LESS IS MORE

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MORE OR LESS

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

therapeuticseducation.org
medicationmythbusters.com

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


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

Pharmacotherapy 2000;20:1524-7
“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
“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.”

All Health Care Providers should have their practice underpinned by the best available evidence
Evidence-based practice is a way of thinking that uses best available evidence in a hierarchical way to answer clinical questions. It's not about guidelines, as they are merely recommendations and do not fit into boxes. It's not about saving money; rationing is not the motive. It's not about ignoring basic science; we need to understand how it works.

It's not about checkbox medicine, where people don't fit into boxes. It's not about something new, as doing the right thing is not a new idea. It's not about RCTs, as they are useful but only help inform decisions based on p-values. It's not necessarily about influencing outcomes, as heart attacks, strokes, renal failure, symptoms, and quality of life are affected.

In summary, evidence-based practice is simply doing the right thing and informing patients while eliciting and integrating preferences.
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
Intervention
Comparator
Outcome

BEST AVAILABLE EVIDENCE PYRAMID

Systematic review/meta-analysis
RCT
Cohort
Case Control
Case Report
“Expert” Opinion

USING CLINICAL EXPERTISE

Diagnostician
Knowledge Broker
Communicator
Being Kind & Careful

INFORMING PATIENTS & ELICITING & INTEGRATING PREFERENCES
“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!
“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, Nicola Montano, Monica Minardi, James Doyle, Paolo Cavagnaro, Antonino Cartabello\textsuperscript{a}

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

EBM 2017;22:1-3
Most targets in guidelines are arbitrary and rarely if ever based on a discussion of the balance of benefits and harms.

Aren't they taking target shooting a bit too far?
<table>
<thead>
<tr>
<th>Year</th>
<th>Major therapeutic advance</th>
<th>Clear advantage</th>
<th>Modest improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2012</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>abiraterone (prostate CA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>boceprevir (Hep C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>meningococcal conjugate vaccine (infant immunization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cholic acid (hereditary bile acid deficiency)</td>
<td></td>
<td>sodium phenylbutyrate coated granules (urea cycle disorders)</td>
</tr>
<tr>
<td></td>
<td>imatinib (ALL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>artesunate (malaria)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sofosbuvir (HepC) conjugate vaccine (infant immunization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>propranolol (severe infantile hemangioma)</td>
<td></td>
<td>permethrin (scabies) ketoconazole HRA (endogenous Cushing’s syndrome)</td>
</tr>
<tr>
<td>2016</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>nivolumab (inoperable melanoma)</td>
<td></td>
<td>trametinib (inoperable melanoma)</td>
</tr>
</tbody>
</table>
Many courts (UK, US, CA)

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

JAMA 2016;315:2063-4
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
“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

Clinical Chemistry 2007;53:1338-42

Dispensing errors ~1-2%
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
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

<table>
<thead>
<tr>
<th>Number of Tests Ordered</th>
<th>Probability of at Least One Abnormal Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td>5</td>
<td>23%</td>
</tr>
<tr>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td>15</td>
<td>54%</td>
</tr>
<tr>
<td>20</td>
<td>64%</td>
</tr>
</tbody>
</table>

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

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

\[ CV_r = \sqrt{CV_i^2 + CV_j^2} \]

MINIMUM DIFFERENCE between two consecutive results which needs to be EXCEEDED in order for one to state a STATISTICALLY SIGNIFICANT change has taken place.
\[ RCV = \sqrt{2} \times 1.96 \times \sqrt{CV_{\text{Analytical}}^2 + CV_{\text{Intraindividual}}^2} \]
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.”
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?

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
How confidence intervals become confusion intervals

James McCormack¹, Ben Vandermeer² and G Michael Allan³*
Bone Density
Cholesterol
Blood Pressure
Glucose
Vitamin D

A Closer Look
“Obtain a baseline DXA, and repeat DXA every 1 to 2 years until findings are stable. Continue with follow-up DXA every 2 years or at a less frequent interval”
1) Average bone loss per year ~ 0.6%
2) Difference in BMD between drug and placebo - 3 years ~5%
3) BMD measurement precision +/- 2-3%

![Bone density distribution graph showing normal, osteopenia, and osteoporosis regions.](image_url)
“Monitoring BMD in the first 3 years after starting treatment with a bisphosphonate is unnecessary and may be misleading”
“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%

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

Arch Intern Med 2007;167:155-60
“In individuals with a modified FRS of 5%-9%, yearly monitoring could be used to evaluate change in risk.”

“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”
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

100% 95% 85% 75%

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

Baseline LDL

33% dec (10-20mg)

Add 10% dec (40-80mg)

4
~160

2.8
~110

2.5
~100

95% CI ~ +/-0.5
“Repeat risk estimation before 8-10 years is not warranted for most people initially not requiring treatment”
Systolic blood pressure

TYPICAL CHANGES SEEN

Start medication - avg 9 mmHg ↓
Increase dose - avg 2-5 mmHg ↓
Seasonal differences - avg 8 mmHg ↓ when warm
Age related (per year) - avg 0.5-0.8 mmHg ↑

Sample size calculation - 40 office measurements before and after treatment to be REASONABLY confident that a 5 mmHg change has occurred
Need changes of at least 10/5 mmHg before you can say there has been a change
Am J Hyper 2008;21:3–4

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

“coefficients of variation for systolic office, ambulatory, and self-monitored blood pressure, compared at baseline and 6 weeks, were 8.6%, 5.5%, and 4.2% respectively”
Br J Gen Pract 2010; 60: 675–80

“a single careful blood pressure measurement taken a few months after the start of treatment is not useful for monitoring”
BMJ 2009;338:b1492
Glucose measurements

Typical A1c change seen with a medication = 0.7% ↓

Seasonal variation 0.2-0.5% Higher in winter

Am J Epi 2004;161:565-74

The A1C Test and Diabetes
National Diabetes Information Clearinghouse
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.
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

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

J Clin Endocrinol Metab 2009;94:1092–3
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

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

<table>
<thead>
<tr>
<th>LDL Cholesterol (statin)</th>
<th>Glucose/A1c (any meds)</th>
<th>Blood pressure (any meds)</th>
<th>Bone density (bisphosphonates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These risk factors can all be used to estimate ballpark risks

<table>
<thead>
<tr>
<th>No point in measuring if increasing statin doses</th>
<th>No point in measuring?</th>
<th>No point in measuring? unless many measurements before and after</th>
<th>No point in measuring if increasing doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>&lt;5%</th>
<th>10-20%</th>
<th>20-40%</th>
<th>40%-60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride</td>
<td>Creatinine</td>
<td>AST</td>
<td>GGT</td>
</tr>
<tr>
<td>Sodium</td>
<td>Globulins</td>
<td>Alkaline</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Osmolality</td>
<td>Glucose</td>
<td>phosphatase</td>
<td>PSA</td>
</tr>
<tr>
<td></td>
<td>Magnesium</td>
<td>BUN</td>
<td>Vitamin D</td>
</tr>
<tr>
<td></td>
<td>pC02</td>
<td>HDL</td>
<td></td>
</tr>
<tr>
<td>5-10%</td>
<td>Potassium</td>
<td>LDH</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>Total</td>
<td>LDL</td>
<td></td>
</tr>
<tr>
<td>Bone density</td>
<td>cholesterol</td>
<td>Phosphorous</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td>Platelets</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td></td>
<td>Rheumatoid</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
<td>factor</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td>Testosterone</td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td></td>
<td>Uric acid</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td>WBC</td>
<td></td>
</tr>
</tbody>
</table>

| 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

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Total cholesterol RCV</th>
<th>LDL RCV</th>
<th>HDL RCV</th>
<th>Triglycerides RCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg. cholesterol inc. per year</td>
<td>0.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. LDL initial dec. with statin</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. LDL dec. with inc. dose of statin</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. HDL inc. with statin</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. LDL dec. with exercise</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glucose</th>
<th>A1c RCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg A1c inc. per year</td>
<td>0.3%</td>
</tr>
<tr>
<td>Avg. A1c dec. with glucose med</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Systolic blood pressure RCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg SBP inc. per year</td>
<td>0.5%</td>
</tr>
<tr>
<td>Avg. SBP dec. with BP med</td>
<td>10%</td>
</tr>
<tr>
<td>Avg. SBP dec. with inc. dose of BP med</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone density</th>
<th>Bone density RCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg. yearly bone density loss</td>
<td>0.6%</td>
</tr>
<tr>
<td>Avg. yearly bone density inc. with med</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Date</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb 21/2017</td>
<td></td>
</tr>
<tr>
<td>Mar 21/2017</td>
<td></td>
</tr>
<tr>
<td>Apr 21/2017</td>
<td></td>
</tr>
</tbody>
</table>

**Potassium (mEq/L)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar 21/2017</td>
<td></td>
</tr>
</tbody>
</table>

**HbA1c (%)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 01/2017</td>
<td></td>
</tr>
<tr>
<td>Feb 01/2017</td>
<td></td>
</tr>
<tr>
<td>Mar 01/2017</td>
<td></td>
</tr>
</tbody>
</table>

95% of HEALTHY people have results somewhere in this range
5% of HEALTHY people have results somewhere in this range

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

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
Deals with reference change values