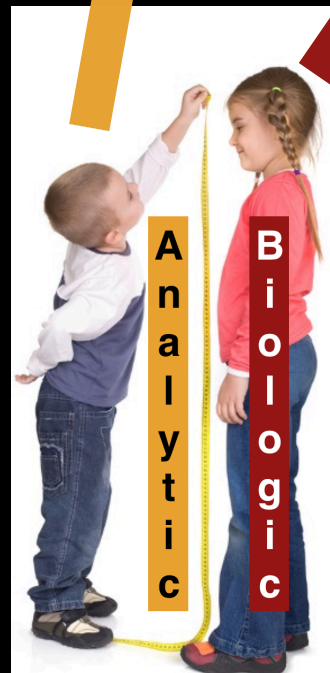
Used with SERIAL results to help deal with the analytic imprecision and **biologic variation**

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

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



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

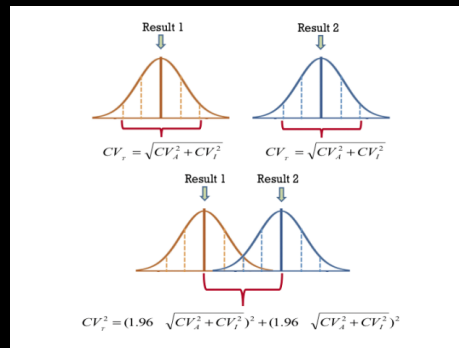


Reference Change Values

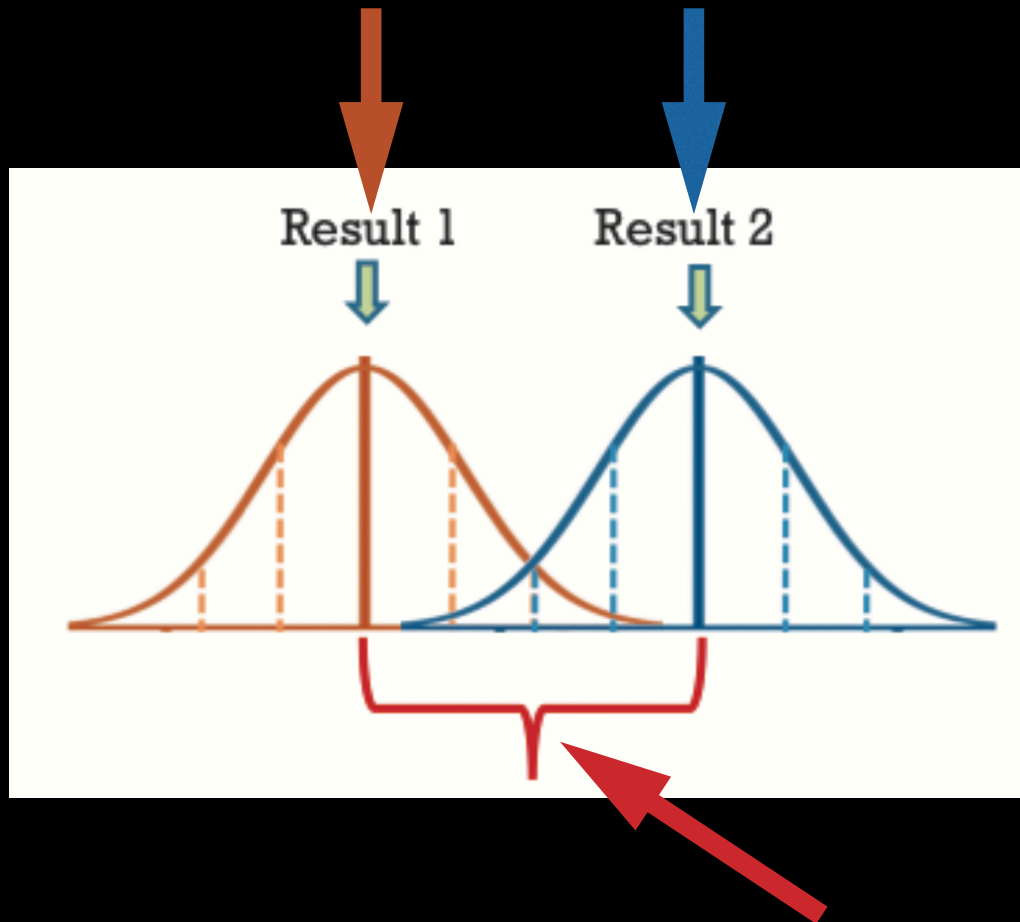
findings of a “significant difference” JUST means we are ruling out that the difference seen is due to chance

NOT

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



We believe these two results are different



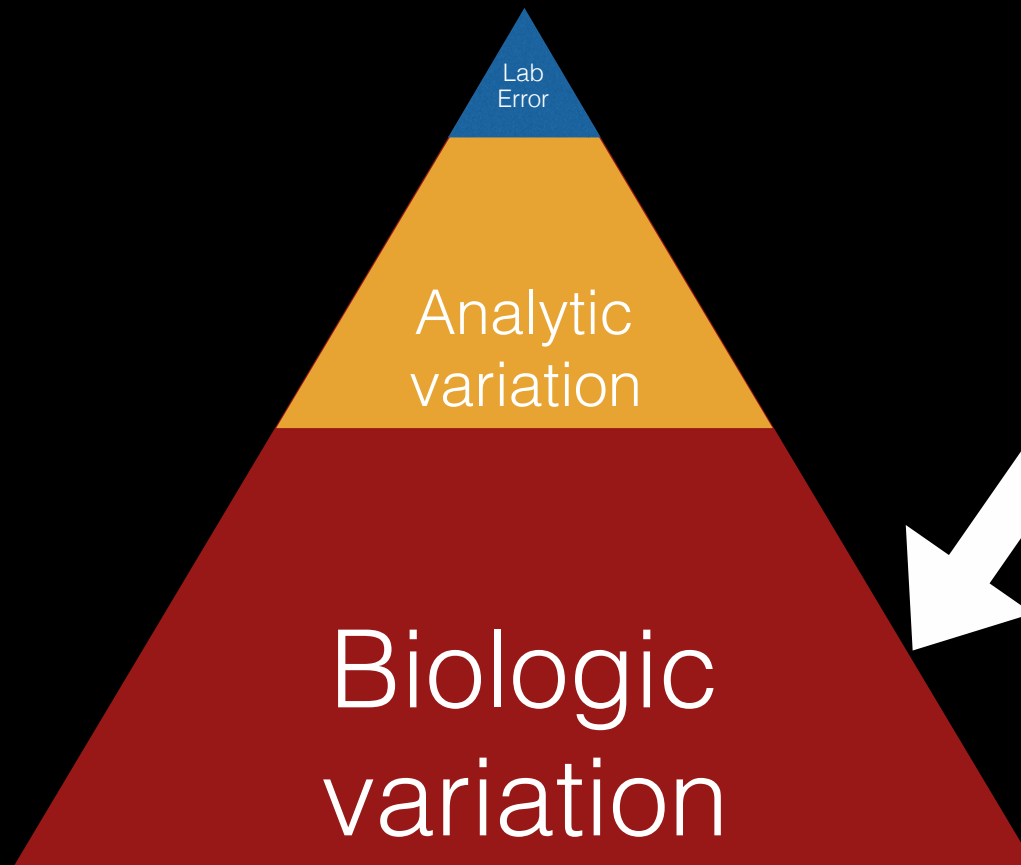
can't necessarily quantify this difference with any precision

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%



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

Glucose

~~X~~Blood pressure~~X~~

Cholesterol

~~X~~Bone Density~~X~~

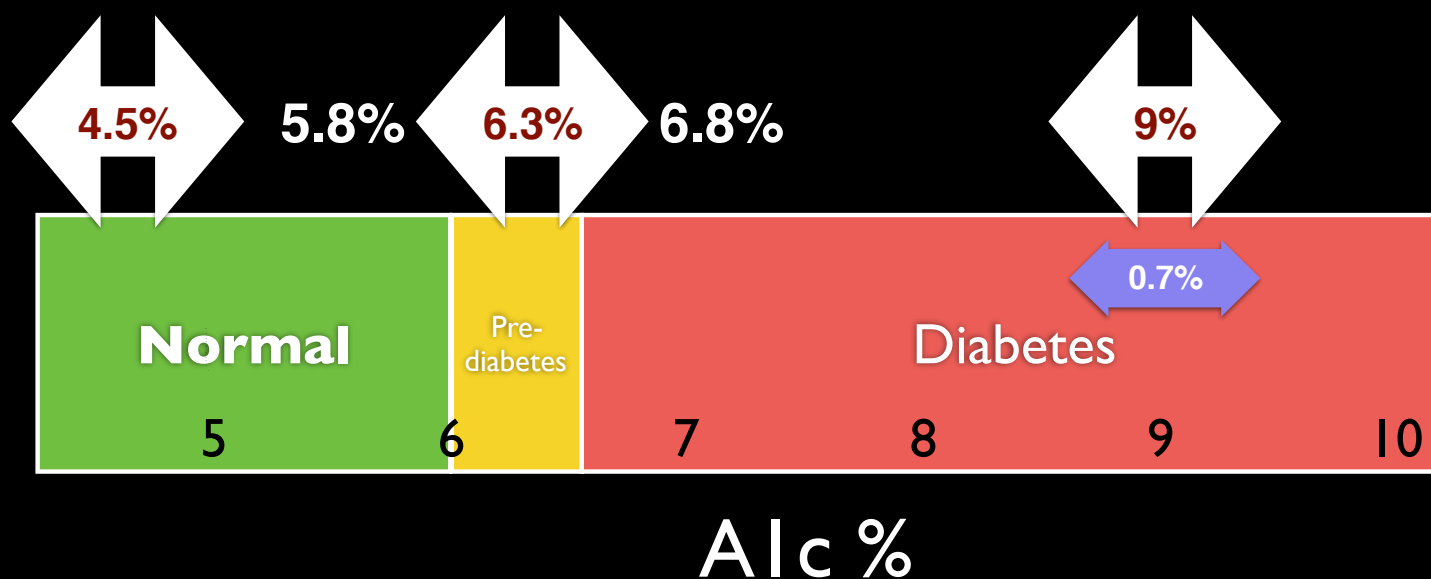




Glucose

Precisely Imprecise

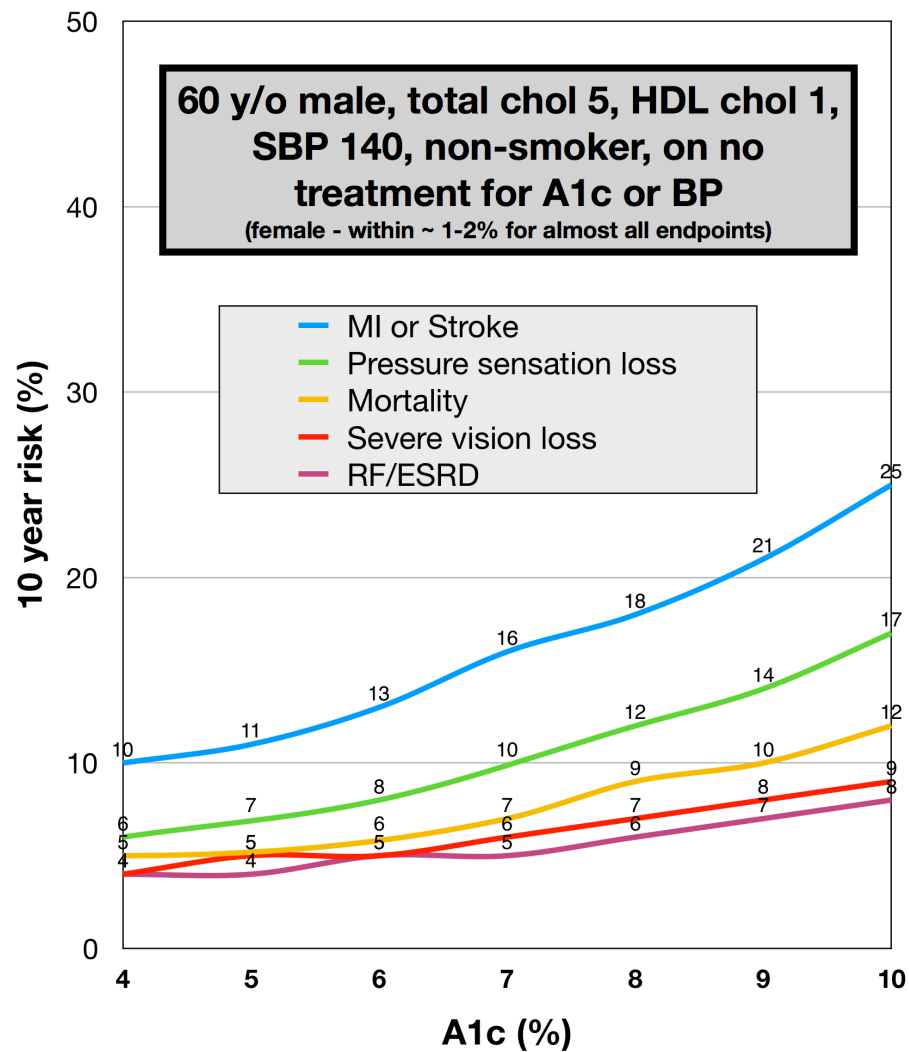
What an A1c result really means



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



T2DM risk
should not
be
categorized
as
YES
or
NO

<https://sanjaybasu.shinyapps.io/recodesi/> - from the ACCORD study



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**”

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

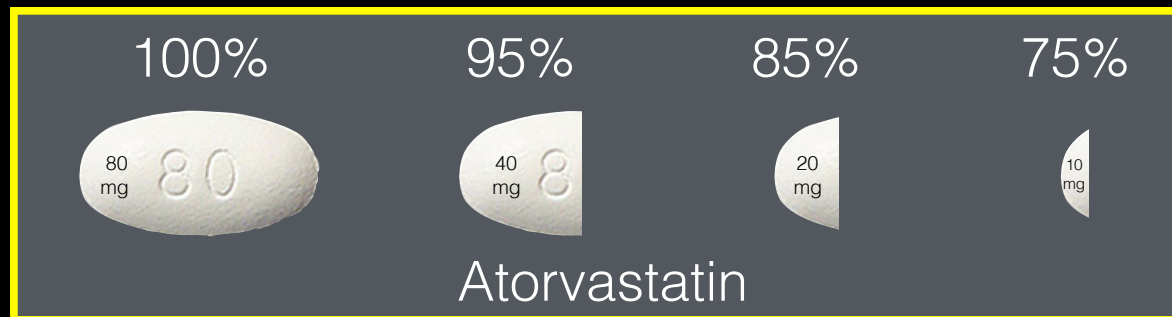
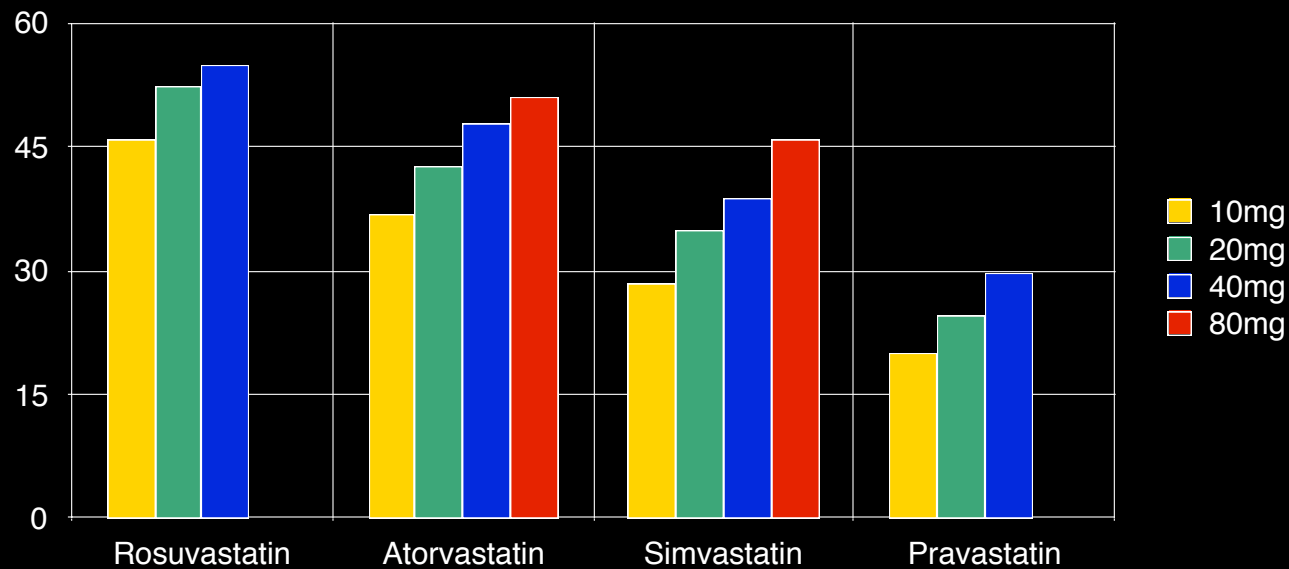
Total chol ~ - 0.80 to 0.80 mmol/L (~30 mg/dL)

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

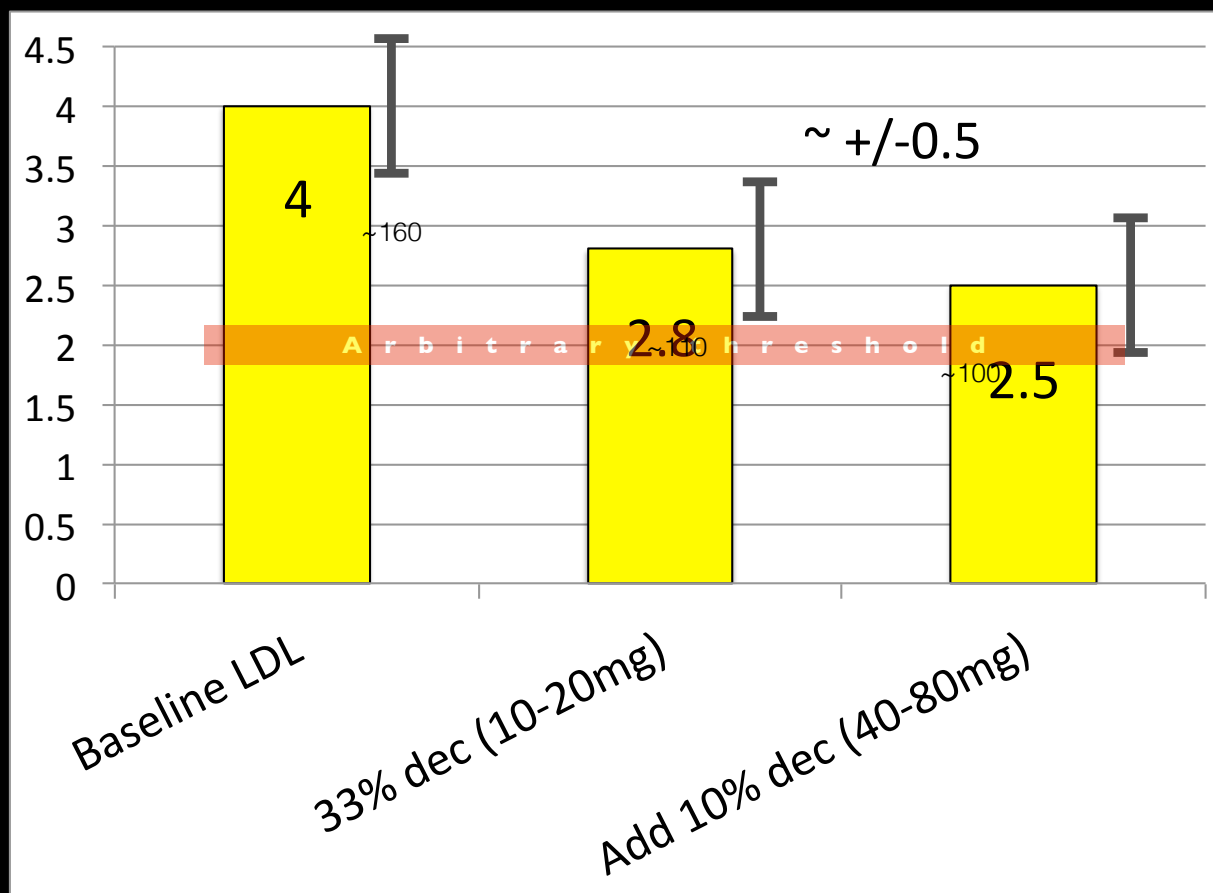
Average increase in cholesterol is 0.5-1%/year

“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”

Languages: English (EN)

The Absolute CVD Risk/Benefit Calculator

Framingham
 US Data, 10 Year Risk
Heart attacks + angina/coronary insufficiency + heart failure + strokes + intermittent claudication

QRISK®2-2014
 UK Data, 10 Year Risk
Heart attacks + strokes

ACC/AHA ASCVD
 US Data, 10 Year Risk
CHD death + nonfatal heart attacks + fatal/nonfatal strokes

PREDICT
 New Zealand Data, 5 Year Risk
Heart attacks + angina + heart failure + strokes/TIAs + peripheral vascular disease

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
Enter present blood pressure regardless of treatment
120 mmHg is used for baseline risk

On treatment for BP
☐ Yes ☒ No
Click YES if taking blood pressure medication
Only applies if SBP is greater than 120 mmHg

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.

Chronic Kidney Disease
☐ Yes ☒ No
CKD status is not part of the risk algorithm but is used for calculating the benefit of certain therapies

Relative Benefit: 0%
Benefit often has nothing to do with the effect on the surrogate marker. At present, you can only select one intervention at a time.[Benefit Estimate Details](#)

Risk Time Period
 10 years

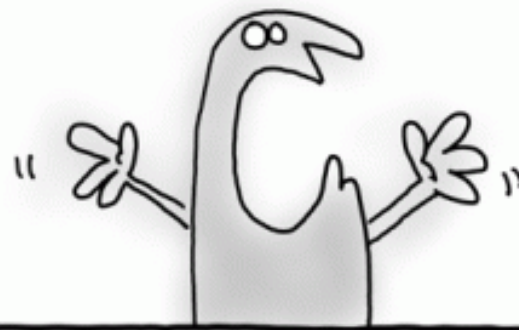
97.9%	No event
2.1%	Total with an event
0.0%	Number who benefit from treatment
NNT ∞	Number needed to treat
2.1%	Baseline events using baseline factors alone
0.0%	Additional events "caused" by risk factors

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

1. Calculate ballpark 5/10-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 Problem
is
NOT Fixable,
it is
Only
KNOWABLE

Bottom Line



Embrace our “nudity”

Magnitude of the Imprecision Around Routinely Ordered Medical Measurements*

	Chloride Sodium Osmolality	Calcium Protein Bone density Hemoglobin A1 C Albumin Systolic BP	Magnesium Glucose Potassium pCO2 Cholesterol Creatinine Alk phos PTT	LDL HDL INR Total Cholesterol Phosphate LDH Uric acid Rheumatoid factor Testosterone	AST GGT Vitamin D BUN	Vitamin B12 ALT TSH Triglyceride Bilirubin total Iron Folate Lactate
SINGLE MEASUREMENT +/- range*	~1-3%	~5-7%	~8-14%	~15-25%	~26-30%	~40-50%
SERIAL MEASUREMENTS Change required**	~2-5%	~6-10%	~11-20%	~21-30%	~35-45%	~50-75%

* based on the analytic and biologic variation

** also known as the reference change value

REVISED

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

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”?



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

Lab Value thoughts

- have you first looked at how the patient is clinically doing?
- will the result of your test change what you would do?
- does a “risk factor” test improve your assessment of risk?
- how big a change do you expect from your treatment?
- what is the sensitivity and specificity of the test? - pre-test and post-test probability
- how long does that change take?
- how big a change is needed to be confident a change has occurred?



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