

## GUIDELINES

What would guidelines look like if they were written by people:

- 1) who will be using them
- 2) with no industry conflicts

### Simplified lipid guidelines

### Prevention and management of cardiovascular disease in primary care

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Can Fam Phy 2015;61:857-67

#### Thresholds for discussion NOT thresholds for treatment

CLINICAL PRACTICE GUIDELINES

# Simplified guideline for prescribing medical cannabinoids in primary care

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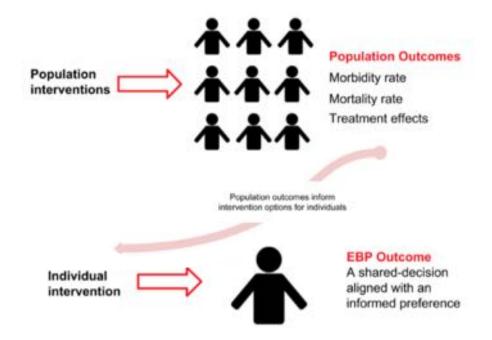
Can Fam Phy 2018;64:111-120



Shared decision is the only outcome that matters when it comes to evaluating evidence-based practice

James McCormack, Glyn Elwyn2

"in the vast majority of circumstances, the only outcome of relevance for EBP is to measure whether a shared decision was made"



doi:10.1136/bmjebm-2018-110922

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

	Solely of	partially lab	-Daseu de	pendent	
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 Acute DIC	CFS CHF	Gastroenteritis Gluten-Sensitive Enteropathy	Iron Overload Disease Iron Storage Disease	Non-Hodgkin lymphoma Non-Small Cell Lung Cancer	Spinal Meningitis SSc
Acute Idiopathic Polyneuritis	Chlamydia 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-Resis
Acute Renal Failure	Chronic Thyroiditis	Guillain-Barré Syndrome	Keratoconiuntivitis Sicca	Obesity Syndrome	Staphylococcus aureus
AD	Circumscribed Scleroderma	H1N1	Kidney Disease	Osteoarthritis	Staphylococcus aureus
Addison Disease	Cirrhosis	H3N2	Lactase Deficiency	Osteoarthrosis	STDs
Adrenal Insufficiency	CKD	H5N1	Lactose Intolerance	Osteoporosis	Stein-Leventhal Syndrome
renal 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 Allergies	Community-Acquired Pneumonia Congenital Adrenal Hyperplasia	Healthcare-Associated Pneumonia Heart Attack	Limited Cutaneous Scleroderma Linear Scleroderma	Pancreatic Insufficiency Pancreatitis	Subacute Cutaneous Lupus 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 Disea
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
Angiitis	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 Atypical Mycobacteria	Disaccharidase Deficiency Discoid Lupus	HIV Infection and AIDS HI	Meningitis and Encephalitis Meningococcal Meningitis	Primary Aldosteronism Primary Hyperaldosteronism	Types of Liver Disease Ulcerative Colitis
Atypical Mycobacteria  Atypical Pneumonia	Disseminated Intravascular Coagulation	Hodgkin Disease	Menopause	Prinzmetal's angina	Unstable angina
Autoimmune Diseases	Disseminated Intravascular Coagulation  Disseminated Intravascular Coagulopathy	Hodgkin Lymphoma	Metabolic Syndrome	Prostate Cancer	Urinary Tract Infection
Autoimmune Thyroiditis	Disseminated Intravascular Coagulopatiny  Disseminated Lupus Erythematosus	Hospital-Acquired Pneumonia	MG	Protein in urine	UTI
Avian Flu	D.JD	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 Deficiencie
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	Myelocele	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	Myelomeningocele	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	

Neonatal Lupus

Sjögren Syndrome

Influenza B

Celiac Disease

Folate Deficiency

"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

## 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

The Industry

YOU

### 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"

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

I am presenting concepts

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

0.3% CV~1-5%

CV~1-25%

~60% pre-analytical

~15% analytical

~ 25% post analytical

## 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

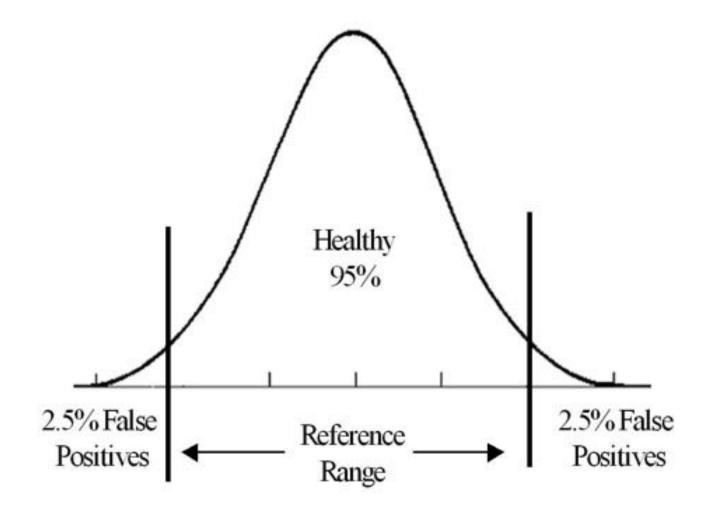


Reference change values (RCV)

# Population-based reference intervals

### Population-based reference intervals

The interval/range where 95% of healthy people fall



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



YOU CANNOT BE SERIOUS!!
That ball was on the line

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:

what are the results NOW, and/or

have they changed from PREVIOUS measurements



Analytic variation

Biologic variation

Every "measurement" will be "different"

Analytic variability Biologic variability

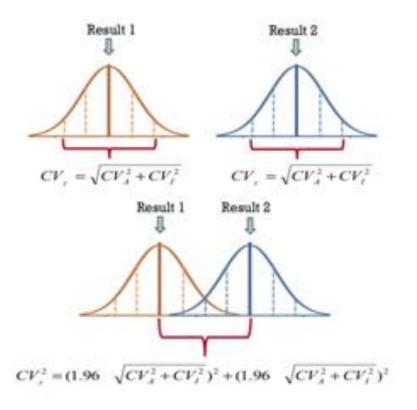
# Reference Change Values (RCV)

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 provide a "p-value" for the differences between two measurements



"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

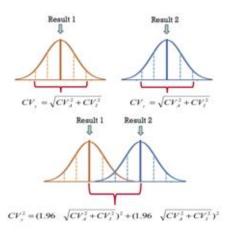
BY TOM SIEGERIED 10:30AM, MARCH 11, 2016

## Reference Change Values

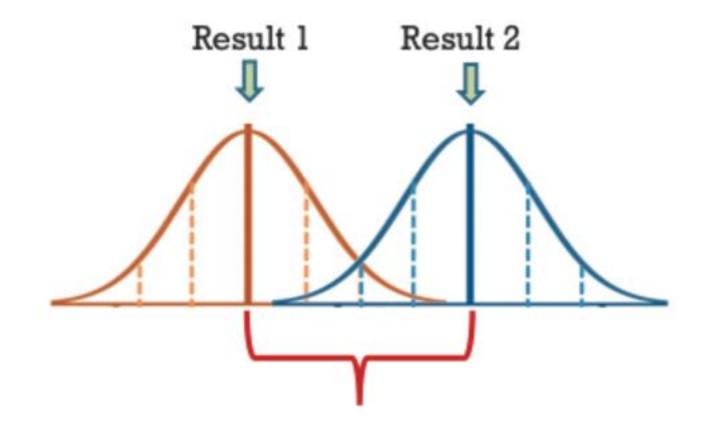
findings of a "significant difference" JUST means we are ruling out that the difference seen is due to chance

### 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	1	1.00	0.87	0.82	0.79	0.77
estimating new set point	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% Lab Error

Analytic variation

# Biologic variation



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

Bone Density
Cholesterol
Blood pressure
Glucose
Vitamin D





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 Heritler, 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 (i=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

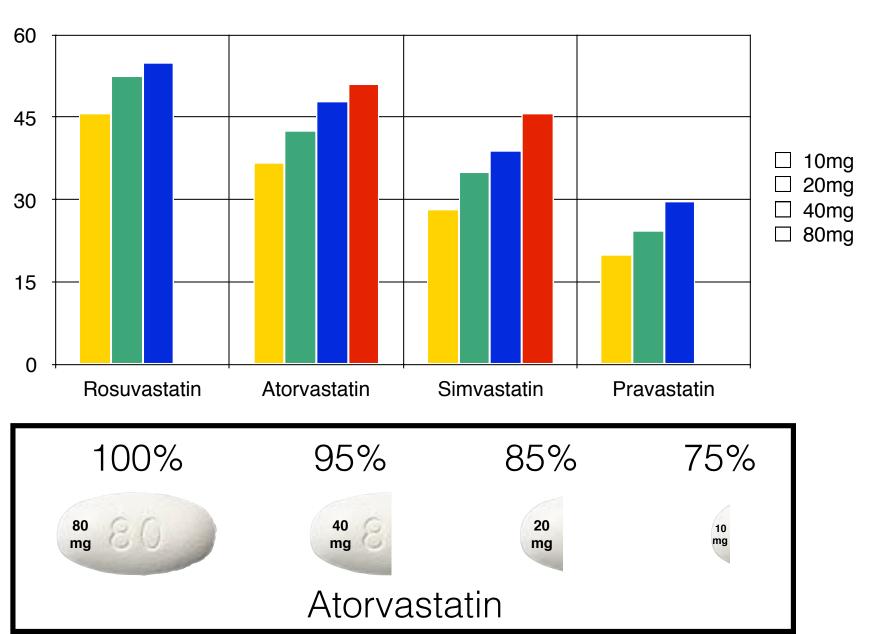
Total chol ~ - 0.80 to 0.80 mmol/L (~30 mg/dL) LDL chol ~ - 0.5 to 0.5 mmol/L (~20 mg/dL)

Average increase in cholesterol is 0.5-1%/year

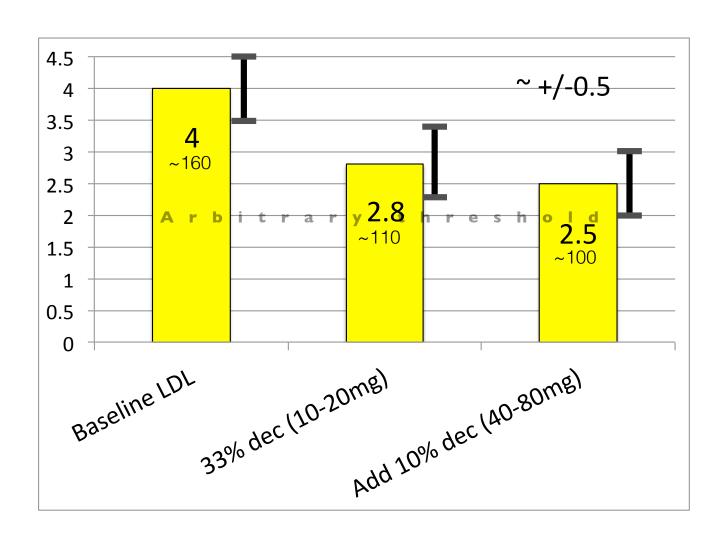
"After initial change only measure every 3-5 years"

# 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

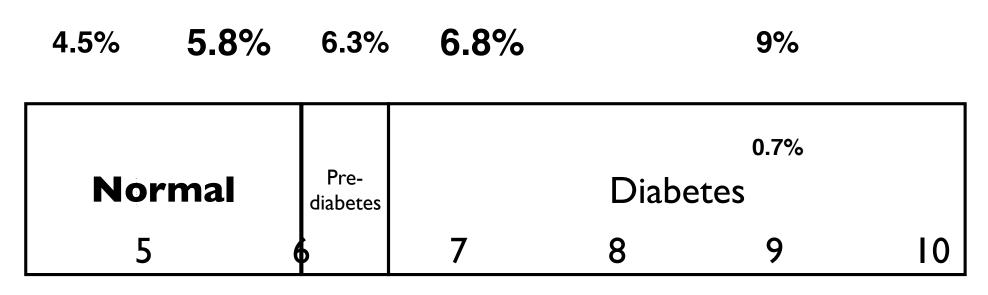
"Repeat risk estimation before 8-10 years is not warranted for most people initially not requiring treatment"



Glucose

# Precisely Imprecise

What an A1c result really means



Alc%

Typical A1c change seen with a medication = 0.7% ■

Seasonal variation 0.2-0.5% Higher in the winter

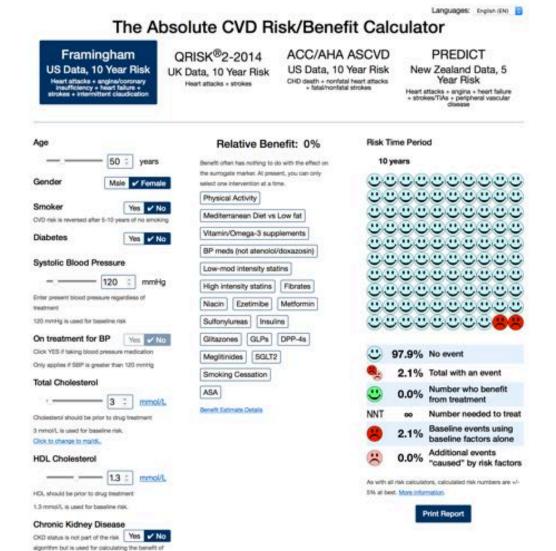
Am J Epi 2004;161:565-74

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

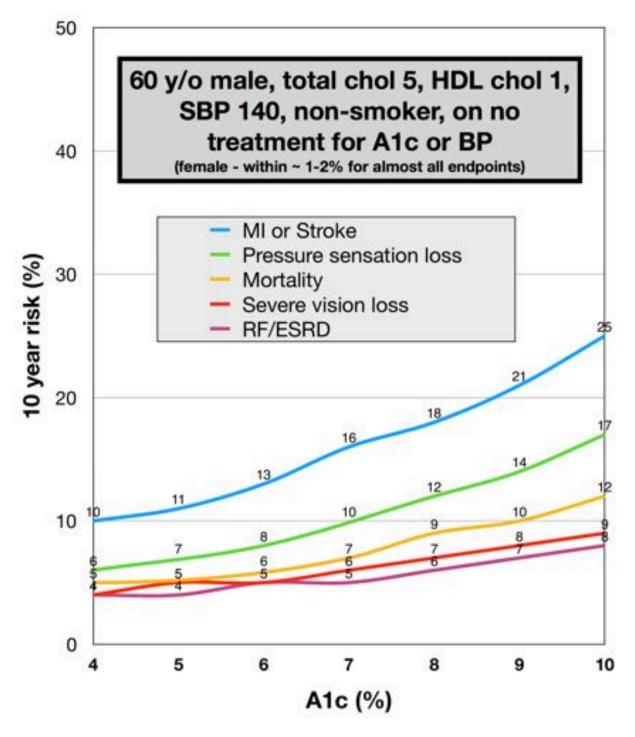
They should be presented in the context of the risk of developing important clinical outcomes - heart attacks, strokes, ESRD etc



certain therapies

Calculate ballpark 5/10yr risk of CVD - BP, chol, diabetes Make estimate of benefit based on the best available evidence Gives a list of adverse effects to discuss

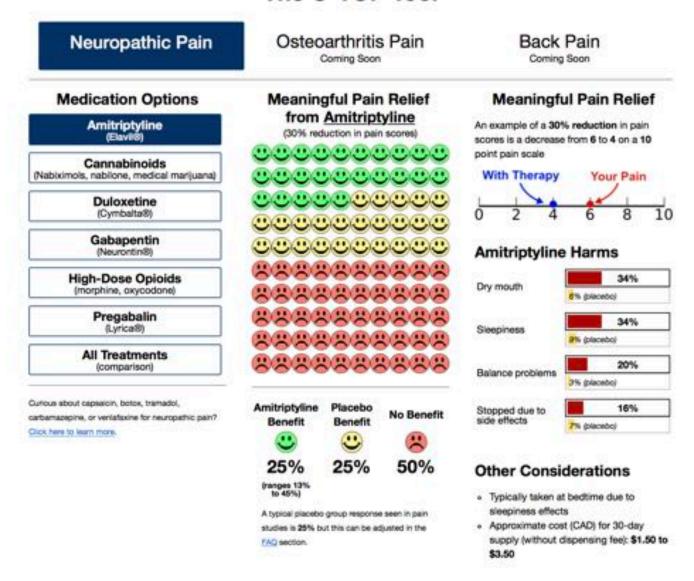
### <u>cvdcalculator.com</u>



T2DM risk should not be categorized as YES or NO

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

#### Comparing Treatment Options for Pain: The C-TOP Tool



pain-calculator.com

## "The obscure we see eventually. The completely obvious, it seems, takes longer."

Edward R Murrow 1908-1965



The Problem İS NOT Fixable, it is Only KNOWABLE

## 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%

<sup>\*</sup> based on the analytic and biologic variation

\*\* also known as the reference change value



Data collated primarily from here - <a href="https://www.westgard.com/biodatabase1.htm">https://www.westgard.com/biodatabase1.htm</a> 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.