Laboratory medicine: Closer clinical collaboration will lead to evidence-based reporting of results

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When using biochemical analytes in the management of patients, the value of the analyte is often considered in relation to the reference range calculated from the distribution of the analyte in a healthy cohort [1]. Such distributions are either symmetrically (Gaussian) or asymmetrically distributed. The middle 95% values of the healthy cohort distribution are utilized as the reference range assumes that the reference cohort is an apt comparison group for the specific pathology. For example, the measurement of cortisol provides an important reminder of the pitfalls of reference range dependence. Although most clinicians are aware of this hormone’s diurnal pattern, the empirical undertaking of an early morning basal sample in order to assess the integrity of the hypothalamic-pituitary-adrenal axis may in certain circumstances be inappropriate, such as in individuals with altered sleep–wake cycle. Furthermore, a numeral value that straddles the higher end of a reported reference range—in an inpatient setting—may falsely reassure a clinician into believing there is adequate adrenal reserve, when actually representing an adrenal crisis. It is therefore imperative that an assayed sample is taken in the context of a thorough understanding of the wider medical and psychosocial setting.

Thus, it is important to evaluate as to what the reference range adds to the clinical decision-making process and whether it should be replaced by action limits. While knowledge of this distribution can be invaluable, it must be used in conjunction with the clinical phenotype while diagnosing a condition, as well as the available evidence base when making treatment decisions. We ask the question as to whether the value obtained from a biochemistry test is perhaps better when compared with both the distributions of healthy individuals and those with the specific pathology. It is further complicated by heterogeneity existing within most disease states, which may require knowledge of differing distributions. Many clinicians can intuitively bypass these issues through innate awareness and experience. They are able to judge whether an abnormal biochemical test is clinically relevant or not, regardless of whether it lies within or outside the normal distribution. Importantly, many medical schools now devote little education in describing the derivation of reference ranges and the impact of heterogeneity. Hence, biochemical tests and reference ranges are often considered by trainee doctors as absolute predictors of health or disease, leading to a deficient practice of medicine. But we know that, even in a “normal” population, statistically speaking, a test result will lie outside the reference range in 5% of cases (1 in 20)! This is perhaps why the term “reference range” is preferential to “normal range.”

We now provide two clinical examples; one where reference ranges have been successfully superseded by evidence-based action limits (dyslipidemia), and another where confusion exists with very different reference ranges quoted and no action limits reported (male adult-onset hypogonadism).

Most clinical biochemistry laboratories do not report lipid distributions in healthy subjects. For example the Mayo Clinic ([https://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/diagnosis-treatment/drc-20350806; accessed on 16th April 2021]) categorizes
total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations in relation to heart disease in a patient friendly guideline format. LDL-cholesterol levels are issued, as follows, in relation to the likelihood of heart disease risk.

- **<1.8 mmol/L (70 mg/dL):** best for people who have heart disease or diabetes.
- **<2.6 mmol/L (<100 mg/dL):** optimal for people at risk of heart disease.
- **2.6–3.3 mmol/L (100–129 mg/dL):** near optimal if there is no heart disease, high if there is heart disease.
- **3.4–4.1 mmol/L (130–159 mg/dL):** borderline high if there is no heart disease, high if there is heart disease.
- **4.1–4.9 mmol/L (160–189 mg/dL):** high if there is no heart disease, very high if there is heart disease.
- **>4.9 mmol/L (190 mg/dL):** very high.

However, the above guidance does not completely mirror the recommendations of the American Heart Association/American College of Cardiology (AHA/ACC) issued in 2018, especially regarding the use of risk scores in primary prevention [2]. Interestingly, the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines, issued in 2019, significantly differ from those issued by the AHA/ACC [3]. In the United Kingdom (UK), the information of lipid levels by the National Health Service (https://www.nhs.uk/conditions/high-cholesterol/cholesterol-levels/; accessed on 16th April 2021) is lagging behind current trial evidence and the ESC/EAS guidelines. Thus, it is not sufficient in a field such as lipidology with constantly advancing evidence, to just adopt action limits, but rather to periodically update them through the continued review of the latest clinical trials/guidelines by international societies. Furthermore, heterogeneity must also be considered, as the lipid thresholds will differ between various dyslipidemia subgroups (e.g., familial hypercholesterolemia and metabolic syndrome) and therefore should also be highlighted in any reports [4].

Adult-onset hypogonadism in males is defined by low testosterone concentrations and associated symptoms [5]. Identifying this clinical phenotype is important as it has a high prevalence (6–12% in males and about 40% in type 2 diabetes) as well as being associated with increased morbidity and mortality [5, 6]. A recent audit by our group in the UK showed male testosterone reference ranges varying significantly between laboratories [7]. Furthermore, no useful clinical guidance was provided in most of the reports, with only a few quoting published action limits. There is mounting evidence regarding the benefits of testosterone therapy in men with adult-onset hypogonadism [5], and it is essential that these should be communicated by the laboratories, to the service users.

The above examples demonstrate how laboratories report analytes in two differing pathologies; one with mature evidence (dyslipidemia) and the other with evidence in its infancy (adult-onset hypogonadism). Even in the former, it is clear that reports issued by the laboratory must include the ever-increasing evidence. In the latter, the laboratory has an obligation, not just to harmonize reference ranges, but to monitor evidence and move the reporting from reference ranges toward action limits, and also educate the requesting clinicians from a myriad of specialties (urology, endocrinology, metabolic physicians, and general practice) in the appropriate management of these patients. The key to the optimization of reporting/education is close collaboration with specialists in all disciplines in which management is influenced by laboratory measurements of analytes.

**Keywords:** Adult-onset hypogonadism, Dyslipidemia, guidelines, Reference ranges

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